

A Pharmacovigilance Approach for Assessing  
Cardiovascular, Osteological, and Carcinogenic Risk Associated with  
Thiazolidinedione Drugs used in the Treatment of Type 2  
Diabetes Mellitus

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## ABSTRACT

Diabetes is a chronic and debilitating disease that affects nearly half a billion people worldwide with the vast majority of diabetics suffering from Type 2 diabetes mellitus (T2DM), a disease characterized by insulin insensitivity that often requires pharmacotherapy to effectively maintain target blood sugar levels. The thiazolidinedione (TZD) class of drugs consists of oral hypoglycaemic agents used alone or in combination with other antidiabetic drugs to treat T2DM. The drugs within this class, which include rosiglitazone and pioglitazone, were originally heralded as providing novel first and second-line treatment of T2DM with glycaemic control and physiological effects comparable to, and in some cases, better than, first-line treatments such as metformin. However, over time they have also been associated with adverse cardiovascular, osteological, and carcinogenic effects in some, but not all clinical trials, observational studies, and meta-analyses. Given the conflicting evidence to date on the safety of TZD drugs, their role in the treatment of T2DM continues to be debated and epidemiological gaps remain. The objectives of this doctoral research are fourfold: 1) to conduct an in-depth review of the epidemiology of TZD pharmacotherapy including pharmacokinetics and modes of action, the results of previous studies investigating health risks and benefits associated with TZD treatment, and new and future uses for this class of drugs; 2) to determine whether diabetic patients treated with TZDs are at increased risk of adverse cardiovascular outcomes; 3) to assess whether TZD pharmacotherapy is associated with an increased risk of bone fractures and whether risks differ depending on fracture site and patient sex; and, 4) to investigate associations between TZD use and risk of bladder cancer. Specific research questions were investigated using nested case-control analyses designed to capture incident users of antidiabetic drugs and electronic health data from Cerner Health Facts®, an electronic medical record database that stores time-stamped

patient records from more than 480 contributing hospitals throughout the United States. Findings from this work are reported in a series of manuscripts, including a published review paper. Key findings include: 1) TZD use was associated with an increased risk of incident myocardial infarction and congestive heart failure compared to never use of TZD drugs with a trend towards a potential early treatment effect within the first year of exposure to pioglitazone; 2) TZD use was associated with an increased risk of closed bone fractures among Type 2 diabetics with use of pioglitazone or rosiglitazone associated with an increased risk across multiple fracture sites in women, but only rosiglitazone use in men and only at peripheral fracture sites; 3) use of either pioglitazone or rosiglitazone were associated with an increased risk of incident bladder cancer compared to never users, however, a low number of bladder cancer cases resulted in underpowered analyses; and, 4) insulin use in a hospital setting may replace a patient's normal course of antidiabetic therapy which, when combined with other potential sources of bias in traditional nested case-control studies using hospital-based data, may lead to overestimation or underestimation of adverse health risks associated with non-insulin antidiabetic therapies. Although these findings warrant replication, the results of the research contained within this dissertation suggest that caution should be exercised when prescribing diabetic patients TZD drugs if they have cardiovascular, osteological, or carcinogenic risk factors. Additional pharmacovigilance studies should also continue to strive to better understand the health risks related to TZD therapy, especially as new therapeutic roles for TZDs in the prevention and treatment of some cancers, inflammatory diseases, and other conditions in non-diabetic populations are being explored.

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## LIST OF ABBREVIATIONS

|         |                                                                                          |
|---------|------------------------------------------------------------------------------------------|
| ACCORD  | Action to Control Cardiovascular Risk in Diabetes                                        |
| ACE     | angiotensin-converting enzyme                                                            |
| ACS     | acute coronary syndrome                                                                  |
| AD      | Alzheimer's disease                                                                      |
| ADA     | American Diabetes Association                                                            |
| ADOPT   | A Diabetes Outcome Progression Trial                                                     |
| ADR     | adverse drug reaction                                                                    |
| AFSSAPS | Agence Française de Sécurité Sanitaire des Produits de Santé                             |
| AGE     | advanced glycation end product                                                           |
| AHA     | American Heart Association                                                               |
| ALP     | alkaline phosphatase                                                                     |
| AMP     | adenosine monophosphate                                                                  |
| AMPK    | adenosine monophosphate-activated protein kinase                                         |
| ATP     | adenosine triphosphate                                                                   |
| A1C     | glycated hemoglobin                                                                      |
| BARI 2D | Bypass Angioplasty Revascularization Investigation 2 Diabetes                            |
| BMC     | bone mineral content                                                                     |
| BMD     | bone mineral density                                                                     |
| BMI     | body mass index                                                                          |
| BW      | body weight                                                                              |
| CAD     | coronary artery disease                                                                  |
| CDC     | Centers for Disease Control and Prevention                                               |
| CHF     | congestive heart failure                                                                 |
| CI      | confidence interval                                                                      |
| CIG     | ciglitazone                                                                              |
| COPD    | chronic obstructive pulmonary disease                                                    |
| CPRD    | United Kingdom Clinical Practice Research Datalink                                       |
| CTX     | C-terminal crosslinking telopeptide of type I collagen                                   |
| CV      | cardiovascular                                                                           |
| CVD     | cardiovascular disease                                                                   |
| DCCT    | Diabetes Control and Complications Trial                                                 |
| DKA     | diabetic ketoacidosis                                                                    |
| DPP-4   | dipeptidyl peptidase 4                                                                   |
| DREAM   | Diabetes REduction Assessment with ramipril and rosiglitazone Medication                 |
| EASD    | European Association for the Study of Diabetes                                           |
| ED      | emergency department                                                                     |
| EMA     | European Medicines Agency                                                                |
| EMR     | electronic medical record                                                                |
| ENaC    | epithelial sodium channels                                                               |
| FAERS   | US FDA Adverse Event Reporting System                                                    |
| FGPS    | Faculty of Graduate and Postdoctoral Studies                                             |
| FPG     | fasting plasma glucose                                                                   |
| FRAX    | University of Sheffield Centre for Metabolic Bone Diseases Fracture Risk Assessment Tool |

|        |                                                                                  |
|--------|----------------------------------------------------------------------------------|
| GH     | growth hormone                                                                   |
| GLIC   | glicazide                                                                        |
| GLIM   | glimepiride                                                                      |
| GLY    | glyburide                                                                        |
| GLP-1  | glucagon-like peptide 1                                                          |
| GnRH   | gonadotropin-releasing hormone                                                   |
| GPRD   | United Kingdom General Practice Research Database                                |
| GSK    | Glaxo Smith Kline                                                                |
| HC     | Health Canada                                                                    |
| HDL    | high-density lipoprotein                                                         |
| HDL-C  | high-density lipoprotein cholesterol                                             |
| HF     | heart failure                                                                    |
| HHS    | hyperosmolar hyperglycaemic state                                                |
| HIPAA  | <i>Health Insurance Portability and Accountability Act</i>                       |
| HR     | hazard ratio                                                                     |
| IARC   | International Agency for Research on Cancer                                      |
| ICD-9  | International Classification of Diseases, Ninth Revision                         |
| IFD    | International Diabetes Federation                                                |
| IHD    | ischemic heart disease                                                           |
| IL-1   | interleukin-1                                                                    |
| IL-6   | interleukin-6                                                                    |
| IRIS   | Insulin Resistance Intervention after Stroke                                     |
| KPNC   | Kaiser Permanente Northern California                                            |
| LDL    | low-density lipoprotein                                                          |
| LDL-C  | low-density lipoprotein cholesterol                                              |
| LH     | luteinizing hormone                                                              |
| LOS    | length of stay                                                                   |
| MCI    | mild cognitive impairment                                                        |
| MET    | metformin                                                                        |
| MI     | myocardial infarction                                                            |
| mmHg   | millimeters of mercury                                                           |
| MPTP   | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine                                     |
| MS     | multiple sclerosis                                                               |
| NA     | not available                                                                    |
| NAFLD  | nonalcoholic fatty liver disease                                                 |
| NASH   | nonalcoholic steatohepatitis                                                     |
| NGSP   | National Glycohemoglobin Standardization Program                                 |
| NHANES | National Health and Nutrition Examination Survey                                 |
| NHEFS  | National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study |
| NPH    | neutral protamine hagedorn                                                       |
| NSAID  | non-steroidal anti-inflammatory drug                                             |
| OGTT   | oral glucose tolerance test                                                      |
| OHA    | oral hypoglycemic agent/drug                                                     |
| OH-BBN | hydroxybutyl(butyl)nitrosamine                                                   |
| OR     | odds ratio                                                                       |



|              |                                                                                                            |
|--------------|------------------------------------------------------------------------------------------------------------|
| PAD          | peripheral arterial disease                                                                                |
| PCI          | percutaneous coronary intervention                                                                         |
| PCOS         | polycystic ovary syndrome                                                                                  |
| PD           | Parkinson's disease                                                                                        |
| PERISCOPE    | Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation |
| PG           | plasma glucose                                                                                             |
| PIO          | pioglitazone                                                                                               |
| PPAR         | peroxisome proliferator-activated receptor                                                                 |
| PROactive    | PROspective pioglitAzone Clinical Trial In macroVascular Events                                            |
| PSA          | prostate-specific antigen                                                                                  |
| PVD          | peripheral vascular disease                                                                                |
| P1NP         | procollagen type I N-terminal propeptide                                                                   |
| RAS          | renin–angiotensin system                                                                                   |
| RCT          | randomized clinical trial or randomized controlled trial                                                   |
| REACT        | Regulatory, Economic, Advisory, Community, and Technological                                               |
| RECORD       | Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycaemia in Diabetes                       |
| REMS         | Risk Evaluation and Mitigation Strategy                                                                    |
| ROR          | reporting odds ratio                                                                                       |
| ROSI         | rosiglitazone                                                                                              |
| RR           | relative risk                                                                                              |
| RXR          | retinoid X receptor                                                                                        |
| SD           | standard deviation                                                                                         |
| SE           | standard error                                                                                             |
| SES          | socioeconomic status                                                                                       |
| SGLT2        | sodium-glucose co-transporter-2 inhibitors                                                                 |
| SHBG         | sex hormone-binding globulin                                                                               |
| SUL          | sulfonylurea                                                                                               |
| TIA          | transient ischemic attack                                                                                  |
| TNF $\alpha$ | tumor necrosis factor alpha                                                                                |
| TRIAD        | Translating Research into Action for Diabetes                                                              |
| TRO          | troglitazone                                                                                               |
| TZD          | thiazolidinedione                                                                                          |
| T2DM         | Type 2 diabetes mellitus                                                                                   |
| UK           | United Kingdom                                                                                             |
| UKPDS        | United Kingdom Prospective Diabetes Study                                                                  |
| UPDRS        | Unified Parkinson's Disease Rating Scale                                                                   |
| US           | United States                                                                                              |
| USD          | United States dollars                                                                                      |
| US FDA       | United States Food and Drug Administration                                                                 |
| VLDL         | very-low-density lipoprotein                                                                               |
| WHO          | World Health Organization                                                                                  |

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*Dedicated to Raine*

*&*

*In loving memory of TBC who always was and forever will be by my side  
2006-2017*

## **PREFACE**

In accordance with the thesis regulations of the Faculty of Graduate and Postdoctoral Studies (FGPS), this thesis consists of one published review paper and three manuscripts that have been prepared for submission for publication. Each manuscript is prefaced with a brief description and contains a statement of contribution of collaborators and coauthors, as required by the FGPS.

## CHAPTER 1: Introduction

Diabetes affects approximately 415 million people worldwide, representing 8.8% of the world's adult population, a number that is estimated to rise to 642 million by 2040 [1]. Type 2 diabetes mellitus (T2DM), a condition that results from the body's ineffective use of insulin, accounts for between 90% and 95% of all diabetes cases [2, 3]. Although lifestyle management such as diet and exercise are first line treatments, many patients also need treatment with one or a combination of two or more oral or injectable hypoglycaemic drugs or insulin to improve glycaemic control [4] and prevent microvascular and macrovascular complications [5]. Drugs that act as insulin sensitizers are widely used since most patients with T2DM demonstrate some degree of insulin resistance [4, 6].

Thiazolidinedione (TZD) class drugs are peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) agonists that act as insulin sensitizing agents; they improve glycaemic control and a variety of other surrogate outcomes in patients with T2DM [5]. PPAR $\gamma$  are transcription factors that once activated by ligands such as TZDs, alter the transcription of several genes involved in glucose and lipid metabolism leading to reduced insulin resistance in adipose tissue, muscle, and the liver [7-9]. Since T2DM frequently results from progressive failure of pancreatic  $\beta$ -cell function in the presence of chronic insulin resistance, TZD drugs also help to preserve  $\beta$ -cell function and improve insulin resistance through sustained glycaemic control [10]. Although PPAR $\gamma$  are found primarily in adipose tissue, they are also expressed in other tissues such as the large intestine, kidney, and skeletal tissue leading to various biochemical and physiological responses when activated [9]. These responses include, among others, fluid retention [11], inhibition of bone formation [12] and resorption [13, 14], and potential suppression of tumour development [15, 16].

The TZD drugs rosiglitazone and pioglitazone have been marketed in North America since 1999 under trade names such as Avandia (rosiglitazone), Avandamet (rosiglitazone in combination with metformin) and Avandaryl (rosiglitazone in combination with glimepiride) by Glaxo Smith Kline (GSK) (in addition to generic versions of rosiglitazone approved for the United States [US] market in 2013), and Actos (pioglitazone), Actoplus Met (pioglitazone in combination with metformin) and Duetact (pioglitazone in combination with glimepiride) by Takeda Pharmaceuticals (as well as generic pioglitazone drugs first given market approval in 2012). The use of these widely prescribed drugs has been associated with an increased risk of adverse cardiovascular, osteological, and carcinogenic events in some studies, though the characterization of the incidence and extent of such events within the T2DM population remains incomplete. For example, adverse cardiovascular events linked to TZD pharmacotherapy have included congestive heart failure (CHF) and acute myocardial infarction (MI) [5, 17-21], although the results of many studies investigating these endpoints have been inconsistent. Some have implicated rosiglitazone but not pioglitazone, and others have implicated them both equally. Many studies have concluded that rosiglitazone is associated with adverse cardiovascular effects: over the past several years this drug has received a great deal of attention from the global drug regulatory community leading to the removal of rosiglitazone from certain markets such as in some European countries [22], its restricted access in others such as Canada [23], and its restricted access [24] then reinstatement in the US [25-26].

In addition to reports of cardiovascular effects, both rosiglitazone and pioglitazone have also more recently been linked to an increased risk of adverse osteological effects such as decreased bone mineral density (BMD) [27] and events such as fractures [28-34]. A comparable risk of fracture has been found for both drugs in some studies [30, 35-37], whereas others have



found that the risk may be more strongly associated with pioglitazone treatment [38, 39]. It is also still unclear whether the risk for fracture with TZDs occurs primarily in older women (who are more likely to be osteoporotic) or if it extends to men and to younger patients. Rosiglitazone and pioglitazone have also been associated with adverse carcinogenic effects, more specifically cancer of the bladder following preliminary indications from Takeda Pharmaceuticals [40] that pioglitazone may be associated with reports of bladder cancer. Initial results from studies in animal models [41-43] and humans [44-45] suggested that the risk may be elevated with TZD exposure, especially exposure to pioglitazone and with longer use of the drug, but more investigation is needed in larger patient populations with longer follow-up periods to clarify associations.

## **OBJECTIVES**

The overall objective of this thesis is to examine associations between TZDs and adverse drug reactions (ADRs) by conducting retrospective, nested case-control analyses using electronic medical records (EMRs) from a large cohort of subjects with T2DM (further described below). Specific objectives are to review the existing literature related to ADRs linked to TZD drugs and examine associations between TZD pharmacotherapy and: 1) adverse cardiovascular outcomes (MI and CHF); 2) bone fractures; and, 3) bladder cancer.

## **SIGNIFICANCE**

### **Adverse Drug Reactions**

Although initial clinical trials detect common and frequent ADRs, other reactions may take longer than the limited timeframe of the pre-market phase of a drug to develop or may occur infrequently. It is estimated that even when comprehensive safety profiles are maintained, over 51% of approved drugs have serious side effects that were not detected before market approval [46]. In addition to this, most clinical trials exclude the elderly, children, pregnant women, patients with multiple diseases, and those on medications that are suspected to interact with the study drug, therefore, a study's participants' experience may not be representative of the real world where the drug is eventually used [47]. Continued monitoring of ADRs in the post-market phase of a drug is needed to maintain a comprehensive safety and effectiveness profile. Given the extent and reach of T2DM, both worldwide and in Canada where it is estimated that approximately nine million Canadian adults have diabetes or pre-diabetes [48], this research provides a unique opportunity to explore potentially serious ADRs associated with TZD class drugs in an extensive cohort of T2DM patients using an active monitoring approach.

Post-market pharmaceutical surveillance may be classified as active or passive. Passive surveillance typically consists of the review of ADR data obtained through spontaneous and voluntary reporting systems which are often submitted by health care professionals or members of the general public [49]. As the term suggests, active surveillance involves the systematic collection, monitoring, and analysis of ADR data that is often regulated and enforced by governmental bodies or regulatory agencies. Currently, in North America and Europe the vast majority of post-market drug surveillance can be considered spontaneous or passive [50]. Market authorization holders are required by law to report any new evidence of ADRs [51], but currently

most nations do not require ongoing safety surveillance or phase IV trials after a drug has completed the approval process [52].

Although mechanisms exist to monitor the occurrence of post-market phase ADRs, the difficulties imposed by resource scarcity and data limitations often delay the detection of severe drug-related adverse events. It is also widely accepted that only a fraction of all ADRs are reported [53]. Neither patients nor physicians may recognize the association between a particular medication and an adverse effect which occurs weeks or months after the drug is first taken. Or, as with the adverse cardiovascular effects of rofecoxib (Vioxx), a non-steroidal anti-inflammatory drug (NSAID) which during its five years on the market was responsible for as many as 139,000 heart attacks and 55,000 fatalities [54], initially seem unrelated. Individual case reports also often lack fundamental details about the health status of the patient, concomitant drug use, accuracy and appropriateness of the dose taken, and misunderstanding or confusion on the part of the reporter may also lead to incomplete or inaccurate reporting of the adverse event and its probable cause [49].

Pharmacovigilance seeks to detect and identify signals or potential problems with pharmaceutical products. The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems” [55]. The primary objective of pharmacovigilance is to monitor newly marketed pharmaceutical products in real-world settings. It allows for the identification of ADRs not readily apparent within the size and time constraints of current safety evaluation and drug approval processes. The role of pharmacovigilance is to collect information regarding the efficacy and risk of pharmaceutical products, including information regarding factors that affect the action of the drug itself (e.g. age, sex, concomitant

medications) in specific subpopulations to inform evidence-based clinical decision making, prompt regulatory action, and communicate risks to health professionals and the public [56]. This methodology will be used to analyze the data for this research regarding the safety of TZD drugs.

## **Data Source**

The Cerner Corporation's Health Facts® data warehouse is a US *Health Insurance Portability and Accountability Act* (HIPAA)-compliant database containing EMR information collected from more than 41 million distinct patients from over 480 contributing subscribers/participating clinical facilities in the US (at the time of the analyses conducted for this dissertation). This datawarehouse is used within some of the largest health systems in the US including the University of Pittsburgh Medical Center and Indiana University Health. To date, Health Facts® is the only US health care database that uses comprehensive time-stamped and sequenced clinical records with pharmacy, laboratory, admission, diagnostic, and billing data from all participating patient care locations. These records include over 1.3 billion laboratory results, over 84 million acute admissions, emergency and ambulatory visits, more than 151 million orders for nearly 4,500 drugs, and detailed pharmacy, laboratory, billing, and registration data. Data generated from Cerner and non-Cerner participating contributing facilities began in the year 2000.

Cerner Health Facts® has several advantages that make it intriguing for epidemiological research. Firstly, it contains a comprehensive source of de-identified, real-world data that is collected as a by-product of patient care. Secondly, and as mentioned above, it includes clinical records with time-stamped and sequenced information on pharmacy, dispensing, laboratory, admission, and billing data from all patient care locations across its network of contributing

facilities. Thirdly, Health Facts® is designed to track a drug or device's usage across diagnoses and major procedures, as well as by geographic region and hospital type, which permits researchers to determine practice patterns, treatments, and outcomes. Fourthly, it has good heterogeneity which allows complex research problems to be investigated. Fifthly, using this dataset is a rare opportunity to collaborate with a large scale data service provider. And finally, the issues explored in this dataset have not yet been studied in this large and comprehensive hospital-based dataset.

## **Rationale and Approach**

As will be described in-depth in **Chapter 2** of this dissertation, there is still a great deal of controversy surrounding adverse cardiovascular, oestological, and carcinogenic effects associated with TZD pharmacotherapy and to date the evidence remains conflicting. This is of concern as TZDs continue to be investigated and/or repurposed for the treatment of cancer, polycystic ovary syndrome (PCOS), and other inflammatory diseases which may lead to future shifts in drug utilization patterns (e.g. use by younger non-diabetic patient populations), and new PPAR-targeting medications are currently under development that could have similar adverse effects. Other researchers continue to study adverse effects associated with TZDs in different datasets including those that are not solely hospital-based (e.g. using the Clinical Practice Research Datalink (CRPD) in the United Kingdom and the Kaiser Permanente Northern California Diabetes Registry in the US) and few studies (approximately 12%) have investigated these issues in US-based hospital datasets. Therefore, key research problems remain to be explored. Conducting the research contained in this dissertation is an opportunity to use a large, unique dataset for further comparison to add to the weight of evidence and explore biases

specifically associated with hospital-based data (i.e. do the observed effects in other studies exist across different datasets).

Using a subset of data spanning from January 2000 to December 2012 and containing more than 1.5 million unique patients with T2DM, nested case-control studies were conducted for each data chapter. This methodological approach was chosen because it takes into account the time varying nature of drug use contained in Cerner Health Facts®, the size of the available patient cohort and number of patient encounters, the long duration of follow-up in the dataset, the enormity of the dataset in terms of computational efficiency, and the rare event setting for the endpoints under investigation (i.e. the probability of a patient undergoing TZD pharmacotherapy and having an event such as an MI, CHF or a fracture is low; bladder cancer is in and of itself a rare disease). Using the Health Facts® datawarehouse also provides an excellent resource to characterize a large diabetic population by identifying the underlying determinants that pose health risks, their interactions, and potential interventions to mitigate risk from a population health perspective (as further described in the next section of this chapter), and to explore the strengths and limitations of working with EMR data, including biases.

For example, one bias that is common when working with hospital-based administrative data is prevalent user bias. Type 2 diabetics often receive antidiabetic drug prescriptions from a general practitioner outside of a hospital or outpatient setting which introduces the possibility of capturing prevalent users in hospital-based administrative data [57]. To address potential prevalent user bias, a design [58] was employed for the epidemiological studies contained within this thesis that first assembled a base cohort population of patients who had a similar level of T2DM disease severity, and from that base cohort, study cohorts of patients who intensified or progressed their diabetic treatment regime to establish study populations that are more likely to

contain incident drug users. Cohort selection, including endpoint-specific criteria, is presented in **Figure 1** and is further described in each data chapter of this dissertation. This bias and others, including a potential bias related to the in-hospital substitution of insulin in place of a patient's normal course of antidiabetic treatment, are further explored throughout this dissertation and in the final discussion chapter.

## **RELEVANCE TO POPULATION HEALTH**

Determining why ADRs occur and who experiences them is a very difficult and complex process. The origins or causes of ADRs can be the result of interplay between a variety of factors and consequently, any actions taken to address issues of drug safety must be multifactorial and a multilevel approach to risk analysis is needed. Key areas that require attention include the formulation of the problem to be investigated, including the scope of the investigation, identifying the underlying determinants that pose health risks within a population, characterizing the available risk-based science, making informed risk-based decisions, developing effective evidence-based policies, and intervening on multiple levels. Taking these aspects into consideration, this research was originally rooted in the Integrated Framework for Risk Management and Population Health [59] developed by the McLaughlin Centre for Population Health Risk Assessment at the University of Ottawa, but will follow the more detailed Framework for the Next Generation of Risk Science (referred to as the "NextGen Framework"; Krewski et al. [60]; **Figure 2**). This updated and comprehensive framework incorporates the key elements of the original Intergrated Framework developed by Krewski et al. [59] in 2007 but expands upon them to harmonize three complementary perspectives on human health risk

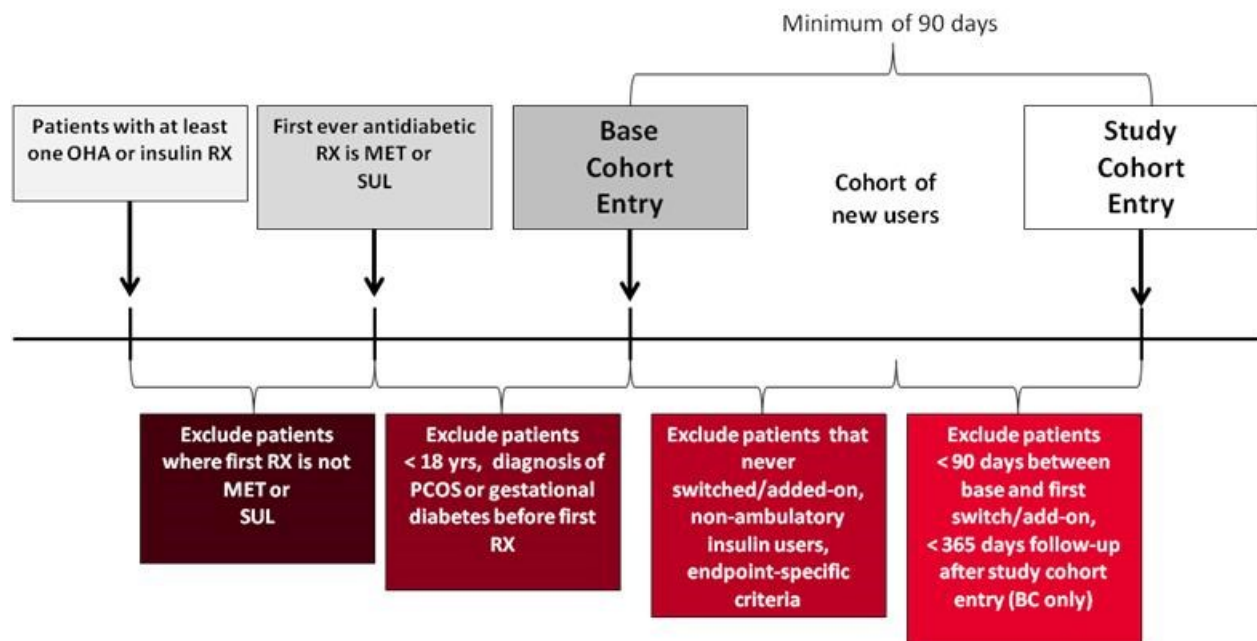


**Figure 1.** An overview of the methodological approach used to control for prevalent user bias. BC: bladder cancer; MET: metformin; OHA: oral antihyperglycaemic agent; PCOS: polycystic ovarian syndrome; RX: prescription; SUL: sulphonylurea.



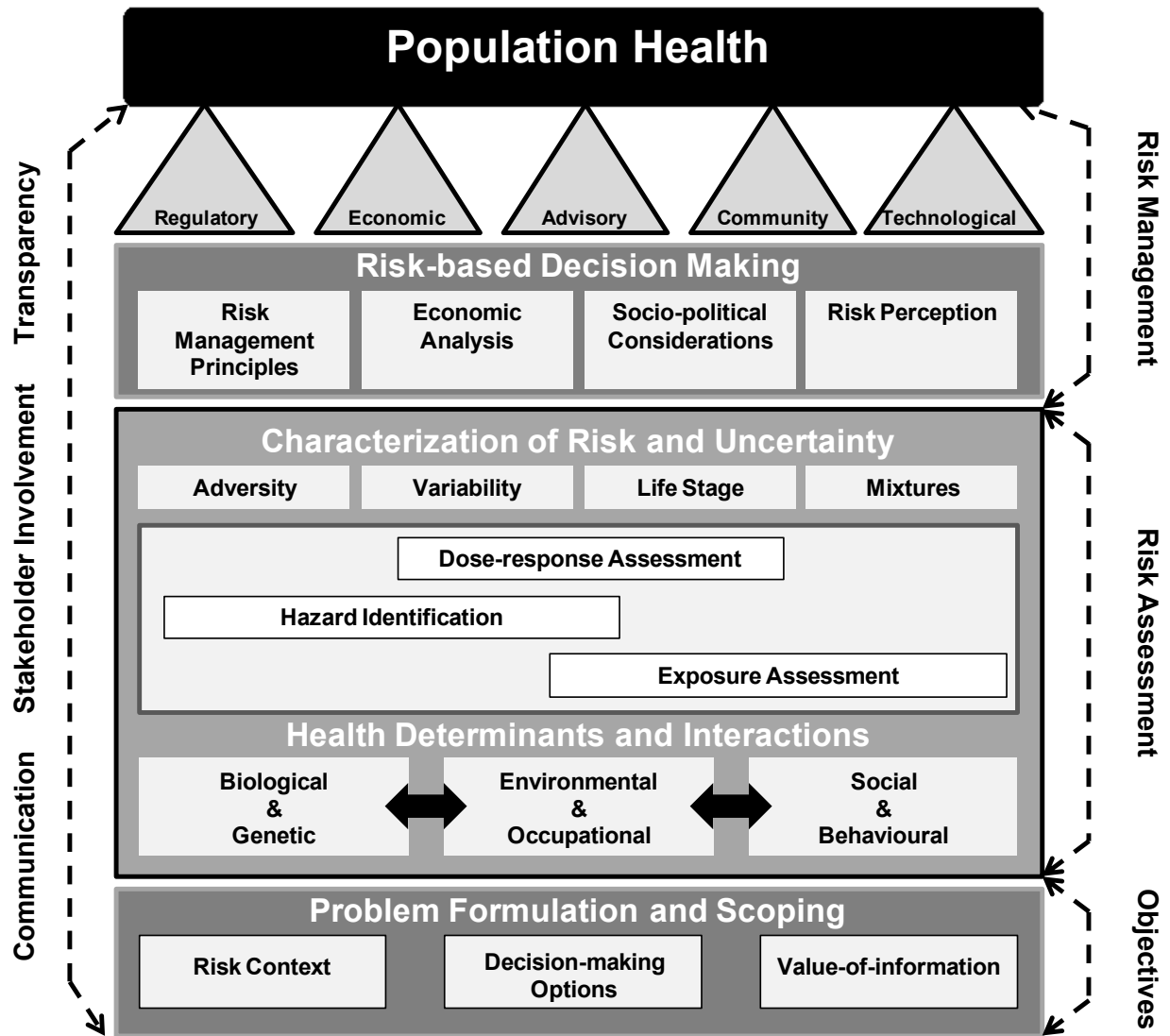


**Figure 2.** The Next Generation Framework for Risk Science. Adapted from: Krewski et al. [60].

assessment (population health, advances in toxicological science, and new developments in risk assessment methodology) to provide a broader perspective with which to analyze and address health risk issues. The NexGen Framework consists of three phases: I) Objectives; II) Risk assessment; and, III) Risk management.

## **I) Objectives**

The goal of Phase I of the NextGen Framework is to determine the risk science objectives that will establish the overall goals of the risk assessment and management process. Through problem formulation and scoping of the problem of interest, consideration is given to the context of the risk(s) at hand, decision-making options available, and the value of the information involved. This phase is undertaken to focus risk assessments so that the scientific information that is gathered is cost-effective, useful, and applicable. It includes consideration of relevant health determinants and their interactions (see *Phase II: Risk assessment*), data gaps that need to be filled, stakeholder concerns and impacts, and possible risk management strategies [60].

## **II) Risk assessment**

Phase II of the NextGen Framework focuses on health determinants, the interactions between these health determinants, and the characterization of risk and uncertainty. Three broad categories of health determinants form the foundation of this phase of the framework: biological and genetic, environmental and occupational, and social and behavioural. Including the interactions between these health determinants in the framework encourages examination of all influences on a particular health outcome rather than examining only a single risk factor, as is usually done in traditional risk assessment [59, 61]. This approach also ensures that the process

of characterizing the health risk of interest is better informed and is initiated from a solid foundation rooted in population health.

The first category of health determinants consists of factors related to biology and genetic endowment. These include biological processes such as development and aging, the functioning of various bodily systems, pathways and mechanisms (e.g. mechanisms of action of pharmaceuticals within the body), and genetic susceptibility to disease or ADRs (e.g. gene polymorphisms in enzymes that affect the action of a drug [62]). The second category contains environmental and occupational determinants. These determinants include the physical environment, both natural and human-built, and employment and working conditions. The third category of determinants is made up of social and behavioural factors. These factors include income and social status, social support networks, education, personal health practices and coping skills, gendered norms, and culture [62, 63]. All three categories are sufficiently broad and interact in such a way as to include most of the factors affecting the health of populations. For example, an individual may be genetically susceptible to a specific ADR [64] and may experience this reaction after taking a TZD drug but they need to develop T2DM in order to be exposed to the drug in the first place. T2DM can result from obesity [65] which in turn can develop due to interactions between environmental factors such as no safe areas in a neighbourhood to exercise [66], occupational factors such as a sedentary job [67], social factors such as low income and lack of money to buy healthy foods [68, 69], and behavioural factors such as consuming alcohol and unhealthy foods [70]. This approach allows for the recognition of the full range of factors influencing health status.

An integrated population health risk assessment approach encourages the use of the best available qualitative and quantitative methodologies in health risk science to assess and

characterize the degree of risk experienced by a population. Population health risk assessment has been defined as a scientific process that involves characterizing risks to the health of a population [59]. That definition continues to be relevant to the assessment of health risks within the context of the NextGen Framework as the new framework takes into account the impact that a variety of health determinants or risk factors have on the level of risk, but further expands upon it by focusing on well-established risk assessment methodologies that are combined with new perspectives and advances in the field [60]. For example, the risk assessment process used in this framework incorporates well established principles of risk assessment such as hazard identification, dose-response assessment, exposure assessment, and risk characterization [71] but builds upon them by also focusing on adversity (e.g. biochemical changes that affect the performance of an individual or reduces their ability to respond to an additional environmental challenge [72]), variability (e.g. individual differences in pharmacokinetics and the intensity of responses to a whole compound or its metabolites [73]), life stage (e.g. age and/or susceptible populations) and mixtures (e.g. combinations of drugs used to treat a disease), and by introducing new methodologies such as novel computational methods and statistical techniques.

For the purpose of this thesis, a comprehensive assessment of health risks associated with a class of diabetes drugs will be conducted through secondary data analysis. Analyses will involve the application of active pharmacovigilance methods and will incorporate a number of determinants (where feasible) including biological (e.g. concomitant medications), environmental (e.g. region), and social factors (e.g. payer class as a surrogate for socioeconomic status [SES]) available within the EMRs of the study population. This approach will take advantage of a key feature of health risk assessment in this framework: it will integrate

information from different sources by taking into account all relevant data on available determinants of health risk and the interactions at play among these factors.

### **III) Risk management**

Population health risk assessment forms the basis for evidence-based population health risk policy analysis [74-76] and ultimately, the development of cost-effective evidence-based population health risk management strategies. Armed with the appropriate scientific evidence, and once relevant risk management principles (e.g. equity, utility, precaution [77]), economic analysis (e.g. cost-benefit), socio-political considerations (e.g. social and cultural values) and risk perception considerations (e.g. public perceptions that vary based on demographic [78]) have been taken into account and risk management decisions have been taken, a wide range of potential strategies may be considered and employed within the NextGen Framework. These strategies consist of multiple interventions, including multi-level and multi-strategy interventions that are often multi-sectoral [79]. These may include: regulatory approaches, economic approaches to risk mitigation, such as those that employ economic incentives or disincentives to limit the introduction of, or exposure to, health risks [80], advisory approaches that communicate with interested and affected parties [81], community action that involves mobilizing existing community resources and increasing meaningful public participation [82] and technological approaches to risk management that rely on technological solutions to reduce risk such as genomics [83]. Together these strategies represent the REACT (Regulatory, Economic, Advisory, Community, and Technological) approach to risk management [59]. Although the focus of this thesis is the analysis of the health risks related to TZD pharmacotherapy, the results of this important research will help to inform policymakers and future drug safety interventions.

## OUTLINE

This thesis seeks to examine and clarify associations between TZD pharmacotherapy and adverse cardiovascular, osteological, and carcinogenic events using the Cerner Health Facts® diabetes cohort to inform further research and decision-making in North America, and elsewhere. It is comprised of six chapters and one annex, including a published review paper [9]. Following this introductory chapter (**Chapter 1**), the subsequent chapters of this thesis comprise the major manuscripts emanating from this work and present a review paper and three nested case-control analyses using active pharmacovigilance methods that take into account the inherent limitations of using hospital-based data, to explore adverse reactions in a population with chronic disease. **Chapter 2** presents a published [9] in-depth review of the epidemiology of TZD pharmacotherapy including pharmacokinetics and modes of action, the results of previous studies investigating health risks associated with TZD treatment, and what the future may hold for this class of drugs. **Chapter 3** explores associations between TZD therapy and the risks of MI and CHF (some of the preliminary results examining the associations between TZDs and adverse cardiovascular events were also published in a conference abstract [84]). **Chapter 4** investigates potential associations between TZD pharmacotherapy and bone fractures including site-specific associations and differences in fracture risk in males and females. **Chapter 5** aims to determine associations between TZDs and cancer of the bladder. **Chapter 6** summarizes the main findings of this thesis, presents an overview of the challenges of working with administrative hospital-based EMR data, including examples of biases, and provides suggestions for future work. Finally, **Annex 1** provides additional context for this research by providing an overview of T2DM, treatment guidelines for T2DM, and describes the various drug classes used in antihyperglycaemic therapy.

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## **CHAPTER 2: Review Paper - Thiazolidinedione drugs in the treatment of type 2 diabetes mellitus: past, present and future**

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### **PREFACE**

This is an accepted manuscript of an article published by Taylor & Francis in *Critical Reviews in Toxicology* (first published online on August 17, 2017), available online: <https://www.tandfonline.com/doi/full/10.1080/10408444.2017.1351420>. The table of contents has been omitted from this reproduction but has been included in the main table of contents of this thesis. The statement of contributions of collaborators and co-authors, including the student's individual contribution, can be found in the acknowledgements within the published manuscript. Given the length of this review paper and its accompanying supplemental materials, the text of the supplemental materials have not been included in this thesis but are available online at the following address: <https://www.tandfonline.com/doi/suppl/10.1080/10408444.2017.1351420?scroll=top>.

# **Thiazolidinedione drugs in the treatment of Type 2 Diabetes Mellitus: past, present and future**

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## **ABSTRACT**

Thiazolidinedione (TZD) drugs used in the treatment of Type 2 Diabetes Mellitus (T2DM) have proven effective in improving insulin sensitivity, hyperglycemia, and lipid metabolism. Though well tolerated by some patients, their mechanism of action as ligands of peroxisome proliferator-activated receptors (PPARs) results in the activation of several pathways in addition to those responsible for glycemic control and lipid homeostasis. These pathways, which include those related to inflammation, bone formation, and cell proliferation, may lead to adverse health outcomes. Because treatment with TZDs has been associated with adverse hepatic, cardiovascular, osteological, and carcinogenic events in some studies, the role of TZDs in the treatment of T2DM continues to be debated. At the same time, new therapeutic roles for TZDs are being investigated, with new forms and isoforms currently in the pre-clinical phase for use in the prevention and treatment of some cancers, inflammatory diseases, and other conditions. The aims of this review are to provide an overview of the mechanism(s) of action of TZDs, a review of their safety for use in the treatment of T2DM, and a perspective on their current and future therapeutic roles.



## 1. INTRODUCTION

The thiazolidinedione (TZD) class of drugs consists of oral hypoglycemic agents used alone or in combination with other hypoglycemic agents (oral or in some cases injectable) to treat Type 2 Diabetes Mellitus (T2DM). The drugs within this class, which include rosiglitazone and pioglitazone, were heralded as providing novel first and second-line treatments for T2DM at the time of their introduction in the late 1990s with glycemic control and physiological effects comparable to, and in some cases, better than, other established first-line treatments such as metformin (e.g. pioglitazone: Betteridge & Vergès 2005; Roden et al. 2005; Yamanouchi et al. 2005; rosiglitazone: Fonseca et al. 2000; Natali et al. 2004; Rosak et al. 2005; Virtanen et al. 2003; troglitazone: Kirk et al. 1999; Strowig et al. 2002; Yu et al. 1999) and second-line treatments such as sulfonylurea drugs (e.g. pioglitazone: Charbonnel et al. 2005; Hanefeld et al. 2004; Tan et al. 2004; rosiglitazone: Derosa et al. 2005; Hanefeld et al. 2007; Smith et al. 2004; troglitazone: Horton et al. 1998; Iwamoto et al. 1996). TZDs were praised not only for their beneficial effects on glycemic control through improved insulin-sensitivity, but also for their anti-inflammatory effects (Agarwal 2006; Consoli & Devangelio 2005, Kapadia et al. 2008; Schmidt et al. 2004).

As agonists of peroxisome proliferator-activated receptors (PPARs), receptors which exist in different subtypes and that are distributed in different tissues depending on the specific subtype, these drugs activate the PPAR $\gamma$  receptor that is present exclusively in epithelial tissues, including the urothelium, but that is most abundant in adipose tissues (Hauner 2002). However, PPARs, which also include the  $\alpha$  and  $\beta/\delta$  subtypes are also found in the liver, immune cells, pancreatic  $\beta$ -cells, and bone, among others (Dubois et al. 2000; Fajas et al. 1997; Gimble et al. 1996); activation of these receptors in non-target tissues has been hypothesized as the

mechanistic basis for the adverse effects of TZDs that have been observed in clinical and observational studies.

Concerns about adverse health effects from TZD pharmacotherapy arose in the late 1990's, and were accentuated with the removal of the TZD drug troglitazone from the market due to hepatotoxicity in the year 2000. Since that time, newfound concerns have been expressed by both the medical community and regulators as additional studies reported adverse cardiovascular effects in patients treated with rosiglitazone, leading to this drug's removal, restriction, and reinstatement in various markets. More recently, pioglitazone has been linked to bone fractures and bladder cancer and continues to be investigated for its effects on these endpoints.

The purpose of this review is threefold. First, it synthesizes past research on TZDs and their biological mechanisms of action and biochemical and metabolic effects, including both therapeutic benefits and adverse health risks. Second, it provides an overview of the current status of TZD drugs through consideration of past research and controversies regarding their safety and efficacy. Finally, it provides an overview of the potential future roles of TZDs and TZD-related isoforms in the treatment of other diseases such as cancer. Literature related to these three topics was searched using Pubmed (Medline), Scopus, and Web of Science databases up to August 2016.

## **2. MECHANISM OF ACTION AND METABOLIC EFFECTS**

### **2.1 Mechanism of action**

A class of TZDs was first discovered in the 1970s but it wasn't until the mid-1990's, after the early development of the fibrate drugs (agonists of the  $\alpha$  PPAR subtype) and after TZD drugs

such as ciglitazone, pioglitazone, and troglitazone had begun clinical development, that it was discovered that TZDs exerted insulin-sensitizing effects through direct activation of PPARs, specifically the  $\gamma$  subtype (Colca et al. 2014b). Since that time, it has been discovered that dependent upon cell type or binding site, TZDs act as synthetic agonists or antagonists of PPARs, a subfamily of nuclear receptors comprised of  $\alpha$ ,  $\beta/\delta$  and  $\gamma$  isoforms (Lehmann et al. 1995; Nuclear Receptors Nomenclature Committee 1999). Like other nuclear receptors, PPARs are comprised of distinct functional domains which are potential targets for modulation of signalling cascades (Ahmadian et al. 2013), including a ligand-binding domain (Moras & Gronemeyer 1998), a highly conserved DNA-binding domain (Poulsen et al. 2012), and a transactivation domain that allows for ligand-independent activation (Werman et al. 1997). After ligand binding, PPARs undergo specific conformational changes that allow for the differential recruitment of protein coactivators (Willson et al. 2001). Because ligands differ in their ability to interact with coactivators, they can induce a number of diverse biologic and metabolic responses (Ahmadian et al. 2013; Poulsen et al. 2012).

PPARs undergo transactivation or transrepression through distinct mechanisms that lead to either the induction or repression of the expression of target genes (Oyekan 2011).

Transactivation is DNA-dependent and binding requires dimerization with members of the retinoid X receptor (RXR) family (Willson et al. 2001). The heterodimerization between PPARs and RXR is ligand-independent, but relies on the interfaces between the ligand-binding domains and DNA-binding domains of each receptor (Chandra et al. 2008; Rochel et al. 2011). The obligate PPAR/RXR heterodimer in turn binds to PPAR responsive regulatory elements in the promoter region of target genes (Ajjan & Grant 2008; Willson et al. 2001), including those involved in adipogenesis, lipid metabolism, inflammation, and the maintenance of metabolic

homeostasis (Barish et al. 2006). Activation of these genes by natural ligands or by drugs such as TZDs translates into clinically beneficial hypoglycemic and hypolipidemic effects, decreased insulin resistance, improved insulin sensitivity, and decreased inflammation (Grossman & Lessem 1997; Yki-Järvinen 2004).

PPARs can also repress gene expression through transrepression. Transrepression occurs in a DNA-binding-independent manner by interfering with other signalling pathways, as well as in a DNA binding-dependent manner through the recruitment of co-repressors to PPARs that are unliganded (Oyekan 2011; Yki-Järvinen 2004). For example, ligand-induced PPAR $\gamma$  has been shown to repress the transcriptional activation of inflammatory response genes *in vitro* by preventing the recruitment of machinery that normally mediates the removal of corepressor complexes required for gene activation, thus resulting in target genes being left in a repressed state (Pascual et al. 2005). Similarly, PPAR $\beta/\delta$  has been shown to control inflammation *in vivo* through a ligand-dependant transcriptional pathway by associating and disassociating with transcriptional repressors (Lee et al. 2003); conversely, PPAR $\alpha$  acts in a ligand-independent manner *in vitro* and *in vivo* (Delerive et al. 1999; Staels et al. 1998). Transrepression may at least partially explain the anti-inflammatory actions of PPARs that have been reported (e.g. Chinetti et al. 2000; Ricote et al. 1998).

## **2.2 PPAR distribution**

All three members of the PPAR family exhibit differences in tissue distribution and ligands (**Figure 1**). PPAR $\alpha$  is expressed mainly in the liver and skeletal muscle but is also expressed at moderate levels in the kidney and brown adipose tissue, and at lower levels in the heart and intestines (Grygiel-Górniak 2014; Jones et al. 1995). PPAR $\alpha$  is involved in the

| PPAR $\alpha$                                                                                                                                                     | PPAR $\beta/\delta$                                                                                                                    | PPAR $\gamma$                                                                                                                                                                                                                                                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Tissue                                                                                                                                                            |                                                                                                                                        |                                                                                                                                                                                                                                                                                                         |
| <b>Main expression</b><br>Liver<br>Skeletal muscle<br><br><b>Other</b><br>Cardiac muscle<br>Kidney<br>Intestinal mucosa<br>Brown adipose                          | <b>Main expression</b><br>Liver<br>Skeletal muscle<br>Esophagus<br>Intestines<br>Kidney<br><br><b>General expression</b><br>Ubiquitous | <b>Main expression</b><br>Brown adipose<br>White adipose<br><br><b>Other</b><br>Intestines<br>Liver<br>Kidney<br>Retina<br>Bone marrow<br>White blood cells<br>Skeletal muscle                                                                                                                          |
| Ligands                                                                                                                                                           |                                                                                                                                        |                                                                                                                                                                                                                                                                                                         |
| <b>Natural</b><br>Unsaturated fatty acids<br>Leukotriene B4<br>8-hydroxyeicosatetraenoic acid<br><br><b>Synthetic</b><br>Fenofibrate<br>Clofibrate<br>Gemfibrozil | <b>Natural</b><br>Unsaturated fatty acids<br>Carbaprostacyclin<br>Components of VLDL<br><br><b>Synthetic</b><br>GW501516               | <b>Natural</b><br>Unsaturated fatty acids<br>15-hydroxyeicosatetraenoic acid<br>9- hydroxyoctadecadienoic acid<br>13- hydroxyoctadecadienoic acid<br>15-deoxy 12,14-prostaglandin J2<br>prostaglandin PGJ <sub>2</sub><br><br><b>Synthetic</b><br>Thiazolidinediones<br>Farglitazar<br>S26948<br>INT131 |

**Figure 1.** Tissue-specific expression of PPARs and examples of natural and synthetic PPAR ligands. Adapted from Grygiel-Górniak (2014).

regulation of lipid metabolism, fatty acid oxidation, glucose homeostasis, and inflammation (Delerive et al. 2001; Devchand et al. 1996; Lehmann et al. 1997; Zandbergen & Plutzky 2007). PPAR $\beta/\delta$ , the least studied PPAR isoform, is expressed ubiquitously and is involved in the control of lipid metabolism (Grygiel-Górniak 2014). In addition, it has been shown to play a role in placental development in both animal models (e.g. Barak et al. 2002; Nishimura et al. 2013) and humans (Wieser et al. 2008).

PPAR $\gamma$  is predominantly expressed in white adipose tissue in both rodents and humans (Chawala et al. 1994; Evans et al. 2004; Hauner 2002; Sharma & Staels 2007; Tontonoz et al. 1994a, 1994b; Tontonoz et al. 1995a; Tontonoz & Spiegelman 2008; Yau et al. 2013). Although it is also expressed in other tissues, including skeletal muscle, liver, certain other epithelial tissues, and macrophages (Clark et al. 2000; Ray et al. 2006; Szatmari et al. 2007; Széles et al. 2007; Wohlfert et al. 2007; Zhang et al. 2004a), the level of PPAR $\gamma$  mRNA in adipose tissue is up to 50-fold higher than in skeletal muscle (Chawala et al. 1994; Hauner 2002; Tontonoz et al. 1994b). To date, seven PPAR $\gamma$  mRNA subtypes have been identified, all of which are derived from the same gene by alternative promoter usage and splicing (Chen et al. 2006; Fajas et al. 1997; Fajas et al. 1998; Zhou et al. 2002). Subtype distribution differs by tissue. For example, whereas PPAR $\gamma$ 2 expression is restricted to adipose tissue with limited expression in other tissues such as the colon (Fajas et al. 1998), PPAR $\gamma$ 1 is more widely distributed (Jeninga et al. 2009).

### **2.3 TZDs as PPAR ligands**

TZDs are synthetic ligands that were developed based on their affinity for the  $\gamma$ -subtype PPAR (with pioglitazone, but not rosiglitazone, also showing weak affinity for the  $\alpha$ -subtype

PPAR *in vitro* at concentrations higher than attained blood levels), with ligand-activated PPAR $\gamma$  acting as a transcription factor stimulating expression of genes involved in metabolic regulation through pathways of lipid storage and glucose homeostasis (Cantini et al. 2010; Hwang et al. 2011). The binding affinity of TZDs for PPAR $\gamma$  varies, with rosiglitazone and pioglitazone considered to be the most potent and most selective PPAR $\gamma$  agonists that have been marketed thus far. *In vitro* studies have shown that rosiglitazone has a 10-fold greater binding affinity than pioglitazone, which in turn has a 10-fold greater binding affinity than troglitazone, a drug that preceded both rosiglitazone and pioglitazone but was withdrawn from the US market for hepatotoxicity (Young et al. 1998; see **Section 3.2**). This is reflected in the differences in clinical dosage for these agents: 4 or 8 mg/day for rosiglitazone, 15 to 30 mg/day for pioglitazone (which may be increased in increments up to 45 mg/day), and 400 to 800 mg/day for troglitazone. A novel TZD drug, rivoglitazone, currently under development, is considered to be more potent than rosiglitazone or pioglitazone (Koffarnus et al. 2013). The initial recommended dose for rivoglitazone based on clinical trials conducted to date (Chou et al. 2012; Kong et al. 2011; Truitt et al. 2010) is 1 mg daily, increasing to a maximum dose of 2 mg daily.

Another novel TZD drug, netoglitazone (MCC-555), that has been under investigation for both the treatment of T2DM and cancer may act as PPAR $\gamma$  agonist, partial agonist, or antagonist, depending on the target cell (Reginato et al. 1998) and has been shown to have antihyperglycemic and antihyperlipidemic effects in animal models (Pickavance et al. 1998). Although its binding affinity for PPAR $\gamma$  is relatively weak compared to other TZDs, netoglitazone is considered to be more potent when compared to other PPAR $\gamma$  ligands (Yamaguchi et al. 2006) with a 50-fold greater potency than rosiglitazone in decreasing blood glucose levels in rodent models (Pickavance et al. 1998). This may be explained through both

PPAR $\gamma$ -dependant and independent mechanisms (Min et al. 2012). Its antihyperlipidemic effects are thought to occur through the modulation of PPAR $\alpha$ , though it has been shown to be 5 to 10-fold less effective than rosiglitazone in inducing adipogenesis in mouse preadipocytes (Upton et al. 1998). Binding affinity has been shown to correlate to biological potency *in vitro* and there appears to be a correlation between the potency of TZDs in binding and activation of PPAR $\gamma$  *in vitro* and reduction of plasma glucose levels *in vivo* (Hauner 2002).

Differences in dosage and binding affinity may also be contributors to reported adverse effects. For example, balaglitazone, a partial agonist of PPAR $\gamma$  that only demonstrates 50% PPAR $\gamma$  activation (Larsen et al. 2008) has been shown to possess a potency similar to pioglitazone in animal models but with a more favorable side effect profile (Agrawal et al. 2012; Henriksen et al. 2009; Larsen et al. 2008). Though this novel drug has shown promise in phase III trials because of reductions in glucose and A1C levels similar to pioglitazone at lower dosages (10 and 20 mg/day compared to 45 mg/day of pioglitazone), but with less significant weight gain and fluid accumulation in patients (Henriksen et al. 2011), it has never been marketed. In light of concerns with adverse reactions related to TZD drugs, new drugs and drug classes, however, still continue to be investigated. For example, a new class of PPAR $\gamma$  ligands not sharing the TZD ring has also been recently developed and includes both agonists (Rikimaru et al. 2011) and antagonists of the  $\gamma$  receptor (Luconi et al. 2010).

## **2.4 Metabolic function**

Stimulation of PPAR $\gamma$  by TZDs has been shown to increase peripheral insulin sensitivity, in the liver and skeletal muscle (Perfetti & D'Amico 2005), and cause adipogenesis leading to decreased endogenous glucose production and postprandial gluconeogenesis, increased fasting



and postprandial glucose clearance, and lower blood glucose and insulin levels, in addition to reported changes in  $\beta$ -cell function, cholesterol levels, triglyceride levels, and levels of inflammation (Inzucchi et al. 2012). For example, expression of PPAR $\gamma$  has been shown to be necessary for adipogenesis both *in vitro* and *in vivo* (Lehrke & Lazar 2005; Spiegelman 1998) with TZDs promoting adipocyte differentiation (He et al. 2003; Kintscher & Law 2005; Zhang et al. 2004b), presumably through the activation of PPAR $\gamma$ . TZDs mediate the differentiation of preadipocytes to adipocytes (Schoonjans et al. 1996), which have a higher number of glucose transporters and insulin receptors (Gregoire et al. 1998), by reducing circulating free fatty acids and increasing subcutaneous adipose tissue deposition (Akazawa et al. 2000; Carey et al. 2002; Guan et al. 2002; Nakamura et al. 2001; Okuno et al. 1998; Viljanen et al. 2005). Ligand-activated PPAR $\gamma$  has also been demonstrated to be sufficient to induce the conversion of fibroblasts to adipocytes (Tontonoz et al. 1995b) and pluripotent mesenchymal stem cells into adipocytes instead of osteoblasts as PPAR $\gamma$  is expressed in bone (Grey 2009).

TZDs also demonstrate an ability to suppress the production and action of the inflammatory cytokine tumor necrosis factor alpha (TNF $\alpha$ ) (Carta et al. 2011a; Yang & Lai 2010), which is overexpressed in the adipose tissue of both obese mice and humans (Aoyama et al. 2009; Hotamisligil et al. 1993; Hotsamagil et al. 1995; Kern et al. 1995; Zhang et al. 2007). In cells, TNF $\alpha$  inhibits insulin signalling at least in part by blocking insulin receptor activity and inducing serine phosphorylation of insulin receptor substrate-1 (Draznin 2006). TZDs appear to work in a TNF $\alpha$ -dependant and independent manner, but may be more important in the development of insulin resistance itself by directly improving insulin sensitivity through TNF $\alpha$  inhibition (Wellen et al. 2004). This mechanism may be a result of the activation of PPAR $\alpha$  by TZDs as PPAR $\alpha$  is also the receptor targeted by the fibric acid class of lipid-lowering drugs

(Grossman 2002; Sakamoto et al. 2000), and pioglitazone, but not rosiglitazone therapy has demonstrated improvements in triglyceride and high-density lipoprotein cholesterol levels in some studies (see **Supplementary Appendix 1, Table S1**), potentially owing to pioglitazone's weak affinity for PPAR $\alpha$ .

Although TZDs target insulin resistance in peripheral tissues through the activation of PPAR $\gamma$ , evidence also suggests that TZDs may also both prevent and treat T2DM through the protection and preservation of pancreatic  $\beta$ -cells via another mechanism (Buchanan et al. 2002; Kanda et al. 2010; Kawasaki et al. 2005; Leclerc & Rutter 2004; Prigeon et al. 1998; Welters et al. 2012). Declining  $\beta$ -cell function has been shown to be the primary reason for deterioration in glucose tolerance from normal glucose levels in different populations (Festa et al. 2006; Jensen et al. 2002; Weyer et al. 1999) and though PPAR $\gamma$  expression occurs in  $\beta$ -cells, TZDs have also been shown to induce AMP-activated protein kinase phosphorylation in  $\beta$ -cells leading to rapid decreases in elevations of glucose concentration (da Silva Xavier et al. 2003; Deng et al. 2014; Saltiel & Olefsky 1996, Wu et al. 2013). Clinical studies have also suggested that TZDs preserve  $\beta$ -cell function (Buchanan et al. 2002; Ehrmann et al. 1997) including the A Diabetes Outcome Progression Trial (ADOPT) where rosiglitazone was shown to slow the rate of loss of  $\beta$ -cell function and improve insulin sensitivity to a greater extent than metformin or glyburide (Kahn et al. 2006) with persistent improvements over time (Kahn et al. 2011).

TZDs have also been investigated for anti-inflammatory effects, including those not directly related to changes in insulin sensitivity that have been demonstrated to be greater than the effects of metformin in reducing inflammatory markers (Erem et al. 2014; Hanefeld et al. 2011; Stocker et al. 2007) and chronic inflammation (Ciaraldi et al. 2013), and greater than the inflammation-reducing effects of other insulin secreting agents such as sulfonylureas and

meglitinides (Nissen et al. 2008). For example, it has been shown that the activation of PPAR $\gamma$  can suppress inflammatory gene expression in endothelial cells *in vitro* (Gao et al. 2011; Gensch et al. 2007; Huang et al. 2008; Wang et al. 2002); *in vivo* evidence suggests that TZDs improve endothelium-dependent vascular function and inflammatory biomarkers of atherosclerosis independent of glucose lowering (Pistrosch et al. 2004), including in non-diabetic individuals (Hetzel et al. 2005; Horio et al. 2005; Marx et al. 2005). TZDs also exhibit a range of pleiotropic effects on cardiovascular cell function including modulation of cell proliferation, migration, and remodeling, as well as the secretion of the pro-inflammatory cytokines TNF $\alpha$ , interleukin-1 (IL-1) and interleukin-6 (IL-6) that play key roles in myocardial inflammatory response (Turner et al. 2007). All of these effects led to the initial hypotheses that TZDs would have positive cardiovascular benefits for diabetics when they were first marketed.

## **2.5 Clinical effectiveness**

TZDs have been shown to improve glycemic control when compared to placebo (Gorter et al. 2012; Phillips et al. 2001) to a greater extent than other oral hypoglycemic drugs, in both monotherapy and combination therapy, with a lower risk of treatment failure and hypoglycemia (e.g. Halimi et al. 2012; Kahn et al. 2006; McIntosh et al. 2012; Nafrialdi 2012; Raskin et al. 2001; Rodriguez et al. 2011; Stargardt et al. 2009; Zintzaras et al. 2014). Both rosiglitazone and pioglitazone reduce glycated hemoglobin (A1C) to a similar extent (Patel et al. 1999; Perfetti & D'Amico 2005), approximately 1% compared to placebo (Gorter et al. 2012), though recent studies have also found that effectiveness in reducing A1C levels may be greater in some subpopulations (including obese patients and women: Flory et al. 2014). TZDs have also been shown to exert positive micro and macrovascular effects and confer positive effects on risk

factors such as lipid profiles, though these effects differ between drugs with only pioglitazone demonstrating significant improvements in triglycerides and cholesterol levels in most studies (Aronoff et al. 2000; Goldberg et al. 2005; Rodriguez et al. 2010; Rodriguez et al. 2011; Rosenblatt et al. 2001; Tan et al. 2004; see also **Supplementary Appendix 1, Table S1**). Raskin et al. (2001) found that adding rosiglitazone to insulin significantly improved glycemic control (with a mean A1C reduction of 1.2%), but found no change in lipid profiles; Suh et al. (2011) reported that when rosiglitazone was added to pre-existing glucose-lowering drugs, lipid profiles were less favourable than those compared for metformin or sulfonylureas. Conversely, Rodriguez et al. (2011) found that when pioglitazone was prescribed to patients in combination with other oral hypoglycemic drugs (metformin or sulfonylureas), the pioglitazone combinations, especially combinations with metformin, were associated with increases in high-density lipoprotein (HDL) cholesterol and decreases in triglycerides as well as in the atherogenic index of plasma when compared to metformin combined with a sulfonylurea. TZDs have also been associated with reductions in both systolic and diastolic blood pressure compared with placebo or other oral hypoglycemic agents possibly due to improvements in endothelial function and modulation of the renin-angiotensin system (Ajjan & Grant 2008).

Most studies have found that TZDs are associated with a low risk of treatment failure. For example, in ADOPT (Kahn et al. 2006) the cumulative incidence of failure in monotherapy (defined as a fasting plasma glucose level > 180 mg/dL) at 5 years was 15% for rosiglitazone versus 21% for metformin, and 34% for the sulfonylurea glyburide (representing a risk reduction of 32% for rosiglitazone, as compared with metformin, and 63%, as compared with glyburide), which could translate into a reduced need for additional glucose-lowering agents. As previously mentioned, rosiglitazone slowed the rate of loss of  $\beta$ -cells and improved insulin sensitivity in the

same study to a greater extent than did either metformin or glyburide with greater duration of control as mean A1C level was maintained at less than 7% for a longer period with rosiglitazone (57 months) than with either metformin (45 months) or glyburide (33 months). It should be noted that not all studies have found greater effectiveness of TZD drugs compared to other oral hypoglycemic agents: Berkowitz et al. (2014) found that use of a TZD (mostly pioglitazone) was significantly associated with an increased risk of adding a second oral agent or insulin (hazard ratio [HR]: 1.61, 95% CI: 1.43-1.80) and that use was not associated with a reduced risk of hypoglycemia, emergency department visits, or cardiovascular events.

### **3. ADVERSE EFFECTS OF TZD THERAPY**

#### **3.1 Weight gain and edema**

The most common adverse effect reported in patients undergoing TZD therapy is weight gain, (Fonseca 2003; Kahn et al. 2006; McIntosh et al. 2012; Nafrialdi 2012; Raskin et al. 2001), which has been demonstrated when TZDs are used in monotherapy, in combination therapy with other oral hypoglycemic agents, and in combination with insulin (Abbas et al. 2012; Raskin et al. 2001), and fluid retention (LaSalle & Cross 2006; Rodriguez et al. 2010). Weight gain typically ranges between 2 and 6 kg (Yau et al. 2013). For example, in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial, patients treated with rosiglitazone had an increase of 2.2 kg in body weight compared to placebo ( $P < 0.0001$ ) (Gerstein et al. 2006); in ADOPT, rosiglitazone-treated patients experienced an increase in body weight of 4.8 kg, which was significantly higher than in patients treated with glyburide or metformin ( $P < 0.001$ ). For pioglitazone, treatment was associated with a significant increase in weight of 3.8 kg compared to a loss 0.6 kg for patients in the placebo group in the PROspective

pioglitazone Clinical Trial In macroVascular Events (PROactive) (Dormandy et al. 2009a).

Conversely, in a study investigating the long-term effects of rosiglitazone on body weight, Shim et al. (2006) found a modest increase in weight of 1.1 kg after 18 months of treatment, suggesting that most gains occur within the first 6 to 12 months of treatment and decrease over time.

TZD-induced weight gain is thought to occur in part due to a change in adipose tissue distribution in the subcutaneous compartment in conjunction with a decrease in the subcutaneous to visceral fat ratio (thus favouring overall fat deposition; Bailey 2005). Because PPAR $\gamma$  receptors are primarily expressed in adipose tissue, the activation of these receptors may be the mechanistic basis for the effects of TZDs on weight. However, some studies have found that approximately 75% of weight gain, at least in the short-term, may be attributable to fluid retention that is more pronounced with concomitant insulin use (Ajjan & Grant 2008; Basu et al. 2006; Hollenberg 2003).

An increased incidence of edema associated with TZD use has also been well-documented, especially in studies where TZDs have been given to patients in combination with insulin (Berlie et al. 2007; Nesto et al. 2004; Raskin et al. 2001; Rosenstock et al. 2002), but it has also been shown to occur in monotherapy and combination therapy with other diabetic drugs. For example, a meta-analysis by Berlie et al. (2007) found that TZDs were associated with a 2-fold increased risk of edema when compared to placebo, other oral hypoglycemic drugs, or insulin (though the risk was greater for rosiglitazone than pioglitazone); in PROactive, pioglitazone was associated with a 26.4% increase in edema compared to 15.1% for placebo (Dormandy et al. 2009a). TZD-induced edema is thought to be related to increased vascular permeability, vasodilatation, and fluid retention in the kidney (Cariou et al. 2012). Although the

underlying mechanism(s) are not completely understood, these effects seem to result at least in part from stimulation of PPARs. Activation of PPAR $\gamma$  in the nephrons of the kidney promotes the expression of epithelial sodium channels (ENaC) in the collecting duct which increases the absorption of salt and water leading to fluid retention (which in turn also increases the risk of heart failure; Guan et al. 2005). Knocking out PPAR $\gamma$  in the collecting duct of the kidney, or using the ENaC inhibitor amiloride, has been shown to prevent both TZD-induced fluid retention and weight gain (Betteridge 2011; Guan et al. 2005; Zhang et al. 2005). However, it has also been suggested that other mechanisms must be involved as TZD-induced edema was still observed in a study using mice with ENaC inactivated in the collecting duct (Vallon et al. 2009).

### **3.2 Hepatotoxic effects**

Shortly after troglitazone was approved by the US FDA in January 1997 and marketed as Rezulin in March of the same year, reports of negative hepatic effects of treatment including liver failure and death began to emerge (Gitlin et al. 1998; Neuschwander-Tetri et al. 1998; Shibuya et al. 1998; Vella et al. 1998). Troglitazone, the first drug of the TZD class, was one of the first insulin-sensitizing drugs for use alone or in combination with other antihyperglycemic drugs (supplemental approval for mono/combination therapy was granted in August of 1997) in the treatment of T2DM. It was approved by the US FDA within 6 months; less than half the time typically taken for diabetic drug approval (Gale 2001; Jenner 2000). Initially, the product monograph for Rezulin did not include a recommendation for monitoring of liver function however, it did include a precaution against prescribing the drug to patients with advanced liver disease noting that elevated hepatic enzymes had been seen in clinical trials (Faich & Moseley 2001).

The first reports of troglitazone-induced hepatotoxicity emerged from a review and combined analysis of the North American clinical trials. Watkins and Whitcomb (1998) reported that out of 2510 patients receiving troglitazone, elevated serum alanine aminotransferase concentrations more than three times the upper limit of normal were detected in 1.9% of troglitazone patients but only 0.6% of controls. No clear association was found between these elevated concentrations and sex, age, daily dose, or concomitant medications. The onset of these elevations was typically delayed, with peak values occurring between 3 and 7 months of troglitazone use. Although hepatocellular injury was confirmed, adverse hepatic effects were reversible with discontinuation of troglitazone treatment resulting in normalization of serum alanine aminotransferase concentrations. Case reports of hepatotoxicity also emerged: Gitlin et al. (1998), for example, reported on two female patients who exhibited severe clinical and histological hepatotoxicity after taking troglitazone for 20 weeks (200 mg/day for 28 days then 400 mg/day for 110 weeks) and 6 weeks (400 mg daily for 63 days with symptoms exhibiting after 35 days), respectively. Both patients had comorbid conditions including obesity and essential hypertension. Both were taking other medications such as insulin; however, no drug-drug interactions were clinically evident and neither patient reported a history of exposure to hepatotoxins or alcohol ingestion. Although both patients recovered within 3 months of discontinuing troglitazone treatment, and effects were reversible in these patients, other case reports, as described below, presented serious irreversible effects.

Serious adverse events associated with troglitazone treatment included liver failure necessitating liver transplant, and even death. For example, Neuschwander-Tetri et al. (1998) reported a 55 year-old female patient taking 400 mg/day of troglitazone for 3.5 months, due to poor glycemic control on insulin alone, who developed symptoms of liver failure. Significant



hepatic dysfunction and elevated aminotransferase levels were still apparent 1 week after discontinuing troglitazone treatment and liver function continued to deteriorate with liver biopsy showing massive loss of liver parenchyma. Liver transplantation was necessary 3 weeks after discontinuation of troglitazone. Vella et al. (1998) presented the case of an 85 year-old man with severe hepatic dysfunction who was diagnosed with troglitazone-induced hepatitis. The patient had been treated with insulin for 10 years and troglitazone therapy had been initiated 5 months before presentation with symptoms of hepatotoxicity. Although troglitazone therapy was discontinued, the patient died 8 weeks after presentation, though it is unclear as to whether the hepatitis was in fact troglitazone-induced or a coincidental finding caused by another factor.

In October of 1997, the US FDA released the first 'Dear Healthcare Professional' letter warning of liver problems and the need for regular screening of patients taking troglitazone (Gale 2001). This was followed by additional warnings and recommendations in December 1997 (US FDA 1997), and again in August 1998 after the US FDA received reports of 100 cases of severe liver damage, including liver failure requiring transplantation in three patients and death in another patient (Misbin 1998). Though market withdrawal occurred in the United Kingdom in reaction to these adverse events after only 2 months on the market (Mitchell 1997), troglitazone continued to be marketed in the US with a recommendation for more frequent patient monitoring (Wise 1997) and as of March of 1999 the US FDA maintained that troglitazone should still remain on the market (Ault 1999a; Stolberg 1999). In response to continued reports of adverse events, in June of 1999 the US FDA released another warning and further recommendations for increasing liver function testing and monitoring to 12 months (Ault 1999b; Graham et al. 2003); however, evidence indicates that adequate serum enzyme monitoring was not being performed (Graham & Green 1999; Graham et al. 2001), and incidents of acute liver failure continued to be

reported (Bell & Ovalle 2000; Booth et al. 2000; Fukano et al. 2000; Herrine & Choudhary 1999; Iwase et al. 1999; Jagannath & Rai 2000; Kohlroser et al. 2000; Li et al. 2000; Malik et al. 2000; Murphy et al. 2000; Prendergast et al. 2000; Schiano et al. 2000). In March of 2000 after 36 months on the market, approximately 10 million filled prescriptions, numerous warnings, and 90 cases of liver failure reported by the US FDA including 60 patient deaths and three patient deaths post-liver transplantation (Lumpkin 2000), troglitazone was withdrawn from the US market due to severe hepatotoxicity (Cluxton et al. 2005). Following market withdrawal, it became apparent that hepatotoxic events related to treatment were unpredictable with severe toxicity being reported within as little as 4 days of treatment, to after more than 1 year of treatment, even when liver function tests appeared to be normal (Isley 2003).

The introduction of rosiglitazone and pioglitazone was accompanied with concerns that hepatotoxicity could be a TZD class effect since the first TZD to be tested, ciglitazone, was never marketed due to hepatotoxicity (Gale 2001). As a result, both rosiglitazone and pioglitazone were introduced to the market with warnings and recommendations for liver monitoring. Although there have been isolated reports of liver dysfunction resulting from treatment with rosiglitazone and pioglitazone (Al-Salman et al. 2000; Bonkovsky et al. 2002; Floyd et al. 2009; Forman et al. 2000; Maeda 2001; Marcy et al. 2004; May et al. 2002; Pinto et al. 2002) many of these reports were based on passive surveillance data (e.g. Floyd et al. 2009) or were case reports of patients who had also taken troglitazone (e.g. Bonkovsky et al. 2002). Diabetics with elevated baseline liver enzymes have not been observed to have a higher risk of hepatotoxicity from rosiglitazone than those with normal liver enzymes (Chalasani et al. 2005) and both pioglitazone and rosiglitazone have been shown to have beneficial effects on liver function in patients with abnormal baseline liver enzymes (Shadid & Jensen 2003; Yeap et al.

2011). Rosiglitazone and pioglitazone are generally considered to be safe from a hepatotoxicity standpoint (Chalasani et al. 2005; Isley 2003; Lebovitz et al. 2002; Rosenstock et al. 2002; Scheen 2001; Tolman & Chandramouli 2003; Tolman et al. 2009), likely because they are given at much lower doses than troglitazone and are metabolized by other pathways (Boelsterli & Bedoucha 2002; Lebovitz et al. 2002). Though the mechanism behind troglitazone-induced hepatotoxicity remains to be elucidated, it is thought that its hepatotoxic effects are most likely chemical-specific to troglitazone itself and not a result of PPAR $\gamma$  activity (Saha et al. 2010).

### **3.3 Cardiovascular effects**

It is well established that cardiovascular disease is a prevalent complication of T2DM. For example, the Framingham Heart Study reported that the risk of congestive heart failure (CHF) was elevated 2.4-fold in men and 5-fold in women with diabetes (Kannel et al. 1974). Insulin resistance is also a significant predictor of CHF (Ingelsson et al. 2005; Reaven 1995; Reaven 2001; Reaven 2005) and many pre-diabetics and diabetics also have comorbidities that contribute to cardiovascular disease such as obesity (International Diabetes Federation 2014), hypertension (Centers for Disease Control and Prevention 2014), dyslipidemia, and microalbuminuria (ADA 2014; Ajjan & Grant 2006). It has been estimated that in the US at least 65% of diabetics die from some form of heart disease or stroke, and that adults with diabetes are two to four times more likely to have cardiovascular disease or a stroke than adults without diabetes (American Heart Association 2012). This makes it difficult to isolate associations between the cardiovascular effects of antidiabetic pharmacotherapy and cardiovascular disease in T2DM.

Cardiovascular safety concerns have been expressed in relation to TZDs, primarily for rosiglitazone, for several years especially with respect to CHF and myocardial infarction (MI) and increased mortality resulting from adverse cardiovascular events (**Tables 1 and 2**, see also **Supplementary Appendices 1 and 2**). Some studies have implicated rosiglitazone alone (Home et al. 2007; Home et al. 2009; Komajda et al. 2010) but not pioglitazone alone in clinical trials (Abe et al. 2010; Belcher et al. 2004; Belcher et al. 2005; Dormandy et al. 2009b; Erdmann et al. 2010; Kaku et al. 2009a; Kaneda et al. 2009; Lee et al. 2013; Matthews et al. 2005; Scheen et al. 2009a; Schernthaner et al. 2004) or rosiglitazone in observational studies where both rosiglitazone and pioglitazone were compared (Graham et al. 2010; Hsiao et al. 2009; Lipscombe et al. 2007; Shaya et al. 2009; Stockl et al. 2009; Tannen et al. 2013; Winkelmayr et al. 2008; Ziyadeh et al. 2009), whereas other observational studies and meta-analyses have implicated both rosiglitazone and pioglitazone (Koro et al. 2008;) or have found negative associations with pioglitazone (Erdmann et al. 2007a; Giles et al. 2008; Giles et al. 2010; Grossman et al. 2009). Other studies have reported no adverse cardiovascular effects associated with rosiglitazone use (Casscells et al. 2008; Dormuth et al. 2009a; Habib et al. 2009; Juurlink et al. 2009; Pantalone et al. 2009) or have found that it exerts cardioprotective or other beneficial cardiovascular effects (Haffner et al. 2002; Hetzel et al. 2005; Margolis et al. 2008; Pala et al. 2010; Walker et al. 2008), whereas others still have found cardioprotective effects for pioglitazone alone (Abe et al. 2010; Basu 2010; Gerrits et al. 2007; Habib et al. 2009; Juurlink et al. 2009; Pantalone et al. 2009; Wilcox et al. 2007). The conflicting nature of these results has caused the medical and regulatory communities to question both the cardiovascular safety and usefulness of TZD pharmacotherapy in the treatment of T2DM within a context of uncertainty.

**Table 1.** Clinical trials investigating adverse cardiovascular effects of TZD pharmacotherapy.

| Study                                 | Design                                                                                                                   | Duration/<br>Study<br>Period              | Patient<br>Population                                                 | Sex     | TZD<br>(dose)             | Number of<br>TZD Exposed<br>Patients | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                       |
|---------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------|---------|---------------------------|--------------------------------------|----------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------|
| <b>Belcher<br/>et al. (2004)</b>      | Randomized<br>controlled trials,<br>active<br>comparators<br>(MET, GLIC) or<br>add-on therapy<br>(PIO or GLIC to<br>MET) | Four trials,<br>each<br>lasting 1<br>year | T2DM, oral<br>treatment-naïve<br>patients in<br>monotherapy<br>trials | M,<br>F | PIO<br>(up to 45<br>mg/d) | 1,857                                | 57<br>(± 9<br>SD)                            | CV effects                      | No significant<br>differences in<br>cardiovascular<br>morbidity or<br>mortality<br>compared to<br>MET or GLIC |
| <b>Schernthaner<br/>et al. (2004)</b> | Randomized<br>controlled trial,<br>active comparator<br>(MET)                                                            | 12<br>months                              | Poorly controlled<br>T2DM                                             | M,<br>F | PIO<br>(up to 45<br>mg/d) | 597                                  | 57<br>(± 9.4<br>SD)                          | Efficacy and<br>safety*         | ↑ edema and<br>body weight;<br>comparable<br>adverse CV<br>effects between<br>both groups                     |
| <b>Belcher<br/>et al. (2005)</b>      | Randomized<br>controlled trial,<br>active<br>comparators<br>(MET, GLIC) or<br>add-on therapy<br>(PIO or GLIC to<br>MET)  | Four trials,<br>each<br>lasting 1<br>year | T2DM, oral<br>treatment-naïve<br>patients in<br>monotherapy<br>trials | M,<br>F | PIO<br>(up to 45<br>mg/d) | 1,857                                | 57<br>(± 9.4<br>SD)                          | Safety and<br>tolerability*     | ↑ edema and<br>body weight;<br>similar CV<br>outcomes across<br>all treatments                                |

**Table 1. Continued**

| Study                                           | Design                                                                                                              | Duration/<br>Study<br>Period | Patient<br>Population                                                                             | Sex     | TZD<br>(dose)                                    | Number of<br>TZD Exposed<br>Patients | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                                                                                                                                                                   | Results                                                                                                                           |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------------------------------------------------------------------------------|---------|--------------------------------------------------|--------------------------------------|----------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
| <b>Dormandy<br/>et al. (2005)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator                                                            | 34.5<br>months<br>(average)  | T2DM, evidence<br>of macrovascular<br>disease                                                     | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 2,605                                | 61.99<br>( $\pm$ 7.6<br>SD)                  | Composite of all-<br>cause mortality,<br>non-fatal MI,<br>stroke, ACS,<br>endovascular or<br>surgical<br>intervention in the<br>coronary or leg<br>arteries, and<br>amputation above<br>the ankle | ↓ in composite<br>all-cause<br>mortality, non-<br>fatal MI, and<br>stroke                                                         |
| <b>Matthews<br/>et al. (2005)</b>               | Randomized<br>controlled trial,<br>active comparator<br>and add-on<br>therapy (MET<br>plus PIO or MET<br>plus GLIC) | 52<br>weeks                  | Poorly controlled<br>T2DM                                                                         | M,<br>F | PIO<br>(15 mg/d<br>titrated<br>up to 45<br>mg/d) | 317                                  | 56<br>( $\pm$ 9.2<br>SD)                     | Efficacy and<br>safety*                                                                                                                                                                           | No significant<br>difference in<br>incidence of<br>adverse events                                                                 |
| <b>Gerstein<br/>et al. (2006)<br/>DREAM</b>     | Randomized<br>controlled trial,<br>placebo<br>comparator                                                            | 3<br>years<br>(median)       | Impaired fasting<br>glucose and/or<br>impaired glucose<br>tolerance, no<br>previous CV<br>disease | M,<br>F | ROSI<br>(8 mg/d)                                 | 2,365                                | 54.6<br>( $\pm$ 10.9<br>SD)                  | Prevention of<br>T2DM                                                                                                                                                                             | ↓ incident<br>T2DM;<br>composite of<br>adverse CV<br>events found 75<br>events in the<br>ROSI group vs.<br>55 in placebo<br>group |

**Table 1. Continued**

| Study                                           | Design                                                     | Duration/<br>Study<br>Period | Patient<br>Population                         | Sex     | TZD<br>(dose)                                    | Number of<br>TZD Exposed<br>Patients                    | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                                                                                                                                                                                                                                                     | Results                                                                                                                                                                                                                 |
|-------------------------------------------------|------------------------------------------------------------|------------------------------|-----------------------------------------------|---------|--------------------------------------------------|---------------------------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Erdmann<br/>et al. (2007a)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator † | 34.5<br>months<br>(average)  | T2DM, evidence<br>of macrovascular<br>disease | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 2,605                                                   | 61.99<br>(± 7.6<br>SD)                       | HF*                                                                                                                                                                                                                                                                                 | ↑ incidence of<br>serious HF; no<br>increase in<br>morbidity or<br>mortality in<br>patients with<br>serious HF                                                                                                          |
| <b>Erdmann<br/>et al. (2007b)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator   | 34.5<br>months<br>(average)  | T2DM, evidence<br>of macrovascular<br>disease | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 2,605                                                   | 61.99<br>(± 7.6<br>SD)                       | Primary: all-cause<br>mortality, non-<br>fatal MI<br>(including silent<br>MI), stroke, major<br>leg amputation,<br>ACS, cardiac<br>intervention<br>(bypass graft or<br>PCI), or leg<br>revascularization;<br><br>Secondary: all-<br>cause mortality,<br>non-fatal MI, or<br>stroke* | ↓ risk of an<br>event of<br>compared to<br>placebo but not<br>statistically<br>significant;<br>consistent ↓ in<br>most individual<br>components of<br>the primary<br>endpoint; ↓ of<br>risk in<br>secondary<br>endpoint |
| <b>Erdmann<br/>et al. (2007c)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator†  | 34.5<br>months<br>(average)  | T2DM, evidence<br>of macrovascular<br>disease | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 1,230<br>(baseline for<br>patients with<br>previous MI) | 61.8<br>(± 7.8<br>SD)                        | MI                                                                                                                                                                                                                                                                                  | ↓ occurrence of<br>fatal and non-<br>fatal MI and<br>ACS                                                                                                                                                                |

**Table 1. Continued**

| Study                                         | Design                                                                                            | Duration/<br>Study<br>Period         | Patient<br>Population                                                                                           | Sex     | TZD<br>(dose)                                              | Number of<br>TZD Exposed<br>Patients                         | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure               | Results                                                                                                                                                                                                                                                                                            |
|-----------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------|-----------------------------------------------------------------------------------------------------------------|---------|------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------|-----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Home<br/>et al. (2007)<br/>RECORD</b>      | Randomized<br>open-label non-<br>inferiority trial,<br>add-on therapy<br>(ROSI or MET to<br>SUL)‡ | 3.75<br>years<br>(mean<br>follow-up) | T2DM,<br>inadequate<br>glycemic control<br>with MET or SUL                                                      | M,<br>F | ROSI<br>(4 mg/d<br>up to a<br>maximum of 8<br>mg/d)        | 2,220                                                        | 58.4<br>(± 8.3<br>SD)                        | Hospitalization or<br>death from CV<br>causes | ↑ risk of HF; no<br>statistically<br>significant<br>differences<br>between the<br>ROSI group and<br>control group<br>for MI or death                                                                                                                                                               |
| <b>Wilcox<br/>et al. (2007)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator, add-<br>on therapy (MET<br>and SUL)†    | 34.5<br>months<br>(average)          | T2DM,<br>macrovascular<br>disease                                                                               | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d)           | 486 previous<br>stroke<br><br>2,119 no<br>previous<br>stroke | -                                            | Stroke*                                       | ↓ risk of all-<br>cause mortality,<br>non-fatal MI,<br>ACS, cardiac<br>intervention,<br>stroke, non-fatal<br>stroke, major<br>leg amputation,<br>or bypass<br>surgery in<br>patients with<br>previous stroke;<br>↓ risk of fatal or<br>non-fatal stroke,<br>CV death, MI,<br>or nonfatal<br>stroke |
| <b>Giles<br/>et al. (2008)</b>                | Controlled<br>trial, active<br>comparator<br>(GLY)                                                | 6<br>months                          | T2DM, with<br>symptomatic HF<br>after 6<br>months of<br>treatment with<br>PIO or GLY with<br>or without insulin | M,<br>F | PIO<br>(30 mg/d<br>titrated to<br>45 mg/d<br>if<br>needed) | 262                                                          | 64.2<br>(± 9.92<br>SD)                       | HF progression<br>and cardiac<br>function*    | ↑ incidence of<br>hospitalization<br>for HF but not<br>CV mortality or<br>worsening<br>cardiac function                                                                                                                                                                                            |



**Table 1. Continued**

| Study                                            | Design                                                                                   | Duration/<br>Study<br>Period        | Patient<br>Population                                      | Sex     | TZD<br>(dose)                                    | Number of<br>TZD Exposed<br>Patients                   | Mean<br>Age of<br>TZD<br>Exposed<br>Patients                 | Endpoint/<br>Outcome<br>Measure                               | Results                                                                                                                                                                |
|--------------------------------------------------|------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------|---------|--------------------------------------------------|--------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Nissen<br/>et al. (2008)<br/>PERISCOPE</b>    | Randomized<br>controlled trial,<br>active comparator<br>(GLIM)                           | 18<br>months                        | T2DM, coronary<br>disease                                  | M,<br>F | PIO<br>(15 to 45<br>mg/d)                        | 270                                                    | 60.0<br>( $\pm$ 9.4<br>SD)                                   | Progression of<br>coronary<br>atherosclerosis*                | ↓ progression of<br>coronary<br>atherosclerosis;<br>↑ edema                                                                                                            |
| <b>Dormandy<br/>et al. (2009b)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator†                                | 34.5<br>months<br>(average)         | T2DM, evidence<br>of macrovascular<br>disease              | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 619                                                    | -                                                            | Disease outcomes<br>according to the<br>presence of PAD       | No change in<br>macrovascular<br>event rate in<br>patients with<br>PAD at<br>baseline; ↑ leg<br>re-<br>vascularization<br>in patients with<br>PAD in the first<br>year |
| <b>Home<br/>et al. (2009)<br/>RECORD</b>         | Randomized non-<br>inferiority trial,<br>add-on therapy<br>(ROSI to MET or<br>SUL)       | 5.5<br>years<br>(mean<br>follow-up) | T2DM,<br>inadequate<br>glycemic control<br>with MET or SUL | M,<br>F | ROSI<br>(4 mg/d<br>up to 8<br>mg/d)              | Background<br>MET 1,117<br><br>Background<br>SUL 1,103 | 57.0<br>( $\pm$ 8.0<br>SD)<br><br>59.8<br>( $\pm$ 8.3<br>SD) | CV outcomes and<br>comparative<br>safety*                     | ↑ HF; no<br>statistically<br>significant<br>differences<br>between the<br>ROSI group and<br>the control<br>group for MI,<br>stroke, or death                           |
| <b>Kaku<br/>(2009)</b>                           | Randomized<br>controlled trial,<br>placebo<br>comparator, add-<br>on therapy (to<br>MET) | 40<br>weeks                         | T2DM, only<br>treated with MET                             | M,<br>F | PIO<br>(15 mg/d<br>increased<br>to 30<br>mg/d)   | 83                                                     | 52<br>( $\pm$ 8.6<br>SD)                                     | Efficacy and<br>safety of MET-<br>PIO combination<br>therapy* | ↑ risk of edema                                                                                                                                                        |

**Table 1. Continued**

| Study                                          | Design                                                                                                                                    | Duration/<br>Study<br>Period | Patient<br>Population                                                                                                                                                 | Sex     | TZD<br>(dose)                                             | Number of<br>TZD Exposed<br>Patients | Mean<br>Age of<br>TZD<br>Exposed<br>Patients                               | Endpoint/<br>Outcome<br>Measure                                                                                               | Results                                                                                                                                                             |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Kaku<br/>et al. (2009)</b>                  | Randomized,<br>open-label,<br>blinded-endpoint<br>trial, active<br>comparator (other<br>oral<br>hypoglycemic<br>drugs), add-on<br>therapy | 2.5- 4<br>years              | T2DM, $\geq 2$ CV<br>risk factors                                                                                                                                     | M,<br>F | PIO<br>(15 or 30<br>mg/d<br>titrated<br>up to 45<br>mg/d) | 293                                  | 58.1                                                                       | Prevention of<br>macrovascular<br>outcomes*                                                                                   | $\uparrow$ glycemic<br>control; $\uparrow$ risk of<br>edema; no<br>statistically<br>significant<br>difference in<br>macrovascular<br>outcomes                       |
| <b>Kaneda<br/>et al. (2009)</b>                | Randomized<br>controlled trial                                                                                                            | 6<br>months                  | T2DM or non-<br>diabetic patients<br>with ST elevation<br>MI ( $< 12$ h from<br>onset)<br>successfully<br>treated with<br>primary bare<br>metal stent<br>implantation | M,<br>F | PIO<br>(15 mg<br>up to 30<br>mg/d)                        | 48                                   | 67<br>( $\pm 12$<br>SD)                                                    | Efficacy,<br>composite all-<br>cause mortality,<br>reinfarction, or<br>HF requiring<br>hospitalization*                       | No statistically<br>significant<br>differences<br>between PIO<br>and controls for<br>all-cause<br>mortality,<br>reinfarction, or<br>HF requiring<br>hospitalization |
| <b>Scheen<br/>et al. (2009a)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator, add-<br>on therapy (MET<br>or SUL) $\dagger$                                    | 34.5<br>months<br>(average)  | T2DM,<br>macrovascular<br>disease                                                                                                                                     | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d)          | 253<br><br>508                       | MET<br>60.8<br>( $\pm 7.6$<br>SD)<br><br>SUL<br>63.2<br>( $\pm 7.7$<br>SD) | Long-term<br>glycemic effects,<br>concomitant<br>changes in<br>medications, and<br>initiation of<br>permanent insulin<br>use* | $\uparrow$ edema and<br>body weight;<br>non-significant<br>differences in<br>HF                                                                                     |

**Table 1. Continued**

| Study                                          | Design                                                                                        | Duration/<br>Study<br>Period | Patient<br>Population                         | Sex     | TZD<br>(dose)                                    | Number of<br>TZD Exposed<br>Patients | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                                                                                                               | Results                                                                                                                                                                       |
|------------------------------------------------|-----------------------------------------------------------------------------------------------|------------------------------|-----------------------------------------------|---------|--------------------------------------------------|--------------------------------------|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Scheen<br/>et al. (2009b)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator, add-<br>on therapy (MET<br>or SUL)† | 34.5<br>months<br>(average)  | T2DM,<br>macrovascular<br>disease             | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | 654                                  | MET-<br>SUL<br>61.7<br>(± 7.5<br>SD)         | Long-term<br>glycemic effects<br>and safety*                                                                                                  | ↑ edema and<br>body weight;<br>rare serious<br>hypoglycemia;<br>non-significant<br>differences in<br>HF                                                                       |
| <b>Abe<br/>et al. (2010)</b>                   | Open-label,<br>parallel-group<br>(other anti-<br>hyperglycemic<br>drugs) controlled<br>trial  | ≤ 96<br>weeks                | T2DM,<br>hemodialysis                         | M,<br>F | PIO<br>(15 to 30<br>mg/d)                        | 31                                   | 65.2<br>(± 12.1<br>SD)                       | Effectiveness and<br>safety*                                                                                                                  | No adverse CV<br>events                                                                                                                                                       |
| <b>Erdmann<br/>et al. (2010)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator†                                     | 34.5<br>months<br>(average)  | T2DM, evidence<br>of macrovascular<br>disease | M,<br>F | PIO<br>(titrated<br>from 15<br>mg to 45<br>mg/d) | -                                    | -                                            | All-cause<br>mortality, MI,<br>stroke, edema,<br>and serious HF in<br>subgroups using<br>nitrates, RAS<br>blockers, or<br>insulin at baseline | Risk for PIO<br>was similar to<br>placebo<br>regardless of<br>baseline use of<br>nitrates, RAS<br>blockers,<br>or insulin; no<br>increased risk of<br>macrovascular<br>events |

**Table 1. Continued**

| Study                                       | Design                                                                                                                     | Duration/<br>Study<br>Period        | Patient<br>Population                                      | Sex     | TZD<br>(dose)                                             | Number of<br>TZD Exposed<br>Patients                   | Mean<br>Age of<br>TZD<br>Exposed<br>Patients       | Endpoint/<br>Outcome<br>Measure                                                                                                                      | Results                                                                                                                                                                                                                                                                          |
|---------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------|------------------------------------------------------------|---------|-----------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Giles<br/>et al. (2010)</b>              | Controlled<br>trial, active<br>comparator<br>(GLY)                                                                         | 1<br>year                           | T2DM, mild<br>cardiac disease                              | M,<br>F | PIO<br>(15 or 30<br>mg/d<br>titrated<br>up to 45<br>mg/d) | 151                                                    | 64 entire<br>study                                 | CV mortality and<br>morbidity,<br>changes from<br>baseline in<br>cardiac structure<br>and function, and<br>lipid panel<br>(secondary<br>endpoints) * | ↑ HF, edema,<br>and weight gain                                                                                                                                                                                                                                                  |
| <b>Komajda<br/>et al. (2010)<br/>RECORD</b> | Open-label non-<br>inferiority trial,<br>active comparator<br>(MET plus SUL),<br>add-on therapy<br>(ROSI to MET or<br>SUL) | 5.5<br>years<br>(mean<br>follow-up) | T2DM,<br>inadequate<br>glycemic control<br>with MET or SUL | M,<br>F | ROSI<br>(4 mg/d<br>up to 8<br>mg/d)                       | Background<br>MET 1,117<br><br>Background<br>SUL 1,103 | 57.0<br>(± 8.0<br>SD)<br><br>59.8<br>(± 8.3<br>SD) | Fatal and non-<br>fatal HF events,<br>HF predictors                                                                                                  | ↑ risk of HF; not<br>associated with<br>increased<br>CV mortality or<br>morbidity but<br>reported an<br>excess number<br>of HF deaths<br><br>HF risk factors<br>included: ↑ age,<br>body weight,<br>and systolic<br>blood pressure,<br>and micro-<br>albuminuria<br>/proteinuria |

**Table 1. Continued**

| Study                                     | Design                                                                                                                                                                                                                                                 | Duration/<br>Study<br>Period | Patient<br>Population                                                                                                          | Sex     | TZD<br>(dose)       | Number of<br>TZD Exposed<br>Patients | Mean<br>Age of<br>TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                                                                                               | Results                                                                                                                                                                                                                                           |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------|---------------------|--------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Bach<br/>et al. (2013)<br/>BARI 2D</b> | Randomized<br>controlled trial,<br>therapeutic<br>comparators<br>(prompt<br>revascularization<br>with intensive<br>medical therapy<br>or intensive<br>medical therapy<br>alone with<br>insulin-<br>sensitization or<br>insulin-provision<br>therapy) ¶ | 4.5<br>years                 | T2DM,<br>documented CAD<br>warranting<br>consideration of<br>revascularization                                                 | M,<br>F | ROSI<br>(NA)        | 992                                  | 62.0<br>(± 9.0<br>SD)                        | Total mortality,<br>composite death,<br>MI, and<br>stroke, and<br>individual<br>incidence of<br>death, MI, stroke,<br>and CHF | Compared to<br>patients not<br>receiving a TZD<br>ROSI was<br>associated with<br>a similar risk of<br>mortality; ↓<br>incidence of<br>composite<br>death, MI, and<br>stroke;<br>incidence of MI<br>and CHF were<br>not statistically<br>different |
| <b>Lee<br/>et al. (2013)</b>              | Randomized<br>controlled trial,<br>placebo<br>comparator                                                                                                                                                                                               | 12<br>months                 | T2DM,<br>symptomatic IHD<br>with a significant<br>coronary lesion<br>that have<br>undergone PCI<br>with drug-eluting<br>stents | M,<br>F | PIO<br>(15<br>mg/d) | 60                                   | 60.3<br>(± 9.53<br>SD)                       | All-cause death,<br>MI, stent<br>thrombosis, and<br>re-PCI (secondary<br>endpoints) *                                         | No statistically<br>significant<br>differences<br>compared to<br>control group                                                                                                                                                                    |

**Table 1. Continued**

| Study                                          | Design                                                                                                                      | Duration/<br>Study<br>Period                                                                                                | Patient<br>Population                                      | Sex     | TZD<br>(dose)                                                                                                                                                                 | Number of<br>TZD Exposed<br>Patients                            | Mean<br>Age of<br>TZD<br>Exposed<br>Patients       | Endpoint/<br>Outcome<br>Measure                                                        | Results                                                                                                                                                                                                                |
|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Mahaffey<br/>et al. (2013)<br/>RECORD</b>   | Open-label non-<br>inferiority trial,<br>active comparator<br>(MET plus SUL),<br>add-on therapy<br>(ROSI to MET or<br>SUL)§ | 25,833<br>person-<br>years<br>follow-up<br>for<br>mortality,<br>23,692<br>person-<br>years<br>follow-up<br>for<br>composite | T2DM,<br>inadequate<br>glycemic control<br>with MET or SUL | M,<br>F | ROSI<br>(4 mg/d<br>up to 8<br>mg/d)                                                                                                                                           | Background<br>MET 1,117<br><br>Background<br>SUL 1,103          | 57.0<br>(± 8.0<br>SD)<br><br>59.8<br>(± 8.3<br>SD) | Death, MI, and<br>stroke, and<br>composite<br>endpoint of CV<br>death, MI or<br>stroke | Same<br>conclusions as<br>the original<br>RECORD<br>analysis: no<br>statistically<br>significant<br>differences for<br>the composite<br>endpoint, slight<br>↑ risk of stroke<br>or MI but<br>similar between<br>groups |
| <b>Erdmann<br/>et al. (2014)<br/>PROactive</b> | Randomized<br>controlled trial,<br>placebo<br>comparator, add-<br>on therapy (to<br>MET or SUL)†                            | 5.8 years<br>(mean);<br>8.7 years<br>(mean<br>combined<br>double-<br>blind and<br>follow-up<br>periods)                     | T2DM,<br>macrovascular<br>disease                          | M,<br>F | Follow-<br>up from<br>PIO<br>(titrated<br>from 15<br>to 45<br>mg/d) in<br>original<br>trial;<br>patients<br>may have<br>received<br>PIO or<br>ROSI<br>during<br>follow-<br>up | 3,599 follow-<br>up patients<br>(1,820<br>previously on<br>PIO) | -                                                  | Macrovascular<br>events                                                                | Decrease in<br>composite<br>macrovascular<br>morbidity and<br>mortality<br>outcomes in<br>PROactive did<br>not persist<br>during 6 years<br>of follow-up                                                               |

ACS: acute coronary syndrome; BARI 2D: Bypass Angioplasty Revascularization Investigation 2 Diabetes; CAD: coronary artery disease; CV: cardiovascular; DREAM: Diabetes REduction Assessment with ramipril and rosiglitazone Medication; GLIC: glicazide; GLIM: glimepiride; GLY: glyburide; HF: heart failure; IHD: ischemic heart disease; MET: metformin; MI: myocardial infarction; PAD: peripheral arterial disease; PCI: percutaneous coronary intervention; PERISCOPE: Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; PIO: pioglitazone; PROactive: PROspectivepioglitAzone Clinical Trial In macroVascular Events; RAS: renin–angiotensin system; RECORD: Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; ROSI: rosiglitazone; SD: standard deviation; SUL: sulfonylurea; TZD: thiazolidinedione; T2DM: type 2 diabetes mellitus.

\*Refer to Supplementary Appendix 1 for results related to effectiveness, CV markers, associated risk factors, or CV function.

†Post-hoc analysis of the trial.

‡Interim analysis of the trial.

¶Longitudinal analysis.

§Re-evaluation of the trial.

**Table 2.** Observational studies investigating adverse cardiovascular events associated with TZD therapy.

| Study                                    | Design                  | Duration/<br>Study<br>Period  | Patient<br>Population                                                                                | Sex  | TZD                       | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                           |
|------------------------------------------|-------------------------|-------------------------------|------------------------------------------------------------------------------------------------------|------|---------------------------|-----------------------------------|-------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------|
| <b>Kermani<br/>&amp; Garg<br/>(2003)</b> | Case studies            | 2001-<br>2002                 | T2DM, signs/<br>symptoms of CHF<br>and pulmonary<br>edema after 1-16<br>months taking<br>PIO or ROSI | M    | ROSI<br>( 4 to<br>8 mg/d) | 5                                 | 66-78                                     | CHF and<br>pulmonary<br>edema   | Symptoms<br>resolved in all<br>patients after<br>administration<br>of diuretics and<br>discontinuation<br>of TZDs |
|                                          |                         |                               |                                                                                                      |      | PIO<br>(45 mg/d)          | 1                                 | 67                                        |                                 |                                                                                                                   |
| <b>Cho<br/>et al. (2005)</b>             | Retrospective<br>cohort | 1<br>year                     | T2DM,<br>anti-<br>hyperglycemic<br>drugs                                                             | M, F | ROSI<br><br>PIO           | 82                                | 61<br>( $\pm$ 10.2 SD)                    | TVR<br>rate<br>following<br>PCI | No $\downarrow$ in repeat<br>TVR following<br>PCI with TZD<br>therapy                                             |
| <b>Hartung<br/>et al. (2005)</b>         | Nested case-<br>control | 1999-<br>2001<br>(enrollment) | T2DM                                                                                                 | M, F | TZD                       | 59<br>cases                       | 67.0<br>( $\pm$ 12.1 SD)<br>all cases     | HF                              | $\uparrow$ risk of<br>hospitalization<br>within 60 days<br>of prescription<br>of a TZD                            |
|                                          |                         |                               |                                                                                                      |      |                           | 216<br>controls                   | 66.4<br>( $\pm$ 12.1 SD)<br>all controls  |                                 |                                                                                                                   |
| <b>Gerrits<br/>et al. (2007)</b>         | Retrospective<br>cohort | 2003-<br>2006                 | T2DM, initiated<br>treatment with<br>ROSI or PIO                                                     | M, F | ROSI                      | 15,104                            | 58<br>( $\pm$ 9.1 SD)                     | MI                              | $\downarrow$ risk in<br>hospitalization<br>for MI for PIO<br>compared to<br>ROSI                                  |
|                                          |                         |                               |                                                                                                      |      | PIO                       | 14,807                            | 58<br>( $\pm$ 8.8 SD)                     |                                 |                                                                                                                   |



**Table 2. Continued**

| Study                                  | Design                  | Duration/<br>Study<br>Period                         | Patient<br>Population                         | Sex  | TZD                                       | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                               |
|----------------------------------------|-------------------------|------------------------------------------------------|-----------------------------------------------|------|-------------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Anglade<br/>et al. (2007)</b>       | Nested case-<br>control | ≤ 30<br>days of<br>surgery                           | T2DM, CTS                                     | M, F | ROSI<br>(average<br>daily dose<br>6 mg)   | 24 pre-<br>operatively            | 65.8<br>(± 6.2 SD)                        | Post-<br>operative<br>AF        | Non-statistically<br>significant ↓ in<br>risk of post-CTS<br>AF with TZD<br>use                       |
|                                        |                         |                                                      |                                               |      | PIO<br>(average<br>daily dose<br>30 mg)   | 14 pre-<br>operatively            |                                           |                                 |                                                                                                       |
|                                        |                         |                                                      |                                               |      | TRO<br>(average<br>daily dose<br>525 mg)  | 2 pre-<br>operatively             |                                           |                                 |                                                                                                       |
| <b>Lee &amp;<br/>Reding<br/>(2007)</b> | Nested case-<br>control | 36<br>days                                           | T2DM, stroke                                  | M, F | ROSI<br>(mean dose<br>6.1 ± 2.2<br>mg/d)  | 18                                | 70.0<br>(± 10.3 SD)<br>TZD group          | Stroke<br>recovery              | ↑ functional<br>recovery with<br>TZD use                                                              |
|                                        |                         |                                                      |                                               |      | PIO<br>(mean dose<br>28.8 ± 11.9<br>mg/d) | 12                                |                                           |                                 |                                                                                                       |
| <b>Lipscombe<br/>et al. (2007)</b>     | Nested case-<br>control | 2002-<br>2006;<br>3.8 years<br>(median<br>follow-up) | T2DM, ≥ 66<br>years, treated with<br>≥ 1 OHAs | M, F | TZD<br>monotherapy                        | 229                               | 73.9<br>(± 5.7 SD)                        | CHF, MI,<br>and<br>mortality    | ↑ risk of CHF,<br>MI, and death<br>with TZD<br>monotherapy;<br>associations<br>primarily with<br>ROSI |
|                                        |                         |                                                      |                                               |      | TZD<br>combination<br>therapy             | 1,463                             | 73.0<br>(± 5.5 SD)                        |                                 |                                                                                                       |

**Table 2. Continued**

| Study                              | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                            | Sex  | TZD                                         | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients        | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                                       |
|------------------------------------|-------------------------|------------------------------|--------------------------------------------------|------|---------------------------------------------|-----------------------------------|--------------------------------------------------|---------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Casscells<br/>et al. (2008)</b> | Cross-<br>sectional     | 2003-<br>2006                | T2DM, Military<br>Health System<br>beneficiaries | M, F | ROSI                                        | 13,400                            | -                                                | MI and<br>CHF                   | No significant<br>difference in<br>incidence of MI<br>or CHF for<br>ROSI compared<br>to other anti-<br>hyperglycemic<br>drugs                                 |
|                                    |                         |                              |                                                  |      | PIO                                         | 7,831                             |                                                  |                                 |                                                                                                                                                               |
| <b>Kasliwal<br/>et al. (2008)</b>  | Prospective<br>cohort   | 8<br>months                  | Prescription for<br>PIO                          | M, F | PIO<br>(15 to<br>45 mg/d)                   | 12,772                            | Median 62<br>(52-70 inter-<br>quartile<br>range) | Safety of<br>PIO                | ↑ reports of<br>edema, weight<br>gain; reports of<br>adverse CV<br>events/death but<br>further analysis<br>needed to<br>determine<br>associations<br>with PIO |
| <b>Koro<br/>et al. (2008)</b>      | Nested case-<br>control | 1999-<br>2006                | T2DM                                             | M, F | ROSI<br>monotherapy<br>or in<br>combination | 1,149<br>cases                    | -                                                | MI                              | ↑ risk of MI with<br>> 12 months<br>therapy for<br>ROSI (15%) and<br>PIO (13%) but<br>not ≤ 12 months<br>of therapy                                           |
|                                    |                         |                              |                                                  |      | PIO<br>monotherapy<br>or in<br>combination  | 910<br>cases                      |                                                  |                                 |                                                                                                                                                               |

**Table 2. Continued**

| Study                             | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                 | Sex  | TZD              | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                                                                |
|-----------------------------------|-------------------------|------------------------------|---------------------------------------|------|------------------|-----------------------------------|-------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Margolis<br/>et al. (2008)</b> | Retrospective<br>cohort | 2002-<br>2006                | T2DM, $\geq 40$ years                 | M, F | Any TZD          | 9,526                             | -                                         | ASVD of<br>the heart            | ↓ risk of MI with<br>longer use of<br>ROSI or PIO                                                                                                                                      |
|                                   |                         |                              |                                       |      | ROSI             | 7,282                             |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | PIO              | 2,244                             |                                           |                                 |                                                                                                                                                                                        |
| <b>Walker<br/>et al. (2008)</b>   | Retrospective<br>cohort | 2000-<br>2007                | Users of ROSI,<br>PIO, MET, or<br>SUL | M, F | ROSI             | 12,440                            | -                                         | MI and CR                       | ↓ risk of MI and<br>CR for TZDs<br>compared to<br>SUL; ↑ risk<br>compared to<br>MET; no<br>significant<br>difference in risk<br>of MI and CR or<br>MI alone<br>between ROSI<br>and PIO |
|                                   |                         |                              |                                       |      | ROSI-MET         | 26,885                            |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | ROSI-SUL         | 10,021                            |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | ROSI-<br>Insulin | 8,035                             |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | PIO              | 16,302                            |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | PIO-MET          | 17,282                            |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | PIO-SUL          | 10,133                            |                                           |                                 |                                                                                                                                                                                        |
|                                   |                         |                              |                                       |      | PIO-Insulin      | 7,924                             |                                           |                                 |                                                                                                                                                                                        |

**Table 2. Continued**

| Study                               | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                                           | Sex  | TZD     | Number TZD<br>Exposed<br>Patients                                               | Mean Age<br>of TZD<br>Exposed<br>Patients                           | Endpoint/<br>Outcome<br>Measure                  | Results                                                                                                                                                  |
|-------------------------------------|-------------------------|------------------------------|-----------------------------------------------------------------|------|---------|---------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Winkelmayr<br/>et al. (2008)</b> | Prospective<br>cohort   | 2001-<br>2005                | T2DM, > 65<br>years, initiated<br>treatment with<br>ROSI or PIO | M, F | ROSI    | 14,101                                                                          | 76.3                                                                | All-cause<br>mortality,<br>MI, stroke<br>and CHF | ↑ risk of<br>mortality and<br>hospitalization<br>for CHF for<br>ROSI compared<br>to PIO; no<br>significant<br>differences for<br>risk of MI or<br>stroke |
|                                     |                         |                              |                                                                 |      | PIO     | 14,260                                                                          | 76.3                                                                |                                                  |                                                                                                                                                          |
| <b>Azoulay<br/>et al. (2009)</b>    | Nested case-<br>control | 1988-<br>2008                | T2DM, anti-<br>hyperglycemic<br>drug use                        | M, F | Any TZD | 522<br>(25 TZD<br>monotherapy<br>cases; 64 TZD<br>combination<br>therapy cases) | 74.1<br>(± 10.5 SD)<br>cases<br><br>73.8<br>(± 10.3 SD)<br>controls | Stroke                                           | No statistically<br>significant ↓ in<br>strokes for TZD<br>mono or<br>combination<br>therapy                                                             |
|                                     |                         |                              |                                                                 |      | ROSI    | 344                                                                             |                                                                     |                                                  |                                                                                                                                                          |
|                                     |                         |                              |                                                                 |      | PIO     | 178                                                                             |                                                                     |                                                  |                                                                                                                                                          |
| <b>Dore<br/>et al. (2009)</b>       | Nested case-<br>control | 2001-<br>2002                | Use of MET and a<br>SUL                                         | M, F | ROSI    | 240<br>prevalent use                                                            | -                                                                   | MI                                               | Non-statistically<br>significant ↑ in<br>rate of MI in the<br>90 days before<br>index date for<br>ROSI and PIO                                           |
|                                     |                         |                              |                                                                 |      | PIO     | 198<br>prevalent use                                                            |                                                                     |                                                  |                                                                                                                                                          |

**Table 2. Continued**

| Study                             | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                    | Sex  | TZD      | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                  | Results                                                                                                                                                                            |
|-----------------------------------|-------------------------|------------------------------|------------------------------------------|------|----------|-----------------------------------|-------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dormuth<br/>et al. (2009)</b>  | Nested case-<br>control | 2003-<br>2007                | T2DM and MET<br>use                      | M, F | ROSI     | 462<br>cases and<br>controls      | 66<br>( $\pm$ 11 SD)                      | MI                                               | No significant<br>risk of MI for<br>ROSI compared<br>to PIO or SUL;<br>transient but<br>non-statistically<br>significant $\uparrow$ of<br>MI after starting<br>ROSI                |
|                                   |                         |                              |                                          |      | PIO      | 235<br>cases and<br>controls      | 66<br>( $\pm$ 12 SD)                      |                                                  |                                                                                                                                                                                    |
| <b>Grossman<br/>et al. (2009)</b> | Prospective<br>cohort   | 2<br>years                   | T2DM                                     | M, F | PIO      | 1,527                             | 59.5<br>( $\pm$ 11.8 SD)                  | Adverse<br>events                                | $\uparrow$ peripheral<br>edema and<br>weight gain<br>compared to<br>non-TZD group;<br>$\uparrow$ percentage of<br>patients with HF<br>and pulmonary<br>edema                       |
| <b>Habib<br/>et al. (2009)</b>    | Retrospective<br>cohort | 2000-<br>2006                | T2DM, anti-<br>hyperglycemic<br>drug use | M, F | ROSI     | 1,056                             | 59.0<br>( $\pm$ 12.6 SD)                  | CV<br>outcomes<br>and all-<br>cause<br>mortality | No significant<br>risk of MI for<br>ROSI or PIO; $\downarrow$<br>all-cause<br>mortality for<br>PIO; $\downarrow$ risk of<br>HF, CVA, TIA<br>and CHD for<br>PIO compared to<br>ROSI |
|                                   |                         |                              |                                          |      | PIO      | 3,217                             | 57.0<br>( $\pm$ 12.0 SD)                  |                                                  |                                                                                                                                                                                    |
|                                   |                         |                              |                                          |      | ROSI-PIO | 307                               | 57.3<br>( $\pm$ 12.1 SD)                  |                                                  |                                                                                                                                                                                    |

**Table 2. Continued**

| Study                          | Design                  | Duration/<br>Study<br>Period | Patient<br>Population   | Sex  | TZD                 | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                     | Results                                                                                                                                                                                  |
|--------------------------------|-------------------------|------------------------------|-------------------------|------|---------------------|-----------------------------------|-------------------------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hsiao<br/>et al. (2009)</b> | Retrospective<br>cohort | 2001-<br>2005                | Newly diagnosed<br>T2DM | M, F | ROSI<br>monotherapy | 2,093                             | 61.24<br>( $\pm$ 13.48 SD)                | MI, HF,<br>angina<br>pectoris,<br>stroke and<br>TIA | $\uparrow$ risk of any CV<br>event, MI,<br>angina pectoris<br>and TIA for<br>ROSI compared<br>to those<br>receiving MET<br>monotherapy;<br>comparable risk<br>for add-on ROSI<br>and PIO |
|                                |                         |                              |                         |      | PIO<br>monotherapy  | 495                               | 60.75<br>( $\pm$ 12.78 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | ROSI-SUL            | 5,141                             | 59.76<br>( $\pm$ 12.83 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | ROSI-MET            | 2,408                             | 57.25<br>( $\pm$ 14.00 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | ROSI-MET-<br>SUL    | 39,982                            | 54.74<br>( $\pm$ 12.39 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | PIO-SUL             | 1,231                             | 58.05<br>( $\pm$ 12.97 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | PIO-MET             | 774                               | 54.94<br>( $\pm$ 13.63 SD)                |                                                     |                                                                                                                                                                                          |
|                                |                         |                              |                         |      | PIO-MET-<br>SUL     | 9,510                             | 54.07<br>( $\pm$ 12.39 SD)                |                                                     |                                                                                                                                                                                          |

**Table 2. Continued**

| Study                              | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                                                    | Sex  | TZD             | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients        | Endpoint/<br>Outcome<br>Measure                                                                                     | Results                                                                                                                                                               |
|------------------------------------|-------------------------|------------------------------|--------------------------------------------------------------------------|------|-----------------|-----------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Juurlink<br/>et al. (2009)</b>  | Retrospective<br>cohort | 2002-<br>2008                | Outpatients, $\geq 66$<br>years of age,<br>treatment with<br>ROSI or PIO | M, F | ROSI            | 22,785                            | Median 72<br>(68-77 inter-<br>quartile<br>range) | Composite<br>of death or<br>hospital<br>admission<br>for MI or<br>HF;<br>separate<br>analysis of<br>each<br>outcome | $\downarrow$ risk of<br>composite<br>outcome, death,<br>and HF for PIO<br>compared to<br>ROSI; no<br>significant<br>difference in risk<br>of MI                       |
|                                    |                         |                              |                                                                          |      | PIO             | 16,951                            | Median 72<br>(68-77 inter-<br>quartile<br>range) |                                                                                                                     |                                                                                                                                                                       |
| <b>Pantalone<br/>et al. (2009)</b> | Retrospective<br>cohort | 1998-<br>2006                | T2DM, anti-<br>hyperglycemic<br>drug use                                 | M, F | ROSI            | 1,079                             | 61.4<br>( $\pm 13.7$ SD)                         | CAD, CHF<br>and<br>mortality                                                                                        | $\downarrow$ risk of<br>mortality for<br>PIO compared to<br>SUL; no<br>significant risk<br>of CAD for<br>ROSI                                                         |
|                                    |                         |                              |                                                                          |      | PIO             | 1,508                             | 61.6<br>( $\pm 13.1$ SD)                         |                                                                                                                     |                                                                                                                                                                       |
| <b>Shaya<br/>et al. (2009)</b>     | Retrospective<br>cohort | 2001-<br>2006                | T2DM, high-risk<br>patients                                              | M, F | ROSI and<br>PIO | 5,712                             | Mean total<br>population<br>51<br>(median 53)    | MI and<br>stroke                                                                                                    | $\uparrow$ risk of MI and<br>stroke for ROSI<br>but not PIO                                                                                                           |
| <b>Stockl<br/>et al. (2009)</b>    | Nested case-<br>control | 2002-<br>2006                | T2DM, OHA or<br>exenatide use                                            | M, F | ROSI            | 219 cases                         | 73.0<br>( $\pm 9.1$ SD)<br>all cases             | MI                                                                                                                  | No statistically<br>significant risk<br>associated with<br>TZD exposure;<br>when stratified $\uparrow$<br>risk of MI<br>within 1 to 60<br>days of exposure<br>to ROSI |
|                                    |                         |                              |                                                                          |      | PIO             | 52 cases                          |                                                  |                                                                                                                     |                                                                                                                                                                       |

**Table 2. Continued**

| Study                             | Design                  | Duration/<br>Study<br>Period | Patient<br>Population       | Sex  | TZD                                            | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure           | Results                                                                                                                                                                                                       |
|-----------------------------------|-------------------------|------------------------------|-----------------------------|------|------------------------------------------------|-----------------------------------|-------------------------------------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Tzoulaki<br/>et al. (2009)</b> | Retrospective<br>cohort | 1990-<br>2005                | T2DM                        | M, F | ROSI mono<br>therapy                           | 8,442                             | 65.7<br>( $\pm$ 10.9 SD)                  | MI, CHF<br>and all-<br>cause<br>mortality | No statistically<br>significant risk<br>of MI for TZDs<br>compared to<br>MET; $\downarrow$ risk of<br>mortality for<br>PIO compared to<br>MET; $\uparrow$ risk of<br>mortality for<br>ROSI compared<br>to PIO |
|                                   |                         |                              |                             |      | ROSI<br>combination<br>therapy                 | 9,640                             | 64.5<br>( $\pm$ 10.8 SD)                  |                                           |                                                                                                                                                                                                               |
|                                   |                         |                              |                             |      | PIO mono or<br>combination<br>therapy          | 3,816                             | 64.8<br>( $\pm$ 10.6 SD)                  |                                           |                                                                                                                                                                                                               |
| <b>Ziyadeh<br/>et al. (2009)</b>  | Retrospective<br>cohort | 2000-<br>2007                | T2DM, use of<br>ROSI or PIO | M, F | ROSI or PIO<br>initiated<br>mono<br>therapy    | 72,104                            | -                                         | MI, CR,<br>and sudden<br>death            | $\uparrow$ risk of MI for<br>ROSI compared<br>to PIO; no<br>significant<br>difference for<br>composite<br>endpoint or<br>sudden death for<br>ROSI compared<br>to PIO                                          |
|                                   |                         |                              |                             |      | ROSI or PIO<br>initiated dual<br>therapy       | 17,822                            |                                           |                                           |                                                                                                                                                                                                               |
|                                   |                         |                              |                             |      | ROSI or<br>PIO-insulin<br>initiated<br>therapy | 5,076                             |                                           |                                           |                                                                                                                                                                                                               |



**Table 2. Continued**

| Study                           | Design                | Duration/<br>Study<br>Period | Patient<br>Population                     | Sex  | TZD              | Number TZD<br>Exposed<br>Patients                                         | Mean Age<br>of TZD<br>Exposed<br>Patients                                                                 | Endpoint/<br>Outcome<br>Measure                                         | Results                                                                                 |
|---------------------------------|-----------------------|------------------------------|-------------------------------------------|------|------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| <b>Bilik<br/>et al. (2010a)</b> | Prospective<br>cohort | 1999-<br>2003                | T2DM, treated<br>with only ROSI or<br>PIO | M, F | ROSI             | 773<br>all health<br>plans;<br>564<br>health plans<br>with both<br>TZDs   | 58<br>( $\pm$ 11 SD)<br>all health<br>plans;<br>59<br>( $\pm$ 12 SD)<br>health plans<br>with both<br>TZDs | CVD<br>incidence,<br>CV<br>mortality,<br>and all-<br>cause<br>mortality | No statistically<br>significant<br>difference in<br>outcomes<br>between ROSI<br>and PIO |
|                                 |                       |                              |                                           |      | PIO              | 711<br>all health<br>plans;<br>334<br>health plans<br>with both<br>TZDs   | 59<br>( $\pm$ 11 SD)<br>all health<br>plans;<br>59<br>( $\pm$ 11 SD)<br>health plans<br>with both<br>TZDs |                                                                         |                                                                                         |
|                                 |                       |                              |                                           |      | Multiple<br>TZDs | 1,815<br>all health<br>plans;<br>261<br>health plans<br>with both<br>TZDs |                                                                                                           |                                                                         |                                                                                         |

**Table 2. Continued**

| Study                            | Design                                                                                                            | Duration/<br>Study<br>Period                                      | Patient<br>Population                                                                                                                                                                      | Sex  | TZD  | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                     | Results                                                                                                                                                |
|----------------------------------|-------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|------|-----------------------------------|-------------------------------------------|-----------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Graham<br/>et al. (2010)</b>  | Retrospective<br>cohort                                                                                           | 2006-<br>2009                                                     | T2DM, > 65 years<br>of age,<br>enrollment in<br>Medicare Parts A<br>or B                                                                                                                   | M, F | ROSI | 67,593                            | -                                         | MI, stroke,<br>HF, and<br>all-cause<br>mortality    | ↑ risk of stroke,<br>HF, and all-<br>cause mortality,<br>and composite<br>of acute MI,<br>stroke, HF, or<br>all-cause<br>mortality for<br>ROSI         |
|                                  |                                                                                                                   |                                                                   |                                                                                                                                                                                            |      | PIO  | 159,978                           |                                           |                                                     |                                                                                                                                                        |
| <b>Roussel<br/>et al. (2013)</b> | Prospective<br>cohort                                                                                             | 2<br>years                                                        | T2DM, high CV<br>risk                                                                                                                                                                      | M, F | TZD  | 4,997                             | 67.1<br>(± 9.6 SD)                        | 2-year<br>mortality,<br>non-fatal<br>MI, and<br>CHF | TZD use not<br>associated with<br>increased<br>mortality, MI, or<br>CHF; except ↑<br>risk of CHF in<br>patients > 80<br>years                          |
| <b>Tannen<br/>et al. (2013)</b>  | Retrospective<br>cohort<br>(replicated the<br>PROactive<br>RCT;<br>replication<br>studies for<br>ROSI and<br>PIO) | 2001-<br>2005 (RCT);<br>2000-<br>2008<br>(replication<br>studies) | T2DM,<br>macrovascular<br>disease and<br>specified CVD in<br>RCT replication<br>and ROSI and<br>PIO replication<br>studies (but not<br>expanded ROSI<br>and PIO<br>replication<br>studies) | M, F | ROSI | -                                 | -                                         | MI                                                  | ↑ risk of MI for<br>ROSI but not<br>PIO in a<br>population with<br>CVD;<br>comparable<br>effects for ROSI<br>and PIO in an<br>unselected<br>population |
|                                  |                                                                                                                   |                                                                   |                                                                                                                                                                                            |      | PIO  |                                   |                                           |                                                     |                                                                                                                                                        |

**Table 2. Continued**

| Study                              | Design                  | Duration/<br>Study<br>Period                                  | Patient<br>Population                                                         | Sex  | TZD | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients                                    | Endpoint/<br>Outcome<br>Measure                                         | Results                                                                                                                                            |
|------------------------------------|-------------------------|---------------------------------------------------------------|-------------------------------------------------------------------------------|------|-----|-----------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Vallarino<br/>et al. (2013)</b> | Retrospective<br>cohort | 2000-<br>2010;<br>2.2 years<br>(mean<br>follow-up<br>for PIO) | T2DM, $\geq 45$<br>years, new users<br>of PIO or insulin                      | M, F | PIO | 38,588                            | 58.1<br>( $\pm 8.7$ SD)                                                      | Safety and<br>incident<br>cases of a<br>composite<br>of MI or<br>stroke | ↓ risk of<br>hospitalization<br>for MI and<br>stroke compared<br>to insulin                                                                        |
| <b>Kannan<br/>et al. (2015)</b>    | Retrospective<br>cohort | 2005<br>-2013;<br>4<br>years<br>(median<br>follow-up)         | T2DM, treated<br>with MET and an<br>additional anti-<br>hyperglycemic<br>drug | M, F | TZD | 1,846                             | Median<br>59.00<br>(52.0, 67.0<br>25 <sup>th</sup> and<br>25 <sup>th</sup> ) | Mortality,<br>CAD, and<br>HF                                            | ↑ survival for<br>MET-TZD<br>compared to<br>MET-SUL;<br>similar risks of<br>mortality, CAD,<br>and HF when<br>ROSI was<br>removed from<br>analysis |

AF: atrial fibrillation; ASVD: atherosclerotic vascular disease ; CAD: coronary artery disease; CHD: coronary heart disease; CHF: congestive heart failure; CR: coronary revascularization; CTS: cardiothoracic surgery; CV: cardiovascular; CVD: cardiovascular disease; CVA: cerebrovascular accident; HF: heart failure; MET: metformin; MI: myocardial infarction; OHA: oral hypoglycemic agent/drug; PCI: percutaneous coronary intervention; PIO: pioglitazone; PROactive: PROspective pioglitAzone Clinical Trial In macroVascular Events; RCT: randomized controlled trial; ROSI: rosiglitazone; SD: standard deviation; SUL: sulfonylurea; TIA: transient ischemic attacks; TRO: troglitazone; TVR: target vessel revascularization; TZD: thiazolidinedione; T2DM: Type 2 diabetes mellitus.

Early trials investigating the effectiveness, safety, and tolerability of TZDs found that TZD pharmacotherapy led to improvements in glycemic control (e.g. Derosa et al. 2006; Matthews et al. 2005; Schernthaner et al. 2004) and inflammatory biomarkers (Haffner et al. 2002; Hetzel et al. 2005) and had positive effects on blood pressure (Belcher et al. 2004), triglyceride level (Betteridge & Vergès 2005; Derosa et al. 2006; Matthews et al. 2005; Schernthaner et al. 2004), and HDL-C levels (Betteridge & Vergès 2005; Derosa et al. 2006; Matthews et al. 2005; Schernthaner et al. 2004 [many of these studies also found increases in LDL-C levels]). Similar results were also reported in an early meta-analysis (Chiquette et al. 2004). Because all of these factors are contributors to, or indicators of, cardiovascular health, TZDs were initially thought to exert positive cardiovascular effects within a patient population that experiences prevalent cardiovascular complications resulting from T2DM.

Most of the early trials focused on pioglitazone (**Table 1**) reporting that it provided similar cardiovascular outcomes to other oral hypoglycemic agents (Belcher et al. 2004; Belcher et al. 2005; Matthews et al. 2005; Schernthaner et al. 2004), or that it exerted protective effects with respect to cardiovascular events and outcomes including mortality. For example, Dormandy et al. (2005) found a decrease in a composite of all-cause mortality, non-fatal MI, and stroke (HR: 0.84, 95% CI: 0.72–0.98,  $P = 0.027$ ) for pioglitazone in the double-blind PROactive trial investigating the effects of pioglitazone in patients with or without a previous history of stroke. In a sub-analysis of the same trial, Wilcox et al. (2007) found a beneficial trend for a composite of all-cause mortality, nonfatal MI, acute coronary syndrome, cardiac intervention, stroke, major leg amputation, bypass surgery, and leg revascularization (HR: 0.78, 95% CI: 0.60-1.02,  $P = 0.0670$ ), as well as for a composite of all-cause mortality, nonfatal MI, and nonfatal stroke for pioglitazone compared to placebo (HR: 0.78, 95% CI: 0.58-1.06,  $P = 0.1095$ ). Pioglitazone was

found to reduce fatal or nonfatal stroke (HR: 0.53, 95% CI: 0.34-0.85,  $P = 0.0085$ ) and cardiovascular death, nonfatal MI, and nonfatal stroke (HR 0.72, 95% CI 0.52-1.00,  $P = 0.0467$ ). These results seemed to suggest that the overall safety and tolerability of pioglitazone therapy was favourable as no change in safety profile was identified in PROactive. However, it should be noted that CHF was not included in these initial analyses.

Though the pioglitazone trials indicated mostly positive effects, and positive effects have continued to be observed in more recent trials such as the Insulin Resistance Intervention after Stroke (IRIS) trial that reported a lower risk of stroke or MI (HR: 0.76, 95% CI: 0.62-0.93,  $P = 0.007$ ) in patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA who received pioglitazone compared to placebo (Kernan et al. 2016), early spontaneous reports associating TZDs with fluid retention and CHF began to emerge shortly after they were marketed (Benbow et al. 2001) and raised questions about potential drug-specific or class-specific adverse cardiovascular effects. This prompted the US FDA to order a revision of the pioglitazone label in early 2002, followed by revision of the rosiglitazone label in December 2002, to note rare reports of unusually rapid increases in weight and to recommend that such patients be assessed for fluid accumulation, excessive edema, and CHF (Abbas et al. 2012). Some observational studies and reports also began to signal that TZDs may be associated with adverse events including peripheral edema, CHF (Hartung et al. 2005; Kermani and Garg 2003), and early indications of MI, especially for rosiglitazone. For example, a World Health Organization and Uppsala safety surveillance report in 2003 led the manufacturer of rosiglitazone to perform an integrated analysis of its early studies, which suggested that there may be an increased incidence of myocardial ischemia in patients undergoing rosiglitazone therapy (Cobitz et al. 2008). This information was not published until 2008 but was publicly

available as of late 2006 (Home 2011). At the same time, an analysis of the DREAM trial (Gerstein et al. 2006) demonstrated that although rosiglitazone delayed the onset of diabetes in patients with impaired fasting glucose and/or impaired glucose tolerance, a broad composite of adverse cardiovascular outcomes found an (non-significant) increase in events in the rosiglitazone group (HR: 1.37, 95% CI: 0.97-1.94,  $P = 0.08$ ), with 75 events in the rosiglitazone treatment group versus 55 in the placebo group. Though these early safety signals prompted questions regarding the cardiovascular safety of TZDs from some researchers, it wasn't until the publication of a meta-analysis in May 2007 that TZD safety garnered widespread attention (Juurink 2010).

In an analysis of 42 short-term clinical studies (most of which compared rosiglitazone with placebo) that included 14 237 patients with a mean follow-up period of 6 months, Nissen and Wolski (2007a) reported that rosiglitazone was associated with a 43% increased risk of MI ( $P = 0.03$ ) and a 64% higher (but only borderline statistically significant) risk of composite cardiovascular mortality ( $P = 0.06$ ). An accompanying editorial in the same journal issue by Psaty and Furberg (2007a) introducing the article questioned patient treatment choice based only on glycemic control and suggested that although there are elevated risks associated with high levels of A1C, that there must be proof of health benefits (and safety) before accepting that an agent that lowers blood glucose levels is beneficial to individuals with T2DM. According to the authors many physicians did not require proof as a criterion for selecting rosiglitazone as a therapy for their patients, thus putting them at risk. An article in the *New York Times* (Saul 2007) reporting on the Nissen and Wolski (2007a) results and quoting the Psaty and Furberg (2007a) editorial, resulted in widespread attention in the mainstream media by questioning whether the manufacturer of rosiglitazone and the US FDA should have released similar data earlier,

mentioning investigations commencing in Congress, and quoting one of the study authors as saying that ‘tens of thousands of people’ have had an MI as a result of rosiglitazone treatment (Bloomgarden 2007; Saul 2007). This article and the associated publicity prompted a 10% drop in Glaxo Smith Kline (GSK) share prices and launched a number of lawsuits (Bloomgarden 2007). It also launched hundreds of studies and publications, and prompted an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial (further described below).

Although these results cast doubt on the cardiovascular safety of TZDs, the Nissen and Wolski (2007a) study methodology received criticism from several authors. For example, Diamond et al. (2007) stated that the meta-analysis was not based on a comprehensive search of relevant studies, that the included studies were combined on the basis of a lack of statistical homogeneity even though the study designs and assessments of outcomes were significantly variable, that the approach that was used required the exclusion of studies with no events, and that alternative meta-analytic approaches generated lower, non-statistically significant odds ratios. The study was also criticized for including patients who did not have T2DM, such as patients with Alzheimer's disease or psoriasis, and for combining the results of these studies with those investigating effects in pre-diabetic patients or patients with T2DM (Cobitz et al. 2008; Diamond et al. 2007). Other authors echoed these concerns (e.g. Bloomgarden 2007; Gerstein & Yusuf 2007; Kaul & Diamond 2008; Mannucci et al. 2007) and reported weakened associations through their own analyses of the data (e.g. Bracken 2007; Diamond & Kaul 2007); yet others questioned whether there was any value at all in using meta-analyses estimate risk (Cleland & Atkin 2007).

Nissen and Wolski (2007b) defended their study methodology stating that the statistical methodology used (Peto odds ratios) was the optimal approach when there are relatively few events in individual trials, that their choices with respect to combining trials were appropriate, and they disagreed with the Bayesian approaches to meta-analysis that other authors used in their own re-analysis of the data. They also stated that a patient-level analysis performed by the manufacturer of rosiglitazone (GSK 2007a) confirmed the findings, and that after re-analyzing the data using various methods, none of the alternative analyses conclusively adjudicated the association between rosiglitazone and the risk of MI or cardiovascular mortality in particular patient groups. In fact, a meta-analysis conducted by Singh et al. (2007) focusing only on four long-term trials with rosiglitazone among individuals with T2DM in which the cardiovascular events were specifically monitored found a very similar increase in MI to that of Nissen and Wolski (2007a). Rosiglitazone increased the risk of MI by 42% (relative risk [RR]: 1.42, 95% CI: 1.06-1.91) compared with other oral hypoglycemic agents, but the authors did not confirm an increased risk of cardiovascular mortality (RR: 0.90, 95% CI: 0.63-1.26,  $P = 0.53$ ). A case-control study by Lipscombe et al. (2007) also found an increased risk of CHF (RR: 1.60, 95% CI: 1.21-2.10,  $P < 0.001$ ), MI (RR: 1.40, 95% CI: 1.05-1.86,  $P = 0.02$ ), and all-cause mortality (RR: 1.29, 95% CI: 1.02-1.62,  $P = 0.03$ ) for TZD monotherapy in older patients with T2DM with associations primarily with rosiglitazone. By contrast, a meta-analysis of 19 trials (Lincoff et al. 2007) suggested that even though it appeared to increase the risk of CHF, pioglitazone may actually reduce the risk of MI, stroke, or death.

In July 2010, the US FDA determined that despite an earlier panel vote in which advisers agreed that rosiglitazone increased cardiovascular risks, the evidence wasn't sufficiently strong to warrant removal from the market (Associated Press 2010). However, in a subsequent September



2010 announcement, the US FDA (2010a) stated that it would require GSK to convene an independent group of scientists to readjudicate components of RECORD to further investigate the integrity of its findings. RECORD, a noninferiority open-label trial of rosiglitazone in 4447 T2DM patients, was originally a 6-year randomized study of patients with inadequate glycemic control when using metformin or a sulfonylurea alone, who were randomized to add-on rosiglitazone, metformin, or a sulfonylurea with dose titration to a target A1C of less than or equal to 7% (Home et al. 2005). The primary study end point was hospitalization for acute MI, CHF, stroke, unstable angina, transient ischemic attack, unplanned revascularisation, amputation of extremities, or any other definitive cardiovascular reason, or cardiovascular mortality (Home et al. 2005, Home et al. 2007). Interim analysis of the trial (after 3.7 years of follow-up) demonstrated an increased risk of CHF with rosiglitazone (HR: 2.15, 95% CI: 1.30-3.57), but no increase in cardiovascular or all-cause mortality (Home et al. 2007). Subsequent analysis of the trial at 5.5 years of follow-up (mean) also found a similarly increased risk of CHF with rosiglitazone (HR: 2.10, 95% CI: 1.35-3.27), but no statistically significant differences between the rosiglitazone and control groups for MI, stroke, or death (Home et al. 2009). A further analysis of the trial data investigating fatal and non-fatal CHF events and CHF predictors with approximately 25 000 person years of follow-up that was adjudicated by a Clinical Endpoint Committee (Komajda et al. 2010) also observed an increased risk of CHF for patients in the rosiglitazone group that was not associated with increased cardiovascular mortality (though an excess number of CHF deaths were reported) or morbidity. The results of these analyses were, however, deemed inconclusive by many and were in conjunction with the study design and interpretation, heavily criticized. Several authors noted that the study was limited by a lower than anticipated event rate, that there was poor adherence by patients to the study medication, and that

there was an imbalance in the use of other concomitant medications such as statins and thiazides that favored the rosiglitazone-treated group and may have masked true associations with adverse cardiovascular events (Kaul et al. 2010; Psaty & Furberg 2007b).

With the continued controversy surrounding rosiglitazone came the continued publication of conflicting results about the cardiovascular safety of the TZD class. For example, several randomized control trials investigating pioglitazone in high-risk patients with coronary or macrovascular disease (e.g. Abe et al. 2010; Erdmann et al. 2010; Kaku et al. 2009b; Kaneda et al. 2009; Nissen et al. 2008; Scheen et al. 2009a, 2009b) found no clear evidence of adverse cardiovascular events, nor did other trials in diabetics that were not at high risk for cardiovascular complications (e.g. Kaku 2009a). Several trials did, however, report an increased risk of edema (Kaku 2009a; Kaku et al. 2009b; Nissen et al. 2008; Scheen et al. 2009a, 2009b). In contrast, in a trial comparing pioglitazone with glyburide in patients with mild cardiac disease or symptomatic CHF (Giles et al. 2008; Giles et al. 2010), an increased incidence of CHF and hospitalization for CHF was observed in pioglitazone patients after 6 months and 1 year of therapy, respectively, but with no corresponding increase in cardiovascular mortality or worsening cardiac function.

Some observational studies have reported no statistically significant evidence of adverse cardiovascular events (CHF, MI, or associated mortality) for any TZD (e.g. rosiglitazone: Casscells et al. 2008; rosiglitazone or pioglitazone: Bilik et al. 2010a; Dore et al. 2009; Habib et al. 2009); others found weak associations with either drug (pioglitazone: Kasliwal et al. 2008; rosiglitazone: Dormuth et al. 2009a [transient]); and some found statistically significant associations for both drugs (e.g. rosiglitazone: Winkelmayr et al. 2008; rosiglitazone and pioglitazone: Koro et al. 2008; Walker et al. 2008 [compared to metformin]). Other studies found

that risks appeared to be lower for pioglitazone when compared to rosiglitazone. For example, Juurlink et al. (2009) observed a lower risk of death for pioglitazone when compared to rosiglitazone in 40 000 patients aged 66 years or older who received either pioglitazone or rosiglitazone over a 6 year period, but no significant difference in the risk of acute MI for either drug. Shaya et al. (2009) reported an increased risk of MI and stroke for rosiglitazone but not for pioglitazone, Tzoulaki et al. (2009) reported an increased risk of mortality for rosiglitazone compared to pioglitazone, and Ziyadeh et al. (2009) reported an increased risk of MI for rosiglitazone compared to pioglitazone. Graham et al. (2010) observed an increased risk of stroke, CHF, and all-cause mortality, and an increased risk for a composite of acute MI, stroke, CHF, or all-cause mortality for rosiglitazone but not pioglitazone. Though some risks were reported for pioglitazone, most studies seemed to point to rosiglitazone as the riskier TZD drug.

In response to the cardiovascular concerns that continued to be raised, the US FDA (2011a) announced in November 2011 that the use of rosiglitazone would be restricted to patients with T2DM who could not control their diabetes with other medications such as biguanides or sulfonylureas, and that any prescription for rosiglitazone would require a Risk Evaluation and Mitigation Strategy (REMS). Rosiglitazone could not be sold without a prescription from a certified doctor, it was required to be purchased by mail order through specialized pharmacies, and patients were required to be informed of the risks associated with use of the drug (Abbas et al. 2012). In June 2013, the US FDA Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee discussed the readjudicated results of the RECORD study and, in a move counter to that taken in 2011, voted to recommend that the REMS for rosiglitazone be eliminated or modified to lessen restrictions of use (US FDA 2013a). The reasoning stated for this vote was that because the

RECORD trial demonstrated no elevated risk of MI or death in rosiglitazone-treated patients when compared to patients treated with other standard antidiabetes drugs, and because the readjudicated results of RECORD were consistent with the original findings of the trial, and therefore not consistent with the results of the Nissen and Wolski (2007b) meta-analysis, the Committee members were reassured that the original study findings were accurate (US FDA 2013a). It should be noted that while the Committee generally agreed that the readjudication was well conducted, not all members were in agreement with the results or the final decision. Restrictions were subsequently removed in November of 2013 (US FDA 2013b). Although many in the pharmacovigilance community were not in agreement with this re-evaluation (Forbes 2013) or with the final decision (Mitka 2013; New York Times 2013), the US FDA maintained that rosiglitazone-containing drugs do not show an increased cardiovascular risk compared to the standard T2DM medicines metformin and sulfonylureas (US FDA 2013b).

Since June of 2013, there remain questions as to the cardiovascular safety of rosiglitazone and TZDs in general as some, but not all studies (e.g. Bach et al. 2013; Mahaffey et al. 2013; Vallarino et al. 2013) continue to find associations with increased risks of MI (Tannen et al. 2013) and CHF (Roussel et al. 2013 [in patients greater than 80 years of age]), especially for rosiglitazone. Although rosiglitazone continues to be prescribed, current rates have declined to negligible levels (see **Section 4.1**) since restrictions were put in place with physicians switching patients to pioglitazone, or more so to other oral antihyperglycemic treatments with more favourable cardiovascular safety profiles (Hampp et al. 2014), and as new treatments for T2DM have become available. Due to continued controversy regarding TZD safety, and specifically the cardiovascular safety of rosiglitazone, it remains to be seen if prescribing rates increase again for treatment of T2DM.

The mechanism(s) behind the adverse cardiovascular effects seen in some of the TZD studies described above is thought to occur as a result of PPAR $\gamma$  activation. The most commonly reported adverse effects of therapy with both rosiglitazone and pioglitazone have been weight gain, fluid retention and edema (Abbas et al. 2012; Bourg et al. 2012) which can sometimes precipitate or exacerbate heart failure (Bełtowski et al. 2013), especially in conjunction with reductions in haematocrit that have been observed following treatment with TZDs in some studies (Berria et al. 2007; Yang & Soodvilai 2008). In fact, at the time of licensing TZD use was contraindicated for patients with CHF as fluid retention was a well-recognized class effect of PPAR $\gamma$  medications (Nesto et al. 2003). It is estimated that peripheral edema occurs in approximately 5% of patients undergoing TZD mono or combination therapy versus approximately 15% when TZDs are used with insulin (Karalliedde & Buckingham 2007).

The mechanisms behind fluid retention and edema are not completely understood but seem to result at least in part from stimulation of PPARs and fluid retention and weight gain have also been demonstrated in animal models (Guan et al. 2005). Rosiglitazone-treated mice have also shown attenuated activation of genes involved in fatty acid oxidation and lipid uptake in the heart (Son et al. 2007) and interference with fatty acid or glucose metabolism has been demonstrated to lead to cardiac hypertrophy or CHF in rodents (Kurtz et al. 1998; Lehman & Kelly 2002). During heart failure, the heart preferentially switches substrate preference from fatty acids to glucose (Barger & Kelly 1999; Sack et al. 1996) and because gene products downstream of PPAR $\gamma$  are critical in regulation of glucose and lipid metabolism in the heart, PPAR $\gamma$  activation may also induce cardiac hypertrophy by modulating nutrient metabolism, or through intravascular volume expansion (Chang et al. 2014). This is initially compensated by cardiac hypertrophy, but then leads to cardiomyopathy and CHF (Katz 1990). In addition, since

adverse events have been reported more frequently with rosiglitazone, the absence of PPAR $\alpha$  activity observed with rosiglitazone compared to pioglitazone may contribute more significant fluid retention (Boden et al. 2007), though the increased mortality associated with muraglitazar, a dual PPAR $\alpha/\gamma$  agonist (Nissen et al. 2005), may disprove this mechanism (Ajjan & Grant 2008).

### **3.4 Osteological effects**

Patients with T2DM were once thought to be protected from osteoporosis and fractures on account of their increased body weight and increased bone mineral density (BMD), which has been demonstrated in many (Barrett-Connor & Holbrook 1992 [in females only]; Broussard & Magnus 2008; Christensen & Svendsen 1999; van Daele et al. 1995; de Liefde et al. 2005; Dennison et al. 2004 [in females]; Gerdhem et al. 2005; Gupta et al. 2009; Hadzibegovic et al. 2008; Hosoda et al. 2008; Isaia et al. 1999 [femoral]; Johnston et al. 1985; Kao et al. 2003; Lunt et al. 2001; Ma et al. 2012; Meema & Meema 1967; Melton et al. 2008; Oz et al. 2006; Pérez-Castrillón et al. 2004 [in females only]; Rishaug et al. 1995 [in males only]; Sahin et al. 2001; Schwartz et al. 2001; Sert et al. 2003 [femoral]; Shan et al. 2009 [lumbar spine]; Strotmeyer et al. 2004; Hadjidakis et al. 2005; Vestergaard 2007), but not all (Anafroglu et al. 2009; Barrett-Connor & Holbrook 1992 [in males only]; Bridges et al. 2005; Giacca et al. 1988; Gregorio et al. 1994; Ishida et al. 1985; Isaia et al. 1987; Lenchik et al. 2003 [in women only]; Majima et al. 2005; Register et al. 2006; Sert et al. 2003 [non-femoral sites for males and females; lumbar spine in males]; Shan et al. 2009 [hip]; Sosa et al. 1996; Suzuki et al. 2000; Takizawa et al. 2008; Tuominen et al. 1999; Wakasugi et al. 1993; Weinstock et al. 1989; Xu et al. 2007; Zhou et al. 2010) studies. It is now suspected that patients with T2DM are in fact more susceptible to hip (Forsén et al. 1999; Janghorbani et al. 2006; Janghorbani et al. 2007; Nicodemus & Folsom

2001; Vestergaard et al. 2005; Vestergaard 2007), proximal humerus (Keegan et al. 2002; Schwartz et al. 2001), distal (de Liefde et al. 2005; Keegan et al. 2002; Schwartz et al. 2001; Vestergaard et al. 2005), non-traumatic fractures (Strotmeyer et al. 2005), and all non-vertebral fractures combined (Bonds et al. 2006; de Liefde et al. 2005; Schwartz et al. 2001, Schwartz & Sellmeyer 2004), even in patients where BMD is increased. Several hypotheses have been put forward to explain this association including lower muscle mass and decreased strength (Akeroyd et al. 2014; Park et al. 2006; Petit et al. 2010) and other complications associated with long-term T2DM leading to falls, and subjects with established and treated T2DM suffering more from disease-related complications such as poor balance and vision, cardiovascular disease, and peripheral neuropathy which might increase the frequency of falling (Barrett-Connor & Kritiz-Silverstein 1996). A number of studies have also shown that diabetes-related metabolic and endocrine alterations adversely affect bone quantity and/or quality and that these skeletal changes in conjunction with the microvascular complications of diabetes may increase the risk of bone fracture (Adami 2009).

In recent years there has been accumulating evidence from clinical trials that treatment choice for T2DM may affect bone health and that TZD pharmacotherapy may be associated with decreased bone density (Berberoglu et al. 2010; Bilezikian et al. 2013; Bodmer et al. 2009; Borges et al. 2011; Bray et al. 2013; Chakreeyarat et al. 2011; Glinborg et al. 2008; Grey et al. 2007; Harsløf et al. 2011; Li et al. 2010; Schwartz et al. 2006; Yaturu et al. 2007) and increased fracture risk, particularly in women (Dormandy et al. 2009a; Home et al. 2009; Kahn et al. 2006; Kahn et al. 2008; Nissen et al. 2008). The topic first attracted attention following a review of the ADOPT data for adverse events of interest (Kahn et al. 2008). The purpose of ADOPT was to investigate the effect of 4 years of randomly-assigned rosiglitazone treatment versus metformin

or glyburide treatment on glycemic control in newly-diagnosed diabetic patients who hadn't previously been prescribed antihyperglycemic drugs (Kahn et al. 2006). When adverse events in the trial were reviewed, a higher rate of fractures observed in women who were assigned to the rosiglitazone treatment arm warranted a postscript in the 2006 paper describing the increased occurrence of fractures in the upper limbs (22 patients versus 10 in the metformin group and 9 in the glyburide group) and lower limbs (36 patients versus 18 in the metformin group and eight in the glyburide group), but not fractures of the hip or vertebrae. Based on the preliminary ADOPT findings the manufacturer of rosiglitazone released a letter to healthcare providers in February 2007 (GSK 2007b), which was followed by a letter from the manufacturer of pioglitazone in March of the same year reporting that an analysis of its clinical trials database found an increase in fractures in women, but not in men (Takeda Pharmaceuticals North America Inc. 2007). Both letters were released in conjunction with warnings from the US FDA (Hampton 2007a). A subsequent detailed report on the ADOPT findings (Kahn et al. 2008) indicated that though fracture rates did not differ between treatment groups in men (1.16 per 100 patient-years for rosiglitazone, 0.98 per 100 patient-years for metformin, and 1.07 per 100 patient-years with glyburide [HR: 1.18, 95% CI: 0.72-1.96 versus metformin and HR: 1.08, 95% CI: 0.65-1.79 versus glyburide]), in women the incidence was 2.74 per 100 patient-years with rosiglitazone (a cumulative incidence of 15.1% at 5 years) versus 1.54 per 100 patient-years for metformin (7.3% cumulative incidence), and 1.29 per 100 patient-years for glyburide (7.7% cumulative incidence); a doubling in the risk of fractures with rosiglitazone treatment that appeared approximately one year after exposure. Compared to metformin (HR: 1.81, 95% CI: 1.17-2.80) and glyburide (HR: 2.13, 95% CI: 1.30-3.51), fractures were more likely to occur in postmenopausal women treated with rosiglitazone who were greater than 50 years of age.



Since the publication of the ADOPT findings, and the reporting of the pioglitazone manufacturer trials, data from most, but not all, clinical trials have corroborated an increased risk of fracture with rosiglitazone or pioglitazone primarily at peripheral sites (**Table 3**). For example, in the RECORD trial (Home et al. 2009) where patients receiving metformin or sulfonylurea monotherapy were randomly assigned to either add-on rosiglitazone or to a combination of metformin and a sulfonylurea, fracture rates were increased primarily in women assigned to the rosiglitazone group. Over a mean follow-up time of 5.5 years 2.2% of patients reported fractures at any site with rosiglitazone versus 1.6% in the metformin-sulfonylurea group (RR: 1.57, 95% CI: 1.26-1.97,  $p < 0.0001$ ; women: RR: 1.82, 95% CI: 1.37-2.41; men: RR: 1.23, 95% CI: 0.85-1.77;  $p = 0.10$ ). The risk was increased mainly for upper limb (RR: 1.57, 95% CI: 1.12-2.19,  $p = 0.0095$ ) and distal lower limb (RR 2.60, 95% CI: 1.67-4.04,  $p < 0.0001$ ) fractures, and was primarily in women (RR of 1.75 for upper limb and 2.93 for distal lower limb). In a 4-year follow-up of the RECORD study Jones et al. (2015) found that consistent with the main study, rosiglitazone was associated with an increased risk of peripheral bone fractures in women, and most likely in men, but that the combined data did not suggest an increase in fractures that contribute to morbidity such as those of the hip, pelvis, femur, and spine.

For pioglitazone, the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial (Nissen et al. 2008) investigating the effects of 18 months of pioglitazone (15 to 45 mg) or glimepiride (1 to 4 mg) on the progression of coronary atherosclerosis in 543 patients with T2DM reported fractures only in the pioglitazone group. Fractures, primarily at peripheral sites, occurred in 3% of pioglitazone-treated patients (six women and two men; average age of patients in the pioglitazone group was 60 years) compared to none of the glimepiride-treated patients (Nissen et al. 2008) which

**Table 3.** Studies investigating the effects of TZD pharmacotherapy on osteological endpoints.

| Study                                         | Design                                                                 | Duration/<br>Study<br>Period | Patient<br>Population              | Sex        | TZD<br>(dose)                   | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients               | Endpoint/<br>Outcome<br>Measure | Results                                                                              |
|-----------------------------------------------|------------------------------------------------------------------------|------------------------------|------------------------------------|------------|---------------------------------|-----------------------------------|---------------------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------|
| <b>Kahn<br/>et al. (2006)<br/>ADOPT</b>       | Randomized<br>controlled<br>trial, active<br>comparators<br>(MET, GLY) | 4<br>years                   | Recently<br>diagnosed<br>T2DM      | M, F       | ROSI<br>(4mg/d or<br>8mg/d)     | 917                               | 56.3<br>( $\pm$ 10.0SD)                                 | Fracture*                       | $\uparrow$ incidence of<br>limb fractures<br>in women but<br>not in men              |
| <b>Takeda<br/>(2007)</b>                      | Randomized<br>controlled<br>trial, active or<br>placebo<br>comparators | $\leq$ 3.5<br>years          | T2DM                               | M, F       | PIO<br>(NA)                     | 8,100                             | -                                                       | Fracture*                       | $\uparrow$ incidence of<br>limb fractures<br>in women but<br>not in men              |
| <b>Kahn<br/>et al. (2008)<br/>ADOPT</b>       | Randomized<br>controlled<br>trial, active<br>comparators<br>(MET, GLY) | 4<br>years                   | Recently<br>diagnosed with<br>T2DM | M<br><br>F | ROSI<br>(4mg/d or 8<br>mg/d)    | 917                               | 56.4<br>( $\pm$ 9.9 SD)<br><br>56.1<br>( $\pm$ 10.2 SD) | Fracture†                       | $\uparrow$ incidence of<br>limb fractures<br>in women but<br>not in men              |
| <b>Meier<br/>et al. (2008)<br/>GPRD</b>       | Case-control                                                           | $\leq$ 18<br>months          | T2DM                               | M, F       | ROSI<br>(NA)<br><br>PIO<br>(NA) | 47 cases, 119<br>controls         | -                                                       | Fracture                        | $\uparrow$ risk of<br>fractures(hip,<br>humerus<br>and wrist) in<br>men and<br>women |
| <b>Nissen<br/>et al. (2008)<br/>PERISCOPE</b> | Randomized<br>controlled<br>trial, active<br>comparator<br>(GLIM)      | 18<br>months                 | Coronary<br>disease and<br>T2DM    | M, F       | PIO<br>(37 mg $\frac{1}{4}$ )   | 270                               | 60.0<br>( $\pm$ 9.4 SD)                                 | Fracture*                       | $\uparrow$ incidence of<br>fracture                                                  |

**Table 3. Continued**

| Study                                           | Design                                                   | Duration/<br>Study<br>Period        | Patient<br>Population                          | Sex  | TZD<br>(dose)                           | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                      |
|-------------------------------------------------|----------------------------------------------------------|-------------------------------------|------------------------------------------------|------|-----------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dormandy<br/>et al. (2009)<br/>PROactive</b> | Randomized<br>controlled<br>trial, placebo<br>comparator | ≥ 30<br>months                      | High risk with<br>T2DM                         | M, F | PIO (titrated<br>15 mg/d to 45<br>mg/d) | 2,605                             | -                                         | Fracture*                       | ↑ incidence of<br>fractures in<br>women but not<br>in men                                                                                    |
| <b>Dormuth<br/>et al. (2009)</b>                | Prospective<br>cohort                                    | 1998-<br>2007                       | Treatment with<br>a TZD or SUL                 | M, F | Any TZD                                 | 10,476                            | 56<br>(±13 SD)                            | Fracture                        | ↑ risk of<br>peripheral<br>fractures for<br>all TZDs, ↑<br>risk of<br>peripheral<br>fractures in<br>women and<br>men for PIO<br>but not ROSI |
|                                                 |                                                          |                                     |                                                |      | ROSI                                    | 6,880                             | 56<br>(±13 SD)                            |                                 |                                                                                                                                              |
|                                                 |                                                          |                                     |                                                |      | PIO                                     | 3,596                             | 57<br>(±13 SD)                            |                                 |                                                                                                                                              |
| <b>Douglas<br/>et al. (2009)</b>                | Case-series                                              | Baseline<br>until first<br>fracture | TZD-exposed<br>and diagnosis of<br>fracture(s) | M, F | Any TZD<br>(NA)                         | 1,819                             | 62.0<br>(±12.8 SD)                        | Fracture                        | ↑ risk of<br>fracture in<br>both men in<br>women during<br>TZD-exposed<br>periods that<br>increased with<br>duration of<br>treatment         |
|                                                 |                                                          |                                     |                                                |      | ROSI<br>(NA)                            | 1,356                             | 62.2<br>(±13.0 SD)                        |                                 |                                                                                                                                              |
|                                                 |                                                          |                                     |                                                |      | PIO<br>(NA)                             | 389                               | 61.7<br>(±12.3 SD)                        |                                 |                                                                                                                                              |

**Table 3. Continued**

| Study                                    | Design                                                                                                                       | Duration/<br>Study<br>Period | Patient<br>Population                                | Sex  | TZD<br>(dose)                                                                   | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients                                      | Endpoint/<br>Outcome<br>Measure | Results                                                                                               |
|------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------------------------------|------|---------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Home<br/>et al. (2009)<br/>RECORD</b> | Randomized<br>controlled<br>trial, TZD<br>add-on (to<br>MET or SUL)<br>and<br>combination<br>comparator<br>(MET plus<br>SUL) | 5-7<br>years                 | T2DM                                                 | M, F | ROSI<br>(4 mg/d<br>titrated to 8<br>mg any time<br>after 8 weeks<br>of therapy) | 321                               | ROSI-MET<br>57.0<br>( $\pm$ 8.0 SD)<br><br>ROSI-SUL<br>59.8<br>( $\pm$ 8.3 SD) | Fracture*                       | $\uparrow$ incidence of<br>limb fractures<br>in women but<br>not in men                               |
| <b>Jones<br/>et al. (2009)</b>           | Cross-<br>sectional                                                                                                          | 3<br>years                   | T2DM and TZD<br>use; controls<br>with T2DM           | M, F | ROSI<br><br>PIO<br><br>TZD<br>combination                                       | 3,908<br><br>2,589<br><br>965     | 52<br>( $\pm$ 0.1 SE)                                                          | Fracture                        | $\uparrow$ incidence of<br>limb fractures<br>in women but<br>not in men for<br>both ROSI and<br>PIO   |
| <b>Mancini<br/>et al. (2009)</b>         | Cross-<br>sectional                                                                                                          | -                            | T2DM                                                 | M    | ROSI-MET<br>(4-<br>8mg/d/1500-<br>400 mg/d)                                     | 21                                | Median 69<br>(47–77<br>range)                                                  | Vertebral<br>fractures;<br>BMD  | $\uparrow$ prevalence<br>of vertebral<br>fractures (than<br>MET alone),<br>not correlated<br>with BMD |
| <b>Perez<br/>et al. (2009)</b>           | Randomized<br>controlled<br>trial, TZD,<br>add-on (to<br>MET), and<br>active<br>comparator<br>(MET)                          | 24<br>weeks                  | T2DM not<br>currently<br>receiving drug<br>treatment | M, F | PIO (15mg<br>2x/d)<br><br>PIO and<br>MET(15 mg/<br>850 mg 2x/d)                 | 189<br><br>201                    | 54.0<br>( $\pm$ 12.1 SD)<br><br>54.7<br>( $\pm$ 12.2 SD)                       | Fracture*                       | No increased<br>incidence of<br>fracture                                                              |

**Table 3. Continued**

| Study                             | Design                  | Duration/<br>Study<br>Period | Patient<br>Population | Sex  | TZD<br>(dose)                           | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                                                 |
|-----------------------------------|-------------------------|------------------------------|-----------------------|------|-----------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Solomon<br/>et al. (2009)</b>  | Retrospective<br>cohort | 1997-<br>2005                | T2DM                  | M    | ROSI<br>monotherapy                     | 554                               | 77<br>( $\pm$ 7 SD)                       | Fracture                        | $\uparrow$ risk of<br>fracture with<br>any TZD use<br>(compared to<br>MET or SUL<br>alone) in<br>women and<br>men                                                       |
|                                   |                         |                              |                       | F    | (NA)                                    | 1,793                             |                                           |                                 |                                                                                                                                                                         |
|                                   |                         |                              |                       |      | PIO<br>monotherapy<br>(NA)              |                                   |                                           |                                 |                                                                                                                                                                         |
|                                   |                         |                              |                       |      | TRO<br>monotherapy<br>(NA)              |                                   |                                           |                                 |                                                                                                                                                                         |
| <b>Tzoulaki<br/>et al. (2009)</b> | Retrospective<br>cohort | 1990-<br>2005                | T2DM                  | M, F | ROSI                                    | 8,442                             | 65.7<br>( $\pm$ 10.9 SD)                  | Fracture*                       | $\uparrow$ risk of non-<br>hip fracture for<br>ROSI<br>combination<br>therapy<br>(compared to<br>MET alone),<br>no excess risk<br>for PIO (not<br>stratified by<br>sex) |
|                                   |                         |                              |                       |      | ROSI<br>combination                     | 9,640                             | 64.5<br>( $\pm$ 10.8 SD)                  |                                 |                                                                                                                                                                         |
|                                   |                         |                              |                       |      | PIO<br>monotherapy<br>or<br>combination | 3,816                             | 64.8<br>( $\pm$ 10.6 SD)                  |                                 |                                                                                                                                                                         |
| <b>Aubert<br/>et al. (2010)</b>   | Case-control            | 540 days                     | T2DM                  | M, F | ROSI<br>(NA)                            | 69,047<br>(48% ROSI)              | 55.9<br>( $\pm$ 5.3 SD)                   | Fracture                        | $\uparrow$ risk of<br>fracture in<br>both men<br>(greater than<br>50 years of<br>age) and<br>women for<br>ROSI and PIO                                                  |
|                                   |                         |                              |                       |      | PIO<br>(NA)                             |                                   |                                           |                                 |                                                                                                                                                                         |

**Table 3. Continued**

| Study                                     | Design                  | Duration/<br>Study<br>Period                                  | Patient<br>Population                                                             | Sex  | TZD<br>(dose)                                               | Number TZD<br>Exposed<br>Patients                                                                                                                                                      | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                     |
|-------------------------------------------|-------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------------|------|-------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| <b>Bilik<br/>et al. (2010b)<br/>TRIAD</b> | Case-control            | 18<br>months<br>before<br>baseline<br>until first<br>fracture | T2DM                                                                              | M, F | ROSI<br>(NA)<br><br>PIO<br>(NA)                             | 58 cases (13%<br>of patients) in<br>women $\geq$ 50<br>years of age<br><br>5 cases (9% of<br>patients) in<br>women < 50<br>years of age<br><br>39 cases (14%<br>of patients) in<br>men | -                                         | Fracture                        | ↑ risk of<br>fractures in<br>post-<br>menopausal<br>women and in<br>men taking<br>TZDs and loop<br>diuretics                |
| <b>Habib<br/>et al. (2010)</b>            | Retrospective<br>cohort | 12 months<br>before<br>index date<br>until first<br>fracture  | T2DM and at<br>least one<br>prescription for<br>an anti-<br>hyperglycemic<br>drug | M, F | ROSI<br>(NA)<br><br>PIO<br>(NA)<br><br>ROSI and PIO<br>(NA) | 999<br><br>3,170<br><br>342                                                                                                                                                            | 57.4<br>( $\pm$ 12 SD)                    | Fracture                        | ↑ risk of<br>fractures in<br>women, but<br>not men;<br>greatest risk<br>for women ><br>65 years of age                      |
| <b>Hsiao &amp;<br/>Mullins<br/>(2010)</b> | Case-control            | < 30<br>days<br>to > 180<br>days                              | T2DM                                                                              | M, F | Any TZDs<br>(> 90% ROSI<br>4 mg/d and<br>PIO 30 mg/d)       | 1,078<br>(case)<br><br>3,651<br>(control)                                                                                                                                              | 60.7<br>( $\pm$ 6.4 SE)                   | Fracture                        | ↑ risk of<br>fractures in<br>women (all<br>sites; strongest<br>association<br>with vertebral<br>fracture) but<br>not in men |

**Table 3. Continued**

| Study                                 | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                                                    | Sex  | TZD<br>(dose)                          | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients            | Endpoint/<br>Outcome<br>Measure                                         | Results                                                                                     |
|---------------------------------------|-------------------------|------------------------------|--------------------------------------------------------------------------|------|----------------------------------------|-----------------------------------|------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| <b>Kanazawa<br/>et al. (2010)</b>     | Cross-<br>sectional     | -                            | T2DM                                                                     | M    | Any TZD<br>(NA)                        | 31                                | -                                                    | Vertebral<br>fracture;<br>biochemical<br>markers of<br>bone<br>turnover | ↑ risk of<br>vertebral<br>fractures in<br>postmenopaus<br>al women but<br>not in men        |
|                                       |                         |                              |                                                                          | F    |                                        | 20                                |                                                      |                                                                         |                                                                                             |
| <b>Chakreeyarat<br/>et al. (2011)</b> | Case-control            | -                            | Postmenopausal<br>(≥ 1 year) with<br>T2DM                                | F    | ROSI<br>(mean dose<br>4.4 ± 0.4 mg)    | 41                                | 59.3<br>(± 0.9 SE)                                   | Fracture;<br>BMD;<br>vitamin D<br>status                                | ↓ BMD (hip),<br>↑ 25-hydroxy<br>vitamin D                                                   |
|                                       |                         |                              |                                                                          |      | PIO<br>(mean dose<br>23.8 ±<br>1.2 mg) | 11                                |                                                      |                                                                         |                                                                                             |
| <b>Bazelier<br/>et al. (2012)</b>     | Retrospective<br>cohort | 1996-<br>2007                | Antidiabetic<br>drug-exposed<br>vs. no use of<br>antidiabetic<br>drug(s) | M, F | Any TZD<br>(NA)                        | 7,603                             | All diabetic<br>patients:<br>62.6<br>(NA)            | Fracture                                                                | ↑ risk of<br>fracture in<br>women<br>(foot/ankle and<br>tibia/fibula),<br>but not in men    |
| <b>Colhoun<br/>et al. (2012)</b>      | Retrospective<br>cohort | 1999-<br>2008                | T2DM; TZD-<br>exposed vs.<br>use of other<br>antidiabetic<br>drug (s)    | M, F | ROSI<br>(NA)<br><br>PIO<br>(NA)        | 37,479                            | Median 58.3<br>(57.5–65.5<br>interquartile<br>range) | Hip fracture                                                            | ↑ risk of hip<br>fracture in men<br>and women<br>(increased with<br>cumulative<br>exposure) |

**Table 3. Continued**

| Study                              | Design                                            | Duration/<br>Study<br>Period | Patient<br>Population                            | Sex  | TZD<br>(dose)                                            | Number TZD<br>Exposed<br>Patients  | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                               |
|------------------------------------|---------------------------------------------------|------------------------------|--------------------------------------------------|------|----------------------------------------------------------|------------------------------------|-------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------------------------|
| <b>Motola<br/>et al. (2012)</b>    | Case/non-case<br>(non-TZD<br>comparator<br>drugs) | 4<br>years                   | Use of TZDs or<br>other<br>antidiabetic<br>drugs | M, F | TZD class<br>(NA)<br><br>ROSI<br>(NA)<br><br>PIO<br>(NA) | 49,589<br>(drug-reaction<br>pairs) | -                                         | Fracture                        | ↑ incidence of<br>upper and<br>lower limb<br>fractures for<br>all TZDs and<br>pelvic<br>fractures for<br>PIO in women |
| <b>Vallarino<br/>et al. (2013)</b> | Retrospective<br>cohort                           | 10<br>years                  | T2DM; new<br>users of PIO or<br>insulin          | M, F | PIO                                                      | 38,588                             | 58.1<br>(±8.7 SD)                         | Fracture                        | ↓ risk of<br>fracture<br>(compared to<br>insulin group)<br>but not<br>statistically<br>significant                    |

ADOPT: A Diabetes Outcome Progression Trial; BMD: bone mineral density; GLIM: glimepiride; GLY: glyburide; GPRD: UK General Practice Research Database; MET: metformin; PIO: pioglitazone; PROactive: PROspectivePIO Clinical Trial In macroVascular Events; RECORD: ROSI evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes; ROSI: rosiglitazone; SD: standard deviation; SE: standard error; SUL: sulfonylurea; TRIAD: Translating Research into Action for Diabetes; TRO: troglitazone; TZD: thiazolidinedione; T2DM: type 2 diabetes mellitus.

\*Not a pre-specified or primary endpoint of the study.

†Sub-study of a trial with other pre-specified endpoints.

‡Average daily dose.



indicates that these occurrences most likely cannot be attributed to the age and gender of the patients in the pioglitazone group alone (mean age was 59.7 in the glimepiride group and patients were 65.9% male versus 68.9% male in the pioglitazone group). In PROactive (Dormandy et al. 2009a), a randomized, double-blind, placebo-controlled cardiovascular outcomes study in high risk patients with T2DM assigned to receive pioglitazone as an add-on to another antihyperglycemic drug (average follow-up period of 34.5 months), 5.1% of pioglitazone-treated female patients experienced fractures (1.0 per 100 patient-years) compared to 2.5% treated with placebo (0.5 per 100 patient-years). No increase in fracture rates was observed in men treated with pioglitazone (1.7%) compared to placebo (2.1%). Similar to the rosiglitazone findings in ADOPT, the majority of fractures were seen in older women (mean age was approximately 62 years of age), and only after approximately one year of exposure. In PROactive, as in previous analyses, limb fractures were most common, including distal limb fractures, proximal limb fractures, and fractures where the location in the limb was undefined. Not all studies, however, have found increased risks. For example, Perez et al. (2009) saw no increased risk of fractures in T2DM patients not previously taking antihyperglycemic drugs who were prescribed a fixed-dose combination of pioglitazone and metformin versus patients prescribed pioglitazone or metformin alone in a twice-daily regimen over 24 weeks. The early stage of diabetes and lower average age of patients (approximately 54 years in the pioglitazone/metformin and pioglitazone groups) and the short 6 month treatment could however, explain why effects were not observed in this study.

Clinical trials have been very useful in identifying potential risk but they have provided limited information in some key areas. For example, clinical trials, which are relatively small, have not been able to detect a significant increase in risk in men (Adami 2009). Moreover, the trials to date have included only a single TZD and have not provided information regarding

potential differences between rosiglitazone and pioglitazone. Observational studies addressing these issues have been published (**Table 3**); however, their results have been inconsistent. Rosiglitazone and pioglitazone have been associated with comparable risk of fracture in some studies (e.g. Aubert et al. 2010; Douglas et al. 2009; Jones et al. 2009; Meier et al. 2008), whereas others have found that rosiglitazone (e.g. Tzoulaki et al. 2009, - after adjustment for cofounders), or that pioglitazone treatment (e.g. Dormuth et al. 2009b) may be more strongly associated with fractures. Some studies have found fractures associated with TZD treatment primarily in older post-menopausal women (e.g. Bazelier et al. 2012; Habib et al. 2010; Hsiao & Mullins 2010; Jones et al. 2009; Kanazawa et al. 2010; Motola et al. 2012 [pelvis]), others have found comparable risk between the sexes (e.g. Aubert et al. 2010; Bilik et al. 2010b [only in men also taking loop diuretics]; Colhoun et al. 2012; Dormuth et al. 2009b; Douglas et al. 2009; Meier et al. 2008; Motola et al. 2012 [upper and lower limb]; Solomon et al. 2009), and few have investigated or found increased risk in men alone (e.g. Mancini et al. 2009). For example, in a nested case-control analysis of patients with a diagnosis of incident fracture in the UK General Practice Research Database (GRPD) (Meier et al. 2008), a similarly increased fracture risk (predominantly hip and wrist) was observed with rosiglitazone (OR: 2.38, 95% CI: 1.39-4.09) and pioglitazone (OR: 2.59, 95% CI: 0.96-7.01) compared to controls. This association was independent of patient age or sex but increased with TZD dose. Similar results were observed in a study by Douglas et al. (2009), wherein patients who experienced a fracture at a range of sites including the hip, spine, arm, foot, wrist, or hand had an increased risk during periods of exposure to rosiglitazone or pioglitazone compared to unexposed periods (RR: 1.43, 95% CI: 1.25-1.62). Risk of fracture was similar in both men and women and increased with duration of TZD exposure (RR: 2.00, 95% CI: 1.48-2.70 for  $\geq 4$  years of exposure). In a retrospective cohort

study investigating adverse cardiovascular effects and all-cause mortality associated with antihyperglycemic drugs Tzoulaki et al. (2009) found that after adjustment for confounders, rosiglitazone combination therapy was associated with a 53% excess risk of non-hip fractures compared with metformin alone (HR: 1.53, 95% CI: 1.25-1.88), whereas the excess risk associated with pioglitazone was non-significant. Alternatively, Dormuth et al. (2009b) found an increased risk of peripheral fractures with pioglitazone but not rosiglitazone use by males and females, and Motola et al. (2012) found an increased risk of pelvic fractures associated with pioglitazone use in women but not men. In a cross-sectional study specific to male patients, Mancini et al. (2009) found a greater prevalence of vertebral fractures in men exposed to rosiglitazone and metformin in combination (that was not correlated with BMD), however, this was the sole study investigating fracture risk in men alone (others, as will be described, have investigated changes in BMD and biochemical markers of bone turnover).

Several meta-analyses examining TZDs and fracture risk have found an increased risk in women but not men. For example, Loke et al. (2009) analyzed combined data from 10 randomized controlled trials and two observational studies and found that long-term TZD use doubled the risk of fractures among women with T2DM but did not significantly increase risk among men. When the same randomized control trial data was re-analyzed for pioglitazone (six studies) and rosiglitazone (four studies) alone (Toulis et al. 2009), rosiglitazone (OR: 1.64, 95% CI: 1.24–2.17), but not pioglitazone (OR: 1.26, 95% CI: 0.92–1.71) was associated with a significantly increased risk of fractures. Because data on women were only available from one study with rosiglitazone, only the pioglitazone studies (n = 5) could be stratified by sex. An increased fracture risk was observed among women, but was not statistically significant after a sensitivity analysis based on a random-effects model, and no increased fracture risk was

observed in men. In another analysis of 22 randomized controlled trials, Zhu et al. (2014) found a significant increase in fractures in women (OR: 1.94, 95% CI: 1.60-2.35) but not in men (OR: 1.02, 95% CI: 0.83-1.27), and that fracture risk for women was comparable for both rosiglitazone and pioglitazone and was independent of age. In a patient data meta-analysis of three healthcare registries that used the same study design, Bazelier et al. (2013a) found that fracture risk was increased for women who were exposed to TZDs and that when individual data were combined women had a 1.4-fold increased risk of any fracture versus other diabetic drug users (adjusted HR: 1.44, 95% CI: 1.35-1.53). No increased risk was observed in men (adjusted HR: 1.05, 95% CI: 0.96-1.14). Fractures were observed at the radius/ulna, humerus, tibia/fibula, ankle, and foot, but not the hip/femur or vertebrae. In addition, current TZD users with more than 25 TZD prescriptions (ever) had a 1.6-fold increased risk of fracture compared with other antihyperglycemic drug users (HR: 1.59, 95% CI: 1.46-1.74).

The underlying biological mechanism responsible for the TZD-associated bone fractures remains unclear. Bone is a metabolically active tissue composed of several cell types, primarily: osteoblasts that generate new bone, osteoclasts that resorb old bone, and osteocytes, the most abundant cells in bone that are derived from osteoblasts that regulate numerous functions including bone remodeling (Wei & Wan 2011). It is known that PPAR $\gamma$  is expressed in skeletal tissue and some evidence from *in vitro* and *in vivo* studies has demonstrated that activation of PPAR $\gamma$  inhibits bone formation by diverting mesenchymal stem cells from bone to fat formation (Gimble et al. 1996), and may increase bone resorption by stimulating the development of osteoclasts (Chan et al. 2007) and increasing osteocyte apoptosis. PPAR $\gamma$  activation may also indirectly affect the skeletal system by modulating circulating levels of hormones and cytokines that influence bone metabolism (Reid et al. 2006; Wei & Wan 2011). These mechanisms may be

responsible for bone loss (Kumar et al. 2013; Sottile et al. 2004; Syversen et al. 2009) and decreased bone strength (Cusick et al. 2013; Kumar et al. 2013; Lazarenko et al. 2007; Syversen et al. 2009; Stunes et al. 2011) that can increase fracture risk.

Empirical evidence on the mechanism behind TZD-induced fracture risk has been conflicting. For example, some *in vitro* studies have suggested that TZDs may inhibit osteoclastic bone resorption and prevent bone loss (Chan et al. 2007; Hounoki et al. 2008; Okazaki et al. 1999a; Zhao et al. 2014), whereas other studies have demonstrated opposite effects. In rodent cells TZDs have been shown to increase calcium release in bone (ciglitazone and troglitazone but not pioglitazone: Schwab et al. 2005), induce adipogenesis (Cho et al. 2012; Hung et al. 2008) at the expense of osteoblast formation (Cho et al. 2012; Patel et al. 2014), decrease alkaline phosphatase (ALP) activity (Hung et al. 2008) which is involved in bone formation, and induce osteocyte apoptosis in a dose-dependent manner (Mabilleau et al. 2010). Apoptotic osteocytes have been shown to express higher levels of sclerostin, a potent bone formation inhibitor (Mabilleau et al. 2010). Rosiglitazone treatment has also been demonstrated to suppress elements of the insulin-like growth factor regulatory system in pre-osteoblasts which plays a role in bone growth and density (Lecka-Czernik et al. 2007). In human cell models, Benvenuti et al. (2007) demonstrated that rosiglitazone counteracts osteoblastogenesis and shifts differentiation of human bone marrow-derived mesenchymal stem cells towards adipocytes, effects that may be attenuated by exposure to androgens or estrogen (Benvenuti et al. 2012), whereas Beck et al. (2013) found that exposure to rosiglitazone or pioglitazone enhanced adipogenesis but did not alter osteoblast differentiation or function. Conversely, Bruedigam et al. (2010) found that rosiglitazone caused acceleration of osteoblast differentiation, without

preferential differentiation into adipocytes, followed by an increased accumulation of reactive oxygen species and apoptosis.

In rats reduced bone formation (Sardone et al. 2011), increased marrow adiposity (Cusick et al. 2013; Sardone et al. 2011), excess bone resorption (Kumar et al. 2013; Sardone et al. 2011), and lower whole body and femoral BMD (Cusick et al. 2013) have been demonstrated in ovariectomized animals exposed to rosiglitazone. Similar findings have been observed in ovariectomized rats exposed to pioglitazone where animals have shown lower whole body and femoral BMD (Cusick et al. 2013; Stunes et al. 2011), impaired bone quality (Stunes et al. 2011), and greater bone marrow adiposity in the lumbar vertebrae (Cusick et al. 2013). In intact rats, rosiglitazone has been demonstrated to down-regulate the serum osteoblastic marker ALP and decrease tibial BMD in males (Lin et al. 2007), though it was not found to affect bone resorption neither in the same study nor in a study by Sottile et al. (2004). In intact female rats exposed to pioglitazone, Syversen et al. (2009) found significantly lower whole body BMD and bone mineral content (BMC), lower femoral BMD, and increases in fat mass. Conversely, Tsirella et al. (2012) found that pioglitazone administration had no impact on bone formation and resorption markers levels, nor did it modify BMD in diabetic or non-diabetic rats.

Mice treated with rosiglitazone have also demonstrated decreases in bone mass (Broulik et al. 2011; Lazarenko et al. 2007) and strength (Lazarenko et al. 2007), including decreased trabecular bone volume (Sorocéanu et al. 2004; Wang et al. 2012a), decreased BMD (Rzonca et al. 2004; Sorocéanu et al. 2004), decreased bone regeneration, and increased fat mass (Liu et al. 2012; Liu et al. 2013). Similar findings have been observed in mice treated with pioglitazone with reported increases in body weight (including fat mass) and reductions of the bone formation marker osteocalcin in obese animals (Henrikson et al. 2009), though some studies have found no

adverse effects on bone loss in mice with pioglitazone (Wang et al. 2012a) or troglitazone (Tornvig et al. 2001).

In humans, several randomized clinical trials (RCTs) have explored measures of bone strength and related biomarkers (see **Supplementary Appendix 3, Table S3**). For example, changes in circulating biomarkers for osteoclast and osteoblast activity in a subset of the ADOPT population suggest that changes in bone resorption may have been partly responsible for the increased fracture risk observed in women (Zinman et al. 2010). In a sub-study of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial (Schwartz et al. 2013), a randomized, multicenter, double two by two factorial design study involving 10 251 middle-aged and older participants with T2DM who are at high risk for CVD, peripheral quantitative computed tomographic scans of the radius and tibia 2 years after randomization on 73 participants were examined. TZD use and A1C levels were measured every 4 months during the trial: 52 participants in the analysis used rosiglitazone, three of which also used pioglitazone. In women, but not men, each additional year of TZD use was associated with an 11% lower polar strength strain index at the radius ( $P = 0.04$ ) and tibia ( $P = 0.002$ ) in models adjusted for A1C levels. TZD use was also associated with a 33% lower total BMC, cortical BMC, and cortical bone area of the radius, 33% lower total bone area and periosteal diameter of the tibia, and 66% lower total bone area, periosteal diameter, and section modulus of the tibia. In a randomized, double-blind study in postmenopausal women with T2DM given rosiglitazone or metformin for a 52-week double-blind phase followed by a 24-week open label metformin phase, rosiglitazone was associated with a reduction in femoral neck BMD (-1.47%) from baseline to week 52; no further loss occurred during the open-label phase of treatment (Bilezikian et al. 2013). A decrease in BMD also occurred at the total hip during rosiglitazone or metformin treatment at 52 weeks (-

1.62 and -0.72%, respectively) but rosiglitazone-associated loss was attenuated after switching to metformin and was similar between treatment groups at the end of the open-label phase. From baseline to week 52 the bone turnover markers C-terminal crosslinking telopeptide of type I collagen (CTX) and procollagen type I N-terminal propeptide (P1NP) significantly increased with rosiglitazone compared with metformin, but decreased significantly during the open-label phase. Other trials have also found decreases in BMD (Borges et al. 2011; Bray et al. 2013; Glinborg et al. 2008; Harsløf et al. 2011) and BMC (Bray et al. 2013), decreases in P1NP (Grey et al. 2007; Zinman et al. 2010) and the bone formation markers osteocalcin (Berberoglu et al. 2010; Grey et al. 2007) and ALP (Berberoglu et al. 2007; Berberoglu et al. 2010; Glinborg et al. 2008; Okazaki et al. 1999b; Zinman et al. 2010), increases in CTX (Gruntmanis et al. 2010; Harsløf et al. 2011; van Lierop et al. 2012; Zinman et al. 2010) and the bone formation marker sclerosin (van Lierop et al. 2012), and increases in osteoclast precursor cells. It should be noted however that some trials have found no effect on biochemical markers of bone turnover or BMD (e.g. Bone et al. 2013; Glinborg et al. 2008 - osteocalcin; Grey et al. 2014).

Observational studies have also reported that TZD treatment increases bone loss and decreases bone strength in women (Chakreeyarat et al. 2011; Li et al. 2010; Schwartz et al. 2006), but because most studies have focused on older patients, particularly postmenopausal women, it is still unclear how the risk of fracture associated with TZDs presumably resulting from changes in bone turnover leading to bone loss (that is more common among postmenopausal women) extends to men. Observational studies reporting increased bone loss and decreased bone strength in women have not found the same effects in men (Li et al. 2010; Schwartz et al. 2006), whereas other studies have shown that men are also at risk (Yaturu et al. 2007). For example, in a retrospective study of BMD values over 4 years, Yaturu et al. (2007)



found that older men (mean age of 70 years) undergoing rosiglitazone therapy experienced significant bone loss at the hip and lumbar spine compared to men not on TZD therapy. Mancini et al. (2009) found no correlation between rosiglitazone-metformin combination therapy and reduced BMD in men (median age of 69 years) in a cross-sectional study; however, an increased prevalence of vertebral fractures was observed compared to metformin alone. It is also unclear how the risk of fracture extends to younger patients as most studies, both clinical trials and observational studies, have focussed on older patients and primarily postmenopausal women. In a single study exploring the effects of pioglitazone treatment on BMD and bone turnover markers in young (median age 32) obese premenopausal women with polycystic ovarian disease and healthy controls (age and weight-matched), Glinborg et al (2008) found that pioglitazone treatment was followed by decreased lumbar and hip BMD and decreased ALP levels and parathyroid hormone levels, though no significant changes were observed in 25-hydroxyvitamin D, CTX, osteocalcin, or sex hormone levels or body composition. It is unclear if similar effects would be observed in younger female or male diabetic patients (though it should be noted that TZDs are more often prescribed to older patients with more advanced T2DM).

Based on the results of studies to date it would be difficult to discount the reported associations of TZD treatment with bone fractures, especially peripheral fractures, or changes in BMD and biochemical markers of bone turnover. Though associations with fracture risk in men and younger patients remain unclear, current treatment guidelines recommend that TZDs should be avoided in patients with fracture risk factors (ADA 2014).

### 3.5 Carcinogenic effects

T2DM has been associated with an increased risk of several cancers including liver, pancreatic, gastric, endometrial, ovarian, renal, colon, breast, and bladder cancers, as well as increased cancer mortality from all combined cancers in several studies (Bosetti et al. 2012; Campbell et al. 2012; Gallagher & LeRoith 2013; Giovannucci et al. 2010; Nicolucci 2010; Renehan et al. 2010; Vigneri 2009; also refer to **Supplementary Appendix 4** and **Table S4**). However, it should be noted that an association between T2DM and increased cancer risk is not uniformly accepted or elucidated given the complex relationships between diabetes, cancer, and other related factors such as obesity and antidiabetic therapy (Klil-Drori et al. 2016). Several mechanisms have been proposed for these potential associations including hyperinsulinemia leading to stimulation of insulin receptors on cancer cells promoting cell division and growth (Johnson & Bowker 2011; Pollack 2008), increases in levels of IGF-1, which has been detected in several cancers (Giovannucci et al. 2010), hyperglycemia (Gallagher & LeRoith 2013), dyslipidemia (Borena et al. 2011), increased estrogen levels, increased adipokines (Vona-Davis & Rose 2009), and increased release of inflammatory cytokines from adipose tissue such as TNF- $\alpha$ , IL-1, and IL-6 (Allavena et al. 2008; Rose & Vona-Davis 2012). Antihyperglycemic drugs have also been shown to modify associations with cancer in Type 2 diabetics with reports of both increased and decreased cancer risks occurring with pharmacotherapy (Giovannucci et al. 2010).

In recent years, increased attention has focused on potential associations between TZDs and tumor development, most notably because of studies finding associations between pioglitazone therapy and bladder cancer (**Table 4**), but also because of the decreased risks of other cancers observed in some, but not all studies (refer to **Supplementary Appendix 4** and

**Table 4.** Studies investigating associations between TZD pharmacotherapy and bladder cancer.

| Study                                           | Design                                                    | Duration/<br>Study<br>Period    | Patient<br>Population                                                                                            | Sex  | TZD<br>(dose)                                 | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                              |
|-------------------------------------------------|-----------------------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dormandy<br/>et al. (2005)<br/>PROactive</b> | Randomized<br>controlled<br>trial, placebo<br>comparator  | 34.5<br>months<br>(average)     | T2DM,<br>evidence of<br>macrovascular<br>disease                                                                 | M, F | PIO<br>(titrated from<br>15 mg to 45<br>mg/d) | 2,605                             | -                                         | Bladder<br>cancer*              | 14 cases in the<br>PIO group vs.<br>6 in the<br>placebo group<br>(6 and 3 cases,<br>respectively,<br>after<br>exclusions)            |
| <b>Dormandy<br/>et al. (2009)<br/>PROactive</b> | Randomized<br>controlled<br>trial, placebo<br>comparator† | ≥ 30<br>months                  | T2DM,<br>evidence of<br>macrovascular<br>disease                                                                 | M, F | PIO<br>(titrated from<br>15 mg to 45<br>mg/d) | 2,605                             | -                                         | Cancer*                         | Double the<br>number of<br>patients with<br>bladder cancer<br>in the PIO<br>group but<br>likely not<br>significant.                  |
| <b>Lewis<br/>et al. (2011)‡</b>                 | Longitudinal<br>cohort study                              | 1997 –<br>2002;<br>3.3<br>years | T2DM                                                                                                             | M, F | PIO<br>(1 - > 28,000<br>cumulative<br>dose)   | 30,173                            | -                                         | Bladder<br>cancer               | ↑ risk with ><br>24 months<br>exposure                                                                                               |
| <b>Piccinni<br/>et al. (2011)</b>               | Case/non-case                                             | 2004<br>-2009                   | Reports<br>associated with<br>antidiabetic<br>drug use in the<br>US FDA<br>Adverse Events<br>Reporting<br>System | M, F | PIO<br>(NA)                                   | 31 cases                          | 70<br>(range<br>53-84)                    | Bladder<br>cancer               | ↑ risk; greater<br>risk in older<br>men;<br>preliminary<br>data indicate a<br>significant risk<br>with > 24<br>months of<br>exposure |

**Table 4. Continued**

| Study                            | Design                                                                 | Duration/<br>Study<br>Period                                    | Patient<br>Population                                                                                                                                      | Sex  | TZD<br>(dose)                                                                              | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                          |
|----------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| <b>Tseng<br/>(2011)</b>          | Prospective<br>cohort                                                  | 2003<br>-2005                                                   | A random<br>sample of<br>1,000,000<br>individuals<br>covered<br>by Taiwanese<br>National Health<br>Insurance;<br>patients with<br>T2DM and<br>without T2DM | M, F | PIO<br>(NA)                                                                                | 422                               | -                                         | Bladder<br>cancer               | No statistically<br>significant risk                                                                                             |
| <b>Azoulay<br/>et al. (2012)</b> | Retrospective<br>cohort using a<br>nested case-<br>control<br>analysis | 1988<br>-2009                                                   | T2DM, newly<br>treated with an<br>OHA                                                                                                                      |      | PIO<br>(cumulative<br>doses of ≤<br>10,500 mg,<br>10,501-28,000<br>mg, and ><br>28,000 mg) | 19 (cases)<br>191 (controls)      | Total<br>cohort 64.1<br>(± 12.0<br>SD)    | Bladder<br>cancer               | ↑ rate; highest<br>in patients<br>exposed > 24<br>months and<br>patients with a<br>cumulative<br>dosage ><br>28,000 mg           |
|                                  |                                                                        |                                                                 |                                                                                                                                                            |      | ROSI<br>(NA)                                                                               | 36 (cases)<br>596 (controls)      |                                           |                                 |                                                                                                                                  |
|                                  |                                                                        |                                                                 |                                                                                                                                                            |      | Ever use of<br>PIO or ROSI<br>(NA)                                                         | 2 (cases)<br>56 (controls)        |                                           |                                 |                                                                                                                                  |
| <b>Chang<br/>et al. (2012)</b>   | Case-control                                                           | January<br>2000-<br>December<br>2000;<br>7.9 years<br>follow-up | T2DM                                                                                                                                                       | M, F | PIO<br>(NA)<br><br>ROSI<br>(NA)                                                            | -                                 | -                                         | Bladder<br>cancer*              | No statistically<br>significant risk<br>with TZDs; an<br>association<br>with ≥ 3 years<br>of PIO use<br>could not be<br>excluded |

**Table 4. Continued**

| Study                              | Design                        | Duration/<br>Study<br>Period | Patient<br>Population                                                                                                                 | Sex  | TZD<br>(dose)                                           | Number TZD<br>Exposed<br>Patients                                         | Mean Age<br>of TZD<br>Exposed<br>Patients                                                                            | Endpoint/<br>Outcome<br>Measure | Results                                                                                             |
|------------------------------------|-------------------------------|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------|---------------------------------------------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------------------------------------|
| <b>Colmers<br/>et al. (2012)</b>   | Meta-analysis                 | Up to<br>March<br>2012       | 4 RCTs, 5<br>cohort studies<br>and 1 case-<br>control study                                                                           |      | All TZDs<br>(NA)<br><br>PIO<br>(NA)<br><br>ROSI<br>(NA) | All patients<br>across studies<br>2,657,365 (not<br>only TZD-<br>exposed) | -                                                                                                                    | Bladder<br>cancer               | ↑ risk in<br>pooled cohort<br>studies only                                                          |
| <b>Mamtani<br/>et al. (2012)</b>   | Retrospective<br>cohort study | 2000 -<br>2010               | T2DM; patients<br>who initiated<br>treatment with a<br>TZD or a SUL                                                                   | M, F | TZDs<br>(NA)<br><br>PIO<br>(NA)                         | 18,459<br><br>10,900                                                      | Median<br>60<br>(inter-<br>quartile<br>range<br>51–69)<br><br>Median<br>62<br>(inter-<br>quartile<br>range<br>53–71) | Bladder<br>cancer               | ↑ risk with ≥ 5<br>years<br>exposure; no<br>difference<br>between PIO<br>or ROSI                    |
| <b>Neumann<br/>et al. (2012) ¶</b> | Prospective<br>cohort         | Up to 42<br>months           | Patients who<br>filled a<br>prescription for<br>an anti-<br>hyperglycemic<br>drug in 2006; at<br>least two<br>prescriptions of<br>PIO | M, F | PIO<br>(NA)                                             | 155,535                                                                   | 40-79<br>years<br>(range)                                                                                            | Bladder<br>cancer               | ↑ risk that<br>increased with<br>higher<br>cumulative<br>dose and<br>longer duration<br>of exposure |

**Table 4. Continued**

| Study                                 | Design                                           | Duration/<br>Study<br>Period | Patient<br>Population                                                                              | Sex    | TZD<br>(dose)                | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                            |
|---------------------------------------|--------------------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------|--------|------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| <b>Song<br/>et al. (2012)§</b>        | Retrospective,<br>matched case-<br>control study | 2005-<br>2011                | Cases of bladder<br>cancer in<br>patients with<br>T2DM; T2DM<br>controls without<br>bladder cancer | M, F   | PIO<br>(NA)                  | 21 cases                          | All cases<br>69.4<br>(± 9.9 SD)           | Bladder<br>cancer               | No statistically<br>significant risk                                                                                               |
| <b>Tseng<br/>(2012)</b>               | Retrospective<br>cohort                          | 2006-<br>2009                | T2DM                                                                                               | M, F   | PIO<br>(NA)                  | 10 cases                          | -                                         | Bladder<br>cancer               | No statistically<br>significant risk<br>though in users<br>of PIO though<br>all events<br>occurred<br>within < 24<br>months of use |
| <b>Unnikrishnan<br/>et al. (2012)</b> | Case reports                                     | -                            | Case reports in<br>Indian patients                                                                 | M<br>F | PIO<br>(range<br>15-30 mg/d) | 7<br>1                            | 43-76<br>(range)                          | Bladder<br>cancer               | Patients in the<br>case reports<br>had taken PIO<br>from 2-9<br>years; 1 male<br>patient died<br>after<br>malignancy<br>spread     |
| <b>Wei<br/>et al. (2012)</b>          | Propensity<br>score matched<br>cohort            | 2001<br>-2010                | T2DM, ≥ 40<br>years,                                                                               | M, F   | PIO<br>(NA)                  | 23 548                            | Main<br>cohort:<br>62.9<br>(± 11.1<br>SD) | Bladder<br>cancer               | No statistically<br>significant risk                                                                                               |

**Table 4. Continued**

| Study                              | Design                  | Duration/<br>Study<br>Period          | Patient<br>Population                                                                                  | Sex  | TZD<br>(dose)                | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure                                                                  | Results                                                                                                          |
|------------------------------------|-------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------|------|------------------------------|-----------------------------------|-------------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| <b>Zhu<br/>et al. (2012)</b>       | Meta-analysis           | Up to<br>January<br>20, 2012          | 5 studies: 1<br>RCT, 1<br>longitudinal<br>cohort, 1 case-<br>control, 2<br>population-<br>based cohort | M, F | PIO<br>(NA)                  | -                                 | -                                         | Bladder<br>cancer                                                                                | ↑ risk;<br>significant<br>with > 12<br>months of<br>therapy and<br>higher<br>cumulative<br>dose                  |
| <b>Bazelier<br/>et al. (2013)</b>  | Retrospective<br>cohort | 1996-<br>2007                         | T2DM                                                                                                   | M, F | TZDs<br>(NA)                 | All users of<br>OHAs<br>179,056   | -                                         | Bladder<br>cancer                                                                                | Similar risk<br>between users<br>of TZDs and<br>other OHAs                                                       |
| <b>Bosetti<br/>et al. (2013)  </b> | Meta-analysis           | Up to June<br>30, 2012                | 3 case-control<br>studies, 14<br>cohort studies                                                        | M, F | PIO (NA)<br><br>ROSI<br>(NA) | -                                 | -                                         | Bladder<br>cancer (also<br>colorectal,<br>liver,<br>pancreatic,<br>lung, breast<br>and prostate) | Modest ↑ risk<br>with PIO but<br>not ROSI;<br>higher for<br>longer duration<br>and greater<br>cumulative<br>dose |
| <b>Ferwana<br/>et al. (2013)</b>   | Meta-analysis           | 44<br>months<br>(median<br>follow-up) | 1 RCT, 2<br>prospective<br>cohort, 2<br>retrospective<br>cohort, 1 nested<br>case-control              | M, F | PIO<br>(NA)                  | -                                 | -                                         | Bladder<br>cancer                                                                                | Slight ↑ risk                                                                                                    |
| <b>Fujimoto<br/>et al. (2013)</b>  | Retrospective<br>cohort | 2000-2011                             | T2DM                                                                                                   | M, F | PIO<br>(NA)                  | 663                               | -                                         | Bladder<br>cancer                                                                                | ↑ prevalence                                                                                                     |

Table 4. *Continued*

| Study                                          | Design                                                                                                         | Duration/<br>Study<br>Period                                                                            | Patient<br>Population                                       | Sex  | TZD<br>(dose)                                                                                                                      | Number TZD<br>Exposed<br>Patients                            | Mean Age<br>of TZD<br>Exposed<br>Patients                                               | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                                  |
|------------------------------------------------|----------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Hsiao<br/>et al. (2013)</b>                 | Nested case-<br>control                                                                                        | 1997-<br>2008                                                                                           | T2DM;                                                       | M, F | PIO<br>(NA)<br><br>ROSI<br>(NA)                                                                                                    | 153 cases<br>523 controls<br><br>346 cases<br>1,585 controls | Cases<br>66.29<br>( $\pm$ 10.28<br>SD)<br><br>Controls<br>66.28<br>( $\pm$ 10.28<br>SD) | Bladder<br>cancer               | $\uparrow$ risk for both<br>PIO and ROSI;<br>risk increased<br>with increased<br>duration of<br>exposure<br>(highest odds<br>in users $\geq$ 2<br>years) |
| <b>Tseng<br/>(2013a)</b>                       | Retrospective<br>cohort                                                                                        | 2006<br>-2009                                                                                           | T2DM                                                        | M, F | ROSI<br>(NA)                                                                                                                       | 102,926 cases of<br>ever-users                               | -                                                                                       | Bladder<br>cancer               | No statistically<br>significant risk                                                                                                                     |
| <b>Vallarino<br/>et al. (2013)</b>             | Retrospective<br>cohort                                                                                        | 2000-<br>2010;<br>2.2 years<br>(mean<br>follow-up<br>for PIO)                                           | T2DM, $\geq$ 45<br>years, new users<br>of PIO or<br>insulin | M, F | PIO<br>(NA)                                                                                                                        | 38,588                                                       | 58.1<br>( $\pm$ 8.7 SD)                                                                 | Cancer                          | Non-<br>statistically<br>significant $\downarrow$<br>risk compared<br>to insulin                                                                         |
| <b>Balaji<br/>et al. (2014)</b>                | Retrospective<br>cohort                                                                                        | -                                                                                                       | Cancer patients<br>with and<br>without T2DM                 | M, F | PIO<br>(NA)                                                                                                                        | 1 case                                                       | -                                                                                       | Bladder<br>cancer               | No statistically<br>significant risk                                                                                                                     |
| <b>Erdmann<br/>et al. (2014)<br/>PROactive</b> | Randomized<br>controlled<br>trial, placebo<br>comparator,<br>add-on<br>therapy (to<br>MET or SUL)<br>$\dagger$ | 5.8 years<br>(mean);<br>8.7 years<br>(mean<br>combined<br>double-<br>blind and<br>follow-up<br>periods) | T2DM,<br>evidence of<br>macrovascular<br>disease            | M, F | Follow-up<br>from PIO<br>(titrated from<br>15 to 45 mg/d)<br>in original<br>trial; patients<br>may have<br>received PIO<br>or ROSI | 3,599 follow-up<br>patients (1,820<br>previously on<br>PIO)  | -                                                                                       | Bladder<br>cancer*              | No statistically<br>significant risk                                                                                                                     |



**Table 4. Continued**

| Study                           | Design                        | Duration/<br>Study<br>Period | Patient<br>Population                                                                                                                                  | Sex  | TZD<br>(dose)                   | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                            |
|---------------------------------|-------------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|------|---------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------|
| <b>He<br/>et al. (2014)</b>     | Meta-analysis                 | Up to<br>July 30,<br>2012    | 9 datasets from<br>10 studies; 1<br>RCT, 4 cohort<br>studies, 3 case-<br>control studies,<br>1 case/non-case<br>study, 1<br>population-<br>based study | M, F | PIO<br>(NA)                     | 2,596,856                         | -                                         | Bladder<br>cancer               | ↑ risk in men<br>but not in<br>women; risk<br>increased with<br>cumulative<br>dose and<br>duration |
| <b>Jin<br/>et al. (2014)</b>    | Retrospective<br>cohort study | 2005-<br>2011                | T2DM                                                                                                                                                   | M, F | PIO                             | 11,240                            | 62.9<br>(±11.7 SD)                        | Bladder<br>cancer               | ↑ risk with > 6<br>months<br>exposure                                                              |
| <b>Kuo<br/>et al. (2014)</b>    | Nested case-<br>control       | 2002<br>-2009                | Newly<br>diagnosed with<br>T2DM; cases:<br>diagnosis of<br>bladder cancer                                                                              | M, F | PIO<br>(NA)                     | 15 cases                          | -                                         | Bladder<br>cancer               | No statistically<br>significant risk                                                               |
| <b>Lee<br/>et al. (2014)</b>    | Retrospective<br>cohort       | 2003-<br>2009                | T2DM                                                                                                                                                   | M, F | PIO<br>(NA)                     | 12 cases                          | -                                         | Bladder<br>cancer               | No statistically<br>significant risk                                                               |
| <b>Monami<br/>et al. (2014)</b> | Meta-analysis                 | Up to<br>August 1,<br>2011   | 22 RCTs<br>reporting at least<br>one cancer                                                                                                            | M, F | PIO<br>(NA)<br><br>ROSI<br>(NA) | 3,710<br><br>9,487                | -                                         | Cancer                          | Non-<br>statistically<br>significant ↑<br>risk with PIO<br>but not ROSI                            |

**Table 4. Continued**

| Study                           | Design                                               | Duration/<br>Study<br>Period                                                                                                                                         | Patient<br>Population                                                                                           | Sex  | TZD<br>(dose)                                                                          | Number TZD<br>Exposed<br>Patients                  | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure              | Results                                                                          |
|---------------------------------|------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|------|----------------------------------------------------------------------------------------|----------------------------------------------------|-------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------|
| <b>Gupta<br/>et al. (2015)</b>  | Retrospective<br>cohort                              | NA; 77%<br>of patients<br>were on<br>PIO<br>therapy for<br>> 2 years                                                                                                 | T2DM                                                                                                            | M, F | PIO<br>(mean dose<br>22,323 mg [2,<br>737-131,400<br>range])                           | 1,111                                              | 53.89<br>(±10.82<br>SD)                   | Bladder<br>cancer                            | No bladder<br>cancer was<br>observed in<br>ever users of<br>PIO or non-<br>users |
| <b>Lewis<br/>et al. (2015)</b>  | Prospective<br>cohort and<br>nested case-<br>control | Until<br>December<br>31, 2012<br>(cohort<br>study);<br>October 1,<br>2002 to<br>March 23,<br>2012<br>(case-<br>control)                                              | T2DM; ≥ 40<br>years of age                                                                                      | M, F | PIO<br>(median<br>cumulative<br>dose in cohort<br>24,000 mg<br>[450-156,000<br>range]) | 34,181 (cohort)<br><br>91 cases (case-<br>control) | -                                         | Bladder<br>cancer and<br>10 other<br>cancers | No statistically<br>significant risk<br>in either<br>studies                     |
| <b>Korhonen<br/>et al. 2016</b> | Retrospective<br>cohort                              | Until<br>December<br>31, 2010<br>(portion of<br>UK<br>dataset) or<br>June 30,<br>2011<br>(remainder<br>of UK<br>dataset and<br>other<br>European<br>data<br>sources) | T2DM; ≥ 40<br>years of age;<br>initiated or<br>switched to PIO<br>treatment or<br>another diabetic<br>treatment | M, F | PIO<br>(categories of<br>≤14,000 mg,<br>14,001-<br>40,000 mg,<br>and >40 000<br>mg)    | 56,337                                             | 63.24<br>(±10.86<br>SD)                   | Bladder<br>cancer                            | No statistically<br>significant risk                                             |

**Table 4. Continued**

| Study                            | Design                  | Duration/<br>Study<br>Period | Patient<br>Population                                                                                                                                                                                  | Sex  | TZD<br>(dose)                                                                                                   | Number TZD<br>Exposed<br>Patients | Mean Age<br>of TZD<br>Exposed<br>Patients | Endpoint/<br>Outcome<br>Measure | Results                                                                                                                                |
|----------------------------------|-------------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| <b>Tuccori<br/>et al. (2016)</b> | Retrospective<br>cohort | 2000-<br>2013                | T2DM; ≥ 40<br>years of age;<br>first ever<br>prescription for<br>a non-insulin<br>antidiabetic<br>drug (base<br>cohort) who<br>then<br>initiated a new<br>antidiabetic<br>drug class<br>(study cohort) | M, F | PIO<br>(categories of<br>≤10,500 mg,<br>10,501-<br>28,000 mg,<br>and >28 000<br>mg in<br>secondary<br>analysis) | 921                               | 64.6<br>(±10.6<br>SD)                     | Bladder<br>cancer               | ↑ risk with<br>PIO; risk<br>increased with<br>cumulative<br>dose and<br>duration; no<br>statistically<br>significant risk<br>with ROSI |
|                                  |                         |                              |                                                                                                                                                                                                        |      | ROSI<br>(NA)                                                                                                    | 2,127                             | -                                         |                                 |                                                                                                                                        |

MET: metformin; NA: not available; OHA: oral hypoglycemic agent/drug; PIO: pioglitazone; PROactive: PROspectivepioglitAzone Clinical Trial In macroVascular Events; ROSI: rosiglitazone; SD: Standard deviation; SUL: sulfonylurea; T2DM: type 2 diabetes mellitus; TZD: thiazolidinedione.

\*Not a pre-specified or primary endpoint of the study.

†Post-hoc analysis of the trial.

‡Yang and Chan 2011 criticized the study design for introducing bias by using time-dependant analysis.

¶Perez 2013 criticized the study design for not including patients over the age of 79 as a report by the authors to the European Medicines Agency showed that results were not statistically significant when patients older than 79 were included in the analysis. See Neumann et al. 2013 [author's response].

§Kim 2012 noted that differences between the results of this study and PROactive may be a result differences between Caucasian and Korean populations; Li and Tian 2013 criticized the study design since a lower proportion of patients with bladder cancer were prescribed pioglitazone.

||de Vries et al. 2013 have suggested that the analysis was distorted by duplicate publication bias because it included three studies that used the same data source.

**Table S4).** While the positive antiproliferative effects of PPAR $\gamma$  activation continue to be explored (see **Section 4**), many studies have also described carcinogenic effects associated with TZDs *in vitro* and *in vivo*. For example a US FDA review of 2-year carcinogenicity studies in mice and rats for six PPAR $\gamma$  and six dual PPAR $\alpha/\gamma$  agonists found that the most commonly occurring tumor types occurred in tissues with high PPAR expression and included hemangiosarcoma in mice, subcutaneous lipoma and/or liposarcoma in rats, and urothelial cell tumors of the urinary bladder and/or renal pelvis in rats (El Hage 2005). Because PPAR $\gamma$  is highly expressed in many human cancer cells, activation of PPARs is thought to play a role in tumor induction (Cariou et al. 2012). However, the specific mechanisms behind associations between TZDs and increased (or decreased) cancer risk in humans remain to be elucidated and could differ depending on cell and tissue type and location.

### ***Bladder cancer***

Associations between TZD pharmacotherapy and bladder cancer have received the most attention with respect to the potential carcinogenic effects of TZDs. Conflicting results have been observed in numerous studies investigating the effects of different TZD drugs on cell proliferation and tumorigenesis with *in vitro* studies suggesting that TZDs could have a therapeutic use in the treatment of bladder cancer, as both troglitazone (Guan et al. 1999; Nakashiro et al. 2001; Yoshimura et al. 2003) and pioglitazone (Nakashiro et al. 2001) have been shown to inhibit the proliferation of human bladder cancer cells; however, *in vivo* studies in animal models also suggest that TZDs, and more specifically pioglitazone, may be associated with the development of bladder tumors. Further adding to the confusion, clinical and

observational studies in humans (**Table 4**) have also produced conflicting results as to the drug and dose/duration-specific carcinogenic effects of TZD treatment.

Urinary bladder cancers were initially reported in male rats at oral doses of 4 mg/kg/day and above (approximately equal to the maximum recommended human oral dose based on mg/m<sup>2</sup>) in the 2-year animal carcinogenicity study included in the licensing application for pioglitazone (US FDA 1999). At that time, there was no evidence of a similar risk in humans based on the data obtained in pre-market clinical trials. Subsequent animal studies after the time of licensing of TZDs also found associations with bladder cancer. For example, Lubet et al. (2004) reported that 34 rats treated with the urinary bladder-specific carcinogen hydroxybutyl(butyl)nitrosamine (OH-BBN; 150 mg/gavage) twice a week for 8 weeks that were then administered a suspected chemopreventive agent in addition to a high dose of rosiglitazone (50 mg/Kg body weight[BW]/day by gavage for 27 weeks [the typical dose of rosiglitazone in a human is equivalent to approximately 1.5 mg/kg BW/day in rats]) all developed large urinary bladder cancers. It should be noted that the 50 mg/kg BW/day dose of rosiglitazone administered in this study was significantly higher than the highest dose of 2 mg/kg BW/day administered to rats during the two-year carcinogenicity study that was originally used in the registration of rosiglitazone (GSK 2012). Tannehill-Gregg et al. (2007) also found that male rats exposed to muraglitazar, a dual PPAR $\alpha$ / $\gamma$  agonist, experienced a dose-related increased incidence of urothelial cell papilloma and urinary bladder carcinoma. However, these results were interpreted cautiously since the development and use of dual PPAR $\alpha$ / $\gamma$  agonists such as muraglitazar was discontinued between 2004 and 2006 (Conlon 2006), primarily because of cardiovascular concerns and increased US FDA demand for cardiovascular outcome studies, but also because of other safety issues such as those related to carcinogenicity due to a high incidence of urothelial

cell carcinoma of the bladder and kidney demonstrated in rodents at doses relevant to humans (US FDA 2005). It was still unclear as to whether these effects were also caused by other PPAR $\gamma$  agonists such as pioglitazone and rosiglitazone, or whether the observed effects were only apparent for certain PPAR agonists and only at higher doses and/or durations. In a study investigating the chemopreventive effects of rosiglitazone therapy (Lubet et al. 2008), rats administered low doses of rosiglitazone (2 and 10 mg/kg BW/day by gavage) after treatment with OH-BBN also demonstrated enhanced bladder carcinogenesis, but when rosiglitazone was administered alone for 10 months (10 mg/kg BW/day) bladder cancer was not observed. In mice exposed to high levels of pioglitazone in studies outside of the rat-specific model studies described above, bladder tumors have not been observed. For example, in a 2-year carcinogenicity study in male and female mice at oral doses up to 100 mg/kg/day of pioglitazone (approximately 11 times the maximum recommended human oral dose based on mg/m<sup>2</sup>), no increased incidence of tumors were observed in any organ or tissue system (US FDA 1999).

There is also conflicting evidence as to whether associations between PPAR agonist exposure and bladder tumors represent a species-specific effect. Many of the carcinogenic effects of PPAR receptor agonists (e.g. PPAR $\alpha$  in liver) appeared to be highly species-specific, and in some cases sex-specific as some, but not all, dual PPAR $\alpha/\gamma$  agonists (such as pioglitazone, though not a true glitazar it has a pharmacodynamic profile comparable to that of the glitazar compounds) have induced urothelial bladder cancers in male rats but not in female rats or in mice (Corton et al. 2000a, 2000b). Other dual agonists, such as the PPAR $\beta/\delta$  agonists, have been demonstrated to not only inhibit inflammatory signalling, but to also exert tumor suppressing, rather than promoting effects (Peters et al. 2015). A review of a 2-year rodent carcinogenicity study of 11 PPAR agonists including pioglitazone (El Hage & Orloff 2005 [conference abstract])

however, found that the agonists were multi-species, multi-sex, and multi-site carcinogens, based primarily on the presence of mouse hemangiosarcomas and subcutaneous liposarcomas and fibrosarcomas in rats. Urothelial cell carcinomas were only reported with increased frequency in the urothelium of rats and not in the urothelium of mice or hamsters, and data was only reported for rodent models and not human studies (El Hage & Orloff 2005 [conference abstract]).

Based on the findings in rodent models, it was originally hypothesized that bladder tumor development was the result of the urinary environment specific to rats. For example, in studies with muraglitazar (Dominick et al. 2006), alteration of urine composition has been demonstrated to be caused by inhibition of citrate synthesis leading to hypocitratermia and hypocitraturia. Because citrate acts as a chelating agent to help to keep urinary components such as calcium in solution (Suzuki et al. 2010), lowering citrate levels can lead to the precipitation of calcium or other salts which may ultimately cause chronic irritation of the bladder and tumors resulting from mucosal irritation (Cohen 2005; Dominick et al. 2006; Faillie et al. 2013; Suzuki et al. 2010; Tseng & Tseng 2012). This phenomenon is thought to be unlikely to occur in humans as humans appear to be more resistant to urinary precipitates and crystals than rats (Suzuki et al. 2010), and because when solid particles are formed in the urine, they tend to only be present for brief periods of time or lead to obstruction and pain necessitating their removal (DeSesso, 1995). Later studies suggested that these effects may not necessarily be related to the formation of microcrystals. For example, Long et al. (2008) found that male and female rats treated with the  $\gamma$ -dominant PPAR $\alpha/\gamma$  agonist naveglitazar developed urothelial cancers without changes in urinary sediments. However, the authors noted that since the urothelium was not histologically examined during the first 6 months of treatment, and a complete evaluation of the urinary bladder mucosa was not conducted, that they could not completely exclude the possibility of

injury to the urothelium by microcrystals (Long et al. 2008). In addition, some animal model studies also found that rosiglitazone exposure in rats increased the expression of proteins in the bladder urothelium that have been suggested as biomarkers for later urothelial cancer development not only in rats but also in humans (Egerod et al. 2005). This suggests that the occurrence of bladder cancer may not be specific to the urinary environment in rats; therefore, TZDs could also pose a carcinogenic risk to humans that is potentially related to other receptor-mediated effects (Hillaire-Buys et al. 2012), other factors that have been explored such as the metabolites produced by the drugs themselves (Faillie et al. 2013; see further discussion below), or any number of other mechanisms related to increased cell proliferation.

In humans, bladder cancer has many risk factors including male sex, Caucasian ethnicity, older age, cigarette smoking, bladder malformations, occupational exposure to chemicals, drug exposure (e.g. cyclophosphamide), urinary schistosomiasis, other urinary conditions such as chronic cystitis, pelvic radiation therapy, and comorbidities such as T2DM (Faillie et al. 2013). In 2012, it was also the eleventh most frequent cancer worldwide for both sexes (3.1% of all cancers), with an age-standardized incidence rate of 5.3 per 100 000 persons per year, and the seventh most frequent cancer in men (4.5% of all cancers), with an age-standardized incidence rate of 9.0 per 100 000 persons per year (IARC and WHO 2012). Though the true latency period of bladder cancer is unknown, estimates from occupational exposures have ranged from a minimum of 4 years (Schulte et al. 1987) up to 50 years (Matsumoto et al. 2005) with mean or median values ranging from 15 to 40 years (Cohen et al. 2000), and estimates from exposure to the cancer chemotherapy agent cyclophosphamide have ranged from 1 to 23 years (Monach et al. 2010).



Though bladder tumors continued to be observed in animal models, little attention was paid to risks in humans until a statistically non-significant increase in bladder tumors was reported in the PROactive trial. The incidence of malignancies in PROactive was similar across the whole cohort, however, more cases of bladder tumors (14 versus six) and fewer cases of breast cancer (three versus 11) were observed in the pioglitazone group versus the placebo group (Dormandy et al. 2005; Dormandy et. al. 2009b), raising the question of a possible increase in bladder cancer risk with pioglitazone even within the relatively short follow-up time of a clinical trial (an average of 34.5 months). The authors noted that after a blinded review of the bladder cancer cases only two were left in the pioglitazone group and one in the placebo group as cases which were reported within 1 year of randomization or who showed known risk factors for bladder cancer were eliminated. However, the Data and Safety Monitoring Committee of the trial concluded that these numbers were too small to consider bladder cancer a safety issue (Dormandy et al. 2009b). At the same time, based on a review of 2-year non-clinical carcinogenicity studies of several PPAR agonists that were currently under development, the US FDA announced in 2005 that all new PPAR drugs (agonists, antagonists, or dual agonist/antagonists) must complete 2-year non-clinical carcinogenicity studies before entering clinical trials greater than 6 months in duration (El Hage 2005). It should be noted that this was due to concerns related to the observation of sarcomas in mice and rats, and not bladder tumors. An extended study was also planned to monitor PROactive patients for up to 10 years as the pre- and post-market clinical trials for TZDs were too short, had insufficient sample sizes, and were not specifically designed to measure the occurrence of bladder cancer (Faillie et al. 2013). Interim analysis of PROactive after 6 years of follow-up did not confirm an increased risk for pioglitazone, as the incidence of bladder cancer among the 1820 pioglitazone users was 0.5%

versus 1% among 1779 placebo users and results were not statistically significant (HR: 0.98, 95% CI 0.55-1.77, P = 0.96) (Erdmann et al. 2014). Increased risks were also not seen in rosiglitazone trials such as ADOPT (Kahn et al. 2006) or RECORD [Home et al. 2009]) and in most observational studies investigating rosiglitazone therapy (Azoulay et al. 2012; Bosetti et al. 2013; Chang et al. 2012). However, concerns continued to be raised about pioglitazone as observational studies began to be published showing evidence of an increased bladder cancer risk.

In 2009, the manufacturer of pioglitazone (Takeda Pharmaceuticals U.S.A Inc. 2009) released a statement that pioglitazone-containing drugs had been associated with reports of bladder cancer in humans. This was followed by an announcement by the US FDA in September of 2010 that it was reviewing data from an ongoing, 10-year study (subsequently published by Lewis et al. 2011) designed to evaluate whether pioglitazone was associated with an increased risk of bladder cancer (US FDA 2010b). It was at this time that associations with bladder cancer first became controversial. In an interim analysis of the longitudinal cohort study of 193 099 patients in the Kaiser Permanente Northern California diabetes registry highlighted in the 2010 US FDA announcement, Lewis et al. (2011) found that ever-use of pioglitazone was not associated with an increased risk of bladder cancer. However, when patients were categorized based on duration of treatment, those who used pioglitazone for greater than 24 months showed a 40% increased risk (HR: 1.4, 95% CI: 1.03-2.0 [Lewis et al. 2011]) which was contrary to the results obtained in clinical trials completed by that time, and the findings of the analysis of the full study (Lewis et al. 2015; further described below). Adding to the confusion, an independent case/non-case analysis of passive reports from the US FDA's Adverse Event Reporting System (FAERS) database (Piccinni et al. 2011) further supported an association, finding 31 cases of

bladder cancer associated with pioglitazone between 2004 and 2009 (ROR: 4.30, 95 % CI: 2.82-6.52) and a significant relationship appearing as early as 2004 (ROR: 4.77, 95 % CI: 1.30-15.88); the year before the PROactive results were published. At the same time, a French prospective cohort study also suggested that pioglitazone use was associated with a statistically significant increase in risk (adjusted HR: 1.22, 95% CI: 1.05-1.43 [published the next year as Neumann et al. 2012]) that was dose ( $\geq 28\ 000$  mg: adjusted HR: 1.75, 95% CI: 1.22-2.50) and duration-dependant ( $\geq 24$  months: adjusted HR: 1.36, 95% CI: 1.04-1.79). Sex-specific analyses further suggested that the association between pioglitazone and bladder cancer was significant only for men (adjusted HR: 1.28, 95% CI: 1.09-1.51) and not women (adjusted HR: 0.78, 95% CI: 0.44-1.37). However, this study was also criticized by some because of a potential for selection bias and the inability to adjust for major confounders such as smoking, diabetes duration, or comorbidity (Neumann et al. 2013; Perez et al. 2013). Of greater consequence, the study excluded patients over 79 years of age which the authors stated was based on limitations of available data (Neumann et al. 2013). However, when the analysis was extended to all patients  $\geq 40$  years of age the results of the original study were no longer statistically significant (adjusted HR: 1.15, 95% CI: 0.99-1.33), implying that the age group selected may have resulted from a *post hoc* decision (Perez et al. 2013).

In June 2011, the preliminary results of the Neumann et al. (2012) study led to the suspension of pioglitazone from the French market (AFSSAPS 2011) and German physicians were warned not to prescribe pioglitazone to patients without a previous history of use (Stephenson 2011). The findings of the Lewis et al. (2011) interim analysis, in conjunction with those from the French study, also prompted the US FDA (2011b) to release a safety announcement that June advising patients that use of pioglitazone for more than one year may be

associated with an increased risk of bladder cancer. Information about this risk was also detailed and added to the "Warnings and Precautions" section of the label for pioglitazone-containing drugs; and the US FDA advised physicians that pioglitazone should not be used in patients with active bladder cancer, that it should be used with caution in patients with a prior history of bladder cancer, and that the benefits of blood sugar control with pioglitazone should be weighed against the unknown risks for cancer recurrence. In July, the European Medicines Agency (EMA) also issued its own warning about the potential for bladder cancer with pioglitazone (EMA 2011a).

In December 2011, a re-evaluation of pioglitazone by the EMA (2011b) revealed the results of an unpublished meta-analysis conducted by the manufacturer using its clinical trial database that included 36 trials (24 lasting < 1 year, 6 lasting 1 to 2 years, and 6 lasting > 2 years [the PROactive study was analyzed separately]) and 22 000 patients. When all studies were included 19 cases of bladder cancer were observed in the pioglitazone group versus seven in the comparator group, but the risk of bladder cancer was not statistically significant when cases occurring within the first year of treatment were excluded. This suggested the possibility of early detection bias as these patients were already more advanced in their progression of T2DM (i.e. undergoing treatment with a second or third-line therapy), and were more likely to be undergoing frequent monitoring and testing such as urinalysis for possible diabetes-associated renal effects, that could also detect the presence of bladder cancer. Conversely, in a meta-analysis of one clinical trial (PROactive) and four observational studies (Chang et al. 2012; Lewis et al. 2011; Neumann et al. 2012; Tseng 2012), Zhu et al. (2012) found that pioglitazone therapy was associated with a statistically significant increased risk when all studies were pooled (RR: 1.17, 95% CI: 1.03-1.32,  $P = 0.013$ ), but not when duration of therapy was less than 1 year or

cumulative dose was less than 28 000 mg. Results were significant in patients with between 12 and 24 months of pioglitazone use (RR: 1.34, 95% CI: 1.08-1.66, P = 0.008), cumulative treatment duration > 24 months (RR: 1.38, 95% CI: 1.12-1.70, P = 0.003), and cumulative dose > 28 000 mg (RR: 1.58, 95% CI: 1.12-2.06, P = 0.001). Another meta-analysis by Colmers et al. (2012) investigating associations between both rosiglitazone and pioglitazone and incidence of bladder cancer found that only pioglitazone was associated with a significant risk (pooled RR: 1.22, 95 % CI: 1.07-1.39) when three cohort studies were pooled (Lewis et al. 2011; Neumann et al. 2012; Tseng 2012) (though it has been noted that the authors failed to address the effects of gender, duration of therapy, or cumulative dose [He et al. 2014]) and further confirmed these results when additional data from a study using the UK GPRD (Azoulay et al. 2012) was included.

In a nested case-control study analyzing data from 115 727 patients in the GPRD who were newly treated with diabetes drugs between 1988 and 2009, Azoulay et al. (2012) found an 83% increased risk of bladder cancer for patients who had ever taken pioglitazone versus never users. The authors noted that although these findings of 74 cases per 100 000 person-years of observation were similar to the rate of cases in the general population of the UK aged 65 years and older in 2008 (73 per 100 000 person-years), the mean age of patients in the study was 64.1 years and younger patients are thought to have a lower risk of developing bladder cancer. In addition, contrary to the findings in the unpublished meta-analysis reviewed by the EMA, Azoulay et al. (2012) found that patients who had taken pioglitazone for more than 2 years had an elevated cancer incidence rate (88 cases per 100 000 person-years), as did patients with a greater cumulative dose (137 per 100 000 person-years for  $\geq 28\,000$  mg). Similar results were not observed for rosiglitazone. The authors noted that based on the results of this study, that

pioglitazone's association with bladder cancer may have in fact been underestimated in previous observational studies (Azoulay et al. 2012).

Though warnings have remained in place since 2011, when the patent for Actos (the marketed brand name for pioglitazone) expired in 2012, both the US FDA and the EMA authorized several generic pioglitazone-containing products (Faillie et al. 2013). Other countries however, have taken a more cautious approach. For example, France has maintained its pioglitazone ban and India banned pioglitazone in June of 2013 (Sadikot and Ghosal 2014). At the same time, more observational studies and meta-analyses have continued to be conducted with mixed, and sometimes conflicting, results. For example, both Azoulay et al. (2012) and Wei et al. (2012) used the same GPRD database but reported opposite results using different methodological approaches: an association between pioglitazone and bladder cancer was found using a retrospective cohort and nested case-control design (Azoulay et al. 2012) versus no association using a propensity score-matched design (Wei et al. 2012). Other studies have found slight to moderate increases in risk of bladder cancer for pioglitazone or any TZD exposure (Bosetti et al. 2013; Ferwana et al. 2013; Fujimoto et al. 2013; He et al. 2014 [men]; Hsiao et al. 2013; Jin et al. 2014; Mamtani et al. 2012; Monami et al. 2014), whereas others have found no increased risk (Balaji et al. 2014; Bazelier et al. 2013b; Erdmann et al. 2014; Gupta et al. 2015 [small number of exposed patients]; Kuo et al. 2014; Lee et al. 2014; Lewis et al. 2015; Song et al. 2012; Tseng 2012; Tseng 2013a; Vallarino et al. 2013; Wei et al. 2012). For example, in a meta-analysis of nine datasets from 10 studies (including PROactive and the Azoulay et al. 2012, Lewis et al. 2011, and Neumann et al. 2012 studies) He et al. (2014) found that pioglitazone was associated with a significant risk of bladder cancer after adjustment for age, gender, and use of other antidiabetic medications. Sub-group analyses further demonstrated that these associations

were significant in men but not in women, and that there was a significant increasing risk with both increasing cumulative duration of use and cumulative dose. A recent study by Tuccori et al. (2016) using the United Kingdom Clinical Practice Research Datalink, found that pioglitazone use was associated with a 63% increased risk of bladder cancer (HR: 1.63, 95% CI: 1.22-2.19) compared to use of other antidiabetic drugs. Similar to Azoulay et al. (2012) study, in the Tuccori et al. (2016) study, use of pioglitazone for greater than two years was associated with an increased risk of bladder cancer (adjusted HR: 1.78, 95% CI: 1.21 to 2.64), and risk increased with greater cumulative dose (< 10 500 mg adjusted HR: 1.63, 95% CI: 1.02-2.60; > 28 000 mg adjusted HR: 1.70, 95% CI: 1.04-2.78). Conversely, a study by Lewis et al. (2015) that presented the full 10-year analysis of the Kaiser Permanente Northern California diabetes registry cohort study ( Lewis et al. 2011) found that ever use of pioglitazone was not associated with bladder cancer risk using either a cohort study design (adjusted HR: 1.06, 95% CI: 0.89-1.26), or a case-control design (adjusted OR: 1.18, 95% CI: 0.78-1.80). The authors stated that the differences between the outcomes of this study, and the interim analyses (Lewis et al. 2011), are most likely not methodological as both methodologies were nearly identical. Nor are they likely a result of warnings leading to increased proteinuria testing because most patients in the study began receiving pioglitazone before the publication of their first report (Lewsi et al. 2015). In addition, bladder cancer risk factors were adjusted for in the study, therefore, the results of the interim analyses may have instead been a result of some other factor such as early detection bias from increased proteinuria testing in diabetics, especially those prescribed pioglitazone (Lewis et al. 2014). A recent study by Korhonen et al. (2016), also found that ever use of pioglitazone was not associated with an increase bladder cancer risk when compared with never use, using both a nearest match chort approach (adjusted HR: 0.99, 95% CI: 0.75-1.30) and a multiple match

cohort approach (adjusted HR:1.00, 95% CI: 0.83-1.21) in a large cohort of patients spanning country-specific healthcare databases from Finland, the Netherlands, Sweden, and the UK, which supports the Lewis et al. (2015) findings.

In December 2016, the US FDA (2016) released an updated safety announcement addressing potential links between pioglitazone use and bladder cancer risk. This announcement was in reaction to the results of a systematic review of several studies, including the PROactive trial (Dormandy et al. 2005), a recent 10-year observational follow-up of the trial that found no persistent bladder cancer risk (Erdmann et al. 2016), and the Lewis et al. (2015) and Tuccori et al. (2016) studies that, as described above, produced conflicting results. Although some uncertainty still exists surrounding the epidemiological data presented to date, the US FDA stated that the updated data suggest that pioglitazone use may be linked to an increased risk of bladder cancer, and that labels of pioglitazone-containing medications would be updated to communicate this risk (US FDA 2016). However, given the nature of the uncertainty presented in the US FDA announcement, and based on the outcomes of the investigations to date and the continued lack of concurrence of the findings, it is apparent that more research is needed to further clarify associations between TZD use and bladder cancer risk. This is especially true given some of the methodological issues that exist across studies. As described by Tuccori et al. (2016), the inclusion of prevalent users of pioglitazone in the majority of the studies to date, the exclusion of certain patient populations, and other limitations such as immortal time bias and a lack of consideration of the complex latency period associated with cancer development, may have led to an underestimation of risk in many of the studies conducted to date. For example, in the IRIS trial (Kernan et al. 2016), bladder cancer occurred in 12 patients in the pioglitazone group compared to 8 in the placebo group; a finding that was not statistically significant. Given



the imbalance between both groups, the risk of bladder cancer may have been underestimated as the study design excluded both patients with a history of, or risk factors for, bladder cancer. Future observational studies should address such limitations wherever possible, in their study designs.

At present, the biological mechanism(s) by which pioglitazone might elevate the risk of bladder cancer in humans remains unclear. As previously described, initial studies suggested that the observed occurrences of bladder cancer that have been associated with PPAR agonist therapy may be specific to the rat (Suzuki et al. 2010); however, the studies described above demonstrate that an increased risk in humans is also plausible. The hypothesis that the effects of TZDs may be related to urolithiasis (as described above for rats) seems unlikely in humans for several reasons. First, the urinary composition of humans is different than in rats (Suzuki et al. 2010) and patients treated with TZDs have been shown to have a similar mean pH to patients treated with other oral antihyperglycemics but a lower pH than those treated with insulin (Torricelli et al. 2014). Second, urinary microsolids formed in the human bladder are usually only present for brief periods of time before obstruction and/or severe pain leads to their surgical removal (DeSesso 1995). Finally, nephrolithiasis, urolithiasis, or increases in microsolids were not observed in clinical trials in diabetic patients (e.g. Bortolini et al. 2013; Dominick et al. 2006 [muraglitazar]).

A second hypothesis that has been put forward is that the interaction between pioglitazone in the urine and the large number of PPAR $\gamma$  receptors in the urothelium of the bladder exerts mitogenic effects through PPAR $\gamma$  activation-promoted differentiation of normal human urothelial cells (Suzuki et al. 2010; Varley & Southgate 2008). Though PPAR $\gamma$  mRNA in human tissue samples and immunohistochemistry has revealed that expression of PPAR $\gamma$  is in

fact significantly higher with increasing grade and increasing stage of bladder cancer (Yoshimura et al. 2003), which may provide some support for this hypothesis, this mechanism has been acknowledged as speculative (Oleksiewicz et al. 2008). This hypothesis seems unlikely for several reasons, including that, as described below, antiproliferative effects have been observed on the urothelium of both of cancerous and non-cancer urothelial cells. First, rosiglitazone, troglitazone, and three other PPAR $\gamma$  agonists described in the US FDA review of 2-year carcinogenicity studies were not associated with urinary bladder tumorigenesis (El Hage 2005). Second, levels of PPAR $\gamma$  expression have been demonstrated to be similar in both rat and mouse urothelium, but tumors were only induced in rats and *in vitro* studies using human urothelial cell lines have shown that PPAR $\gamma$  agonists inhibit cell proliferation and potentiation of differentiation, rather than stimulate proliferation (Guan et al. 1999; Nakashiro et al. 2001; Varley et al. 2004; Varley & Southgate 2008; Yoshimura et al. 2003). Finally, PPAR agonists are highly lipophilic with only a small percentage of the drugs excreted in urine (Bortolini et al. 2013; Suzuki et al. 2010), implying that pioglitazone would have limited contact with PPAR receptors in the bladder.

As the previous two hypotheses have been largely discounted, several others have been proposed in an attempt to explain the mechanistic basis (or lack thereof) behind the effects observed in humans. For example, some cases of bladder cancer, especially those observed after only brief exposure to pioglitazone, may be coincidental and a function of the increased cancer risk of T2DM itself rather than TZD exposure (Giovannucci et al. 2010; Faillie et al. 2013; Larsson et al. 2006; MacKenzie et al. 2011). They could also result from other lifestyle factors that are known risks for bladder cancer such as occupational exposure to chemicals or smoking, that may not have been controlled for in all studies due to a lack of available data/patient history.

However, mice exposed to cigarette smoke and pioglitazone have demonstrated inconsistent effects as pioglitazone has been shown to both inhibit DNA damage in exfoliated urothelial cells and induce histopathological changes in the urinary tract (La Maestra et al. 2013) suggesting that the mechanism behind the development of TZD-induced bladder tumors does not involve genotoxicity. In addition, neither the TZD structural group, nor the pharmacologically active TZD metabolites, have been identified as structural alerts for genotoxicity or mutagenicity and are therefore unlikely to be DNA-reactive. Finally, as mentioned previously, the adverse effects associated with pioglitazone could be the result of its pharmacologically active metabolites, the keto derivative M-III and the hydroxy derivative M-IV (Krieter et al. 1994). Though rosiglitazone is metabolized through hydroxylation, N-demethylation, and conjugation (Mogensen 2007), none of the metabolites are considered to demonstrate insulin-sensitizing activity (Desai & Lee 2007). However, as other metabolites may play a role in the development of bladder cancer, this avenue warrants further exploration. At this point, the mechanism(s) of action behind the observed increases in the risk of bladder cancer in patients undergoing TZD therapy remain to be elucidated through further investigation.

## **4. CURRENT STATUS AND FUTURE DIRECTIONS**

### **4.1 Treatment of T2DM and antihyperglycemic prescribing practices**

TZDs were first marketed in the late 1990s, and were praised for delivering glycemic control and physiological effects comparable to, and in some cases, better than, other established first-line treatments such as metformin and second-line treatments such as sulfonylureas. However, in light of the adverse events that have been described in this review, attitudes towards

TZD use and usefulness in the treatment of T2DM have changed, not only in clinical practice, but also in the overall number of prescriptions dispensed to patients.

TZDs are no longer recommended as first-line treatments or for use as a monotherapy for the treatment of T2DM. The American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (Inzucchi et al. 2015) recommend a treatment sequence that begins with metformin monotherapy (which is well-established and generally well-tolerated by patients), followed by the addition of one or two oral antihyperglycemic drugs, including TZDs, if an A1C target cannot be maintained using metformin alone, or with metformin in combination with another oral antihyperglycemic drug (which may include a TZD). In practice, studies have found that metformin is not always the first drug prescribed to a patient. For example, in a retrospective cohort study looking at initial oral antihyperglycemic agent class and the subsequent need for treatment intensification, Berkowitz et al. (2014) found that between 2009 and 2013 only 57.8% of 15 516 patients began treatment for T2DM with metformin and that 6.1% began with TZD therapy. It should be noted that this study was conducted after the initial warnings of increased risks of MI and CHF for TZDs. Prior to 2009 and the first warnings of cardiovascular risks, more patients were prescribed a TZD or were switched to a TZD drug than after the warnings. In a study investigating the distribution of diabetic medications among adults with T2DM in the US using the 1999-2004 National Health and Nutrition Examination Survey (NHANES) and prescription medication data, Dodd et al. (2009) found that of the approximately 60% of diabetic adults using oral hypoglycemic agents 12.7% used a TZD alone or in combination between 1999 and 2004, with 21.4% using a TZD in 2003-2004. Only 11.6% of patients were using metformin monotherapy between 1999 and 2004. The most common form of oral agent therapy also shifted over the study period from

sulfonylurea monotherapy in 1999-2000 (23%) to any oral agent in combination with a TZD in 2003-2004 (21.4%) ( $P = 0.03$ ) (Dodd et al. 2009).

Though there are several advantages to TZD drugs such as a low risk of hypoglycemia, high durability, improvements in HDL-C and triglyceride levels, potential cardiovascular benefits associated with pioglitazone therapy, and low cost (Inzucchi et al. 2015), and the ADA and EASD have taken the position that pioglitazone is most likely not associated with bladder cancer, they also recognize adverse effects such as edema, weight gain, bone fractures for pioglitazone, increases in LDL-C levels for rosiglitazone, and the adverse cardiovascular effects potentially associated with rosiglitazone (Inzucchi et al. 2015). Physicians are advised to follow ADA guidelines for the treatment of T2DM which include guidance that there are no circumstances in which TZDs are preferable to other drugs classes, that the warnings and precautions for use of TZDs must be taken into account when considering their prescription, and that TZDs should not be used in patients with CHF, previous or concurrent bladder cancer, or severe osteoporosis. Physicians have obviously taken notice of the potential risks and heeded the warnings released by regulatory bodies, as prescriptions of TZDs for the treatment of T2DM have steadily decreased or changed over time, especially for rosiglitazone. For example, when exploring nationally projected data on antidiabetic prescriptions for adults dispensed from US retail pharmacies in 2012, Hampp et al. (2014) found that that rosiglitazone use plummeted to less than 13 000 prescriptions dispensed in retail or mail-order pharmacies as a result of the restrictions put in place in 2011. It is hypothesized that part of this trend is a result of physicians and hospitals switching patients from rosiglitazone to pioglitazone, which many consider to be safer and more cost-effective in the long-term. For example, in a drug utilization review of the use of pioglitazone and rosiglitazone in an inner city US hospital after warnings were released

related to the potential adverse cardiovascular, osteological and carcinogenic effects associated with TZD therapy (Marks 2013), a hospital-wide switch occurred changing all rosiglitazone prescriptions to pioglitazone. This switch resulted in a cost savings to the hospital in the first year with no reported episodes of worsening of control of T2DM, decreased efficacy of pharmacotherapy, or adverse effects (Marks 2013). However, these changes in prescribing practices are also most likely partly attributable to the development and marketing of new classes of drugs used in the treatment of T2DM including the DPP-4 inhibitors, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, and the glucagon-like peptide-1 (GLP-1) receptor agonists. It should be noted that in some cases, patients undergoing pharmacotherapy with these new drug classes may also be using a TZD in combination with one of these drugs, or as a part of the drug's formulation (e.g. the DPP-4 alogliptin combined with pioglitazone in one tablet).

Though prescriptions of TZDs for the treatment of T2DM will most likely not rebound to previous levels due to the potential risks that have been documented and the numerous warnings that have been released since they were first marketed, prescriptions will likely continue to be seen in diabetics (e.g. the US FDA has approved, or is in the process of approving a number of new pioglitazone-containing drugs such as pioglitazone combined with alogliptin [US FDA 2013]), and increasingly in other patient populations. At present, TZDs both old and new continue to be used in clinical studies and are most likely being prescribed by some physicians for off-label uses. The anti-inflammatory effects of TZDs have been documented in numerous studies, both *in vitro* and *in vivo*, which, and as will be described below, has led to continued and newfound interest in their applicability and potential effectiveness in the treatment of other diseases and conditions.

## 4.2 Anti-inflammatory and other effects

As TZDs have been demonstrated to have anti-inflammatory effects, they continue to be investigated for use in the treatment of several diseases and conditions other than T2DM, including cancer, neurodegenerative diseases, acromegaly, and polycystic ovary syndrome (PCOS) (**Table 5**). The following subsection provides a brief overview of some of the current and potential future uses for TZDs in addition to glycemic control.

### *Cancer Treatment*

TZDs have been associated with an increased incidence of some cancers (e.g. bladder cancer) in some studies; however, other studies have also demonstrated decreased risks of cancers in diabetics who have received TZD pharmacotherapy (see references listed in **Supplementary Appendix 4, Table S4** for more information). As a result of these observations, and the anti-inflammatory and antiproliferative effects of PPAR agonists that have been observed *in vitro* and *in vivo* in animal models, TZDs have garnered great interest for their potential applicability in the treatment of some types of cancers. Investigations into the molecular mechanisms that may underlie PPAR $\gamma$ -induced anti-carcinogenic effects have been, and continue to be, an area of active research. Though the underlying mechanisms are still unclear, the anticancer effects of TZDs are thought to result from the activation of PPAR $\gamma$  leading to reductions in inflammation, cell apoptosis, arrestation of cell proliferation, growth factor inhibition, promotion of cell redifferentiation, and other mechanisms that may be PPAR $\gamma$ -independent (Blanquicett et al. 2008). New TZD and TZD-like drugs continue to be developed and tested in the hopes of finding new treatments for cancer or other newfound therapeutic uses to account for their declining prescription rates in the treatment of T2DM, even as the

**Table 5.** Examples of other diseases and conditions under investigation as targets for TZD therapy.

| <b>Disease/Condition</b>                         | <b>TZD</b>     |
|--------------------------------------------------|----------------|
| <b>Acromegaly</b>                                | PIO, ROSI      |
| <b>Alzheimer's</b>                               | PIO, ROSI, TRO |
| <b>Cushing's</b>                                 | PIO, ROSI      |
| <b>Depression, bipolar disorder, and anxiety</b> | PIO            |
| <b>Erectile dysfunction</b>                      | PIO            |
| <b>Huntington's</b>                              | ROSI           |
| <b>Nonalcoholic steatohepatitis</b>              | PIO, ROSI      |
| <b>Parkinson's</b>                               | ROSI           |
| <b>Polycystic kidney disease</b>                 | PIO, ROSI      |
| <b>Polycystic ovarian syndrome</b>               | PIO            |
| <b>Psoriasis</b>                                 | CIG, ROSI, TRO |
| <b>Stress</b>                                    | ROSI           |

CIG: ciglitazone; PIO: pioglitazone; ROSI: rosiglitazone; TRO: troglitazone.



controversy surrounding the potential adverse effects of PPAR agonists continues (see **Section 4.3**).

Many studies have explored the anticancer effects of TZDs *in vitro* in cell lines and *in vivo* in animal models (see references listed in **Supplementary Appendix 5, Table S5** for more information), but few have investigated their antiproliferative effects in humans. Of the numerous cancers investigated, only gliomas, breast, lung, and prostate cancers have progressed to human trials or have been the focus of observational studies. For example, only one clinical trial and one chart review have investigated the effects of TZDs in the treatment of gliomas, with mixed results. While the patient chart review indicated that there may be a possible antineoplastic effect of TZDs on gliomas, since only 16% of glioma patients were diabetics and only 6% of these patients had used a TZD (Grommes et al. 2010), the phase II study (Hau et al. 2007) found that disease stabilization lasting longer than 3 months occurred in only four of 14 patients receiving pioglitazone as an add-on to rofecoxib and low-dose chemotherapy. Clinical data supporting the efficacy of TZDs in lung cancer is also limited, though numerous *in vitro* studies have demonstrated their efficacy in cancer cell lines (e.g. Satoh et al. 2002; Serizawa et al. 2014; Tsubouchi et al. 2000). In one case-control study investigating the protective effects of metformin and pioglitazone against lung cancer, Mazzone et al. (2012) found that the use of metformin and/or the use of TZDs were associated with a lower likelihood of developing lung cancer in diabetic patients (the control group was 1.5 times more likely to have used these medications), and increased with greater exposure duration (the control group was 2.3 times more likely to have used metformin and/or a TZD for > 24 months). Clinical trials have yet to be completed to confirm whether TZDs may in fact exert positive effects in lung cancer patients.

Few studies have also been conducted for prostate cancer as only one case report and one clinical trial took place using troglitazone over a decade ago, but a more recent clinical study has been published investigating pioglitazone as an add-on/combination therapy. In the case report (Hisatake et al. 2000), when troglitazone was administered to one patient with occult recurrent prostate cancer for over 1.5 years it was shown to reduce prostate-specific antigen (PSA) levels, suggesting that troglitazone may be an effective clinical therapy. In the older phase II clinical trial consisting of 41 patients with advanced prostate cancer, Mueller et al. (2000) found that troglitazone treatment (800 mg/day) for greater than 12 weeks led to a high incidence (39%) of prolonged stabilization of PSA in the entire patient population, and a 98% decrease in serum PSA but only in one patient. More recently, an open-label phase II study (Vogelhuber et al. 2015) found that of 61 patients prescribed daily doses of imatinib mesylate, pioglitazone (60 mg/day), etoricoxib, treosulfan and dexamethasone for 6 months, 60.6% responded or had stable disease and 37.7 % were PSA responders. Progression-free survival was 467 days in the intent-to-treat population, indicating that this treatment regime may be an alternative treatment option in prostate cancer. However, without additional research it is difficult to infer how much pioglitazone contributed to these effects or the potential synergisms among the drugs used in the study.

Of all of the cancers investigated thus far, breast cancer has perhaps received the most attention with a large number of studies demonstrating antineoplastic activity of TZDs *in vitro* and in several studies *in vivo* in animal models. Studies have been conducted in humans and, although an observational study found positive survival effects in patients treated with metformin and TZDs (He et al. 2012), clinical outcomes in trials have not been encouraging. For example, the first phase II trial investigating the effects of troglitazone in patients with metastatic breast

cancer found no clinical benefits (Burstein et al, 2003), and a pilot trial that examined short-term (2 to 6 weeks) treatment with rosiglitazone (8 mg/day) between the time of diagnostic biopsy and definitive surgery in 38 women with early-stage breast cancer found no significant effects on breast tumor cell proliferation (Yee et al 2007). A more recent phase I trial investigating the effects of exemestane in combination with metformin and rosiglitazone in non-diabetic obese postmenopausal women with hormone receptor-positive metastatic breast cancer found that the treatment regimens were well-tolerated, and that four of 14 patients receiving metformin and rosiglitazone achieved stable disease for 6 months or longer; however, rosiglitazone was not the specific focus of this trial. It is clear that more investigation is needed to determine if in fact TZDs do provide benefits to breast cancer patients alone or in combination with other drugs.

### *Acromegaly*

Treatment of acromegaly, which is characterized by the secretion of excessive growth hormone (GH) from pituitary adenomas leading to overexpression of IGF-1 (Giustina et al. 2000; Jones & Clemmons 1995; Katznelson 2005) is a challenge as many patients do not respond to or tolerate the drugs commonly used to control tumor growth or induce shrinkage such as dopamine agonists or somatostatin analogues (Katznelson et al. 2001; Wass & Shalet 2002). Excessive GH also leads to insulin resistance in approximately 80% of patients with acromegaly, with impaired glucose tolerance occurring in approximately 40% of patients and T2DM in 10% to 20% (Turner 2001). Although surgery is the preferred treatment choice for this disease (and leads to complete resolution of T2DM for approximately 75% of these patients), surgery is not always successful and is associated with an increased incidence of late relapse (Gradišer et al. 2007). New drug

options that are more effective and/or better tolerated by patients are currently being explored in hopes of finding alternative or add-on therapies for patients.

PPAR $\gamma$  has been shown to control GH transcription and secretion in addition to apoptosis and cell growth in GH-secreting adenomas (Bogazzi et al. 2004). Because of this, it been hypothesized that drugs that activate PPAR $\gamma$  may be useful in the treatment of such tumors, with TZDs shown to reduce levels of IGF-1 and GH (Lecka-Czernik et al. 2007). For example, rosiglitazone has been demonstrated to decrease production of GH by cells in culture and to decrease tumor growth and GH levels in rodents inoculated with GH-secreting cells (Bogazzi et al. 2004). However, studies in humans have provided conflicting results. In a study investigating the effects of 6 weeks of rosiglitazone therapy (8 mg/day) on seven acromegaly patients with active disease (Bastemir et al. 2007), treatment did not reduce basal and nadir GH levels or IGF-1 levels ( $P > 0.05$ ). Similar results were obtained in a 4-month open-label prospective study evaluating the effects of pioglitazone (45 mg/day) on 16 patients with active acromegaly (Kim et al. 2012). Alternatively, in a pilot clinical trial consisting of five patients with uncontrolled acromegaly, the addition of rosiglitazone (titrated to 20 mg/day) to their existing treatment regime did lead to a reduction of IGF-1 levels ( $P < 0.001$ ), but not serum GH levels (Bogazzi et al. 2011). However, a case series (Tamez-Pérez et al. 2011) investigating the clinical and laboratory responses of four patients to 6 months of treatment with rosiglitazone (4 mg/day) found that both basal and nadir GH and IGF-1 levels were significantly decreased ( $P < 0.05$  and  $P < 0.01$ , respectively) in three patients. Because of the small size and duration of these studies it is still unclear whether TZDs provide any benefits in the treatment of acromegaly itself, though they may be useful in treating T2DM that occurs in many acromegaly patients.

## *Neurodegenerative disorders*

There is growing evidence that TZDs may improve various neurodegenerative disorders such as Huntington's disease (Chiang et al. 2012; Chiang et al. 2015), Alzheimer's disease (AD) (O'Reilly & Lynch 2012; Pedersen et al. 2006), multiple sclerosis (MS) (Kaiser et al. 2009; Shukla et al. 2010), and Parkinson's disease (PD) (Carta et al. 2011b), as PPAR $\gamma$  has been implicated in the development of several brain diseases and traumas (Bordet et al. 2006; Landreth 2006; Sundararajan et al. 2006). For example, Huntington's disease is an autosomal dominant neurodegenerative disease characterized by motor dysfunction, weight loss, dementia, and psychiatric symptoms (Chao et al. 2016; Chiang et al. 2012). Studies using a transgenic mouse model for Huntington's disease have demonstrated that treatment with rosiglitazone can confer protective effects on the brain through the reduction of protein aggregates and increased availability of PPAR $\gamma$  which leads to normal expression of downstream genes in the cortex (Chiang et al. 2012; Chiang et al. 2015). However, studies have only been conducted in animal models to date.

Multiple sclerosis, an autoimmune disorder characterized by elevated inflammatory biomarkers, central nervous system white matter lesions, axonal degeneration, and cognitive impairment is a common cause of disability in young adults (McKay et al. 2016; Torkildsen et al. 2016). At present there is no cure for MS, though numerous treatments such as interferon beta have been developed over the past 20 years, and new treatments, including those that target PPAR $\gamma$ , are currently being investigated but are in early stages. For example, in a pilot test (Kaiser et al. 2009) of the effects of one year of add-on pioglitazone (30 mg/day) to interferon beta-1alpha in patients with relapsing remitting MS, magnetic resonance imaging of patients in the pioglitazone group (n = 11) showed a significant reduction in gray matter atrophy and

reduced lesions compared to the placebo group (n = 10), though there were no significant differences in clinical symptoms and the size of the study cohort was small.

Another area of investigation has been the use of TZDs in AD, a disease characterized by progressive memory loss and cognitive function that is pathologically expressed as extracellular amyloid- $\beta$  peptide plaques and intracellular neurofibrillary tangles that cause neuronal death in the brain (Hersi et al. 2016; Tanzi & Bertram 2005). PPAR $\gamma$  is expressed in the brain at low levels under physiological conditions and PPAR $\gamma$  mRNA levels have been shown to be elevated in AD patients (de la Monte & Wands 2006), suggesting that PPAR $\gamma$  could play a role in the modulation of the pathophysiology of AD (Heneka et al. 2011). *In vitro* studies have demonstrated that rosiglitazone protects neuroblastoma cells against the neuronal toxicity induced by advanced glycation end products (AGEs) by decreasing oxidation, cell apoptosis, and inflammation, presumably through activation of PPAR $\gamma$  (Wang et al. 2011). However, TZDs may also act through PPAR $\gamma$ -independent mechanisms as troglitazone has been demonstrated to inhibit the phosphorylation of Tau, the protein that makes up the intracellular neurofibrillary tangles present in AD that have been genetically linked to frontotemporal dementia (Cho et al. 2013). In animal models, long-term treatment of AD mice with pioglitazone has also been shown to decrease hyperphosphorylated tau deposits in the hippocampal region of brain as well as enhance learning and increase short- and long-term plasticity (Searcy et al. 2012).

In humans, treatment with TZDs has demonstrated positive effects on the memory and cognitive function of AD patients. For example, in a pilot study of 30 patients with mild AD or amnesic mild cognitive impairment (MCI) who were randomized to either 6 months of rosiglitazone (4 mg/day; n = 20) or placebo (n = 10) (Watson et al. 2005), patients who received rosiglitazone exhibited better delayed recall and selective attention than patients in the placebo

group. In another prospective, randomized, open-controlled study (Hanyu et al. 2009), 32 patients with mild to moderate AD and amnesic MCI who were currently undergoing treatment for T2DM with an oral antihyperglycemic agent or diet for T2DM and who were given pioglitazone (30 mg/day) in addition to their current therapy for 6 months, demonstrated both cognitive and metabolic results exceeding those in the control group. Similar results have also been seen in other trials investigating the effects of pioglitazone on cognitive and functional improvement (Sato et al. 2011), and in anecdotal case reports of long-term treatment with pioglitazone (Read et al. 2014), although conflicting results have been seen with rosiglitazone. For example, other studies have shown that rosiglitazone therapy may only be beneficial in AD patients with certain genetic characteristics (Risner et al. 2006), or that long-term therapy with rosiglitazone does not slow the progression of AD (Tzimopoulou et al. 2010) or improve cognitive function (Harrington et al. 2011). More research is needed to further investigate whether some of the beneficial effects of TZDs observed may be specific to pioglitazone and not rosiglitazone.

Recently, TZDs have been proposed as therapeutic prospects in the treatment of PD, a chronic neurodegenerative disease that is characterized by progressive loss of dopaminergic neurons (Martino et al. 2016; Ridder & Schwaninger 2012) thought to result from mitochondrial dysfunction, oxidative stress, and inflammation (Gupta et al. 2008). TZDs have demonstrated positive effects in numerous animal models (Carta et al. 2011b), but little study has occurred clinically. For example, pioglitazone (30 mg/day) has been shown to protect PD rats against hypolocomotion, depressive-like behavior, impairment of learning and memory, and dopaminergic neurodegeneration caused by intranigral 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), in addition to increased activation of caspase-3, an effector enzyme of

the apoptosis cascade that is considered one of the pathological features of PD (Barbiero et al. 2014). In humans, one clinical trial and one cohort study have been conducted to date. In a multicentre, double-blind, placebo-controlled, futility clinical trial (NINDS NET-PD FS-ZONE Investigators 2015) participants with a diagnosis of early PD on a stable regimen of 1 mg/day of rasagiline or 10 mg/day of selegiline were randomly assigned to 15 mg/day pioglitazone, 45 mg/day pioglitazone, or placebo. When the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score was assessed after 44 weeks of treatment, pioglitazone was not associated with a slowing of the progression of PD (4.42 [95% CI: 2.55-6.28] for 15 mg pioglitazone, 5.13 [95% CI: 3.17-7.08] for 45 mg pioglitazone, and 6.25 [95% CI: 4.35-8.15] for placebo), leading investigators to recommend that no further investigations into the therapeutic uses of pioglitazone in PD need be undertaken. In a cohort study of 29 397 Medicare patients enrolled in state pharmaceutical benefits programs who initiated treatment with a TZD or sulfonylurea between 1997 through 2005 with no prior diagnosis of PD (Connolly et al. 2015), TZD use was not associated with a longer time to diagnosis of PD than was sulfonylurea use, regardless of duration of exposure. These results indicate that TZDs may have greater effects in other neurodegenerative diseases and that the mechanism(s) behind the development and progression of PD may not be appropriate targets for TZD therapy. More research is required to confirm these hypotheses.

### *Nonalcoholic steatohepatitis*

Non-alcoholic steatohepatitis (NASH) is a subtype of non-alcoholic fatty liver disease (NAFLD) that is characterized by liver cell injury and inflammation that can eventually progress to fibrosis, cirrhosis, and HCC, and that may necessitate eventual liver transplantation (Ratzliff et



al. 2010; Karlas et al. 2013). NAFLD has been estimated to affect between 6 and 45% of the general population, up to 70% of patients with T2DM, and nearly 90% of patients with morbid obesity (Fazel et al. 2016). It is estimated that NASH affects approximately 20% of patients with NAFLD, and that 30 to 40% of these patients will eventually develop complications such as fibrosis (Spengler & Loomba 2015). At present, there is no US FDA-approved treatment specific for NASH, though potential treatments such as vitamin E therapy and the use of insulin-sensitizing drugs have been investigated for several years.

The use of TZDs in the treatment of NASH has been explored in numerous clinical studies (e.g. Aithal et al. 2008; Belfort et al. 2006; Idilman et al. 2008; Neuschwander-Tetri et al. 2003; Promrat et al. 2004; Ratziu et al. 2008; Sanyal et al. 2010), with differing results. For example, in a pilot study investigating whether a combination of pioglitazone with vitamin E (an antioxidant) would be more effective in treating NASH patients than vitamin E alone, Sanyal et al. (2004) found that 10 patients treated with the combination therapy that included pioglitazone, demonstrated greater improvements in NASH histology, including significant decreases in steatosis ( $P < 0.002$ ), cytologic ballooning ( $P < 0.01$ ), Mallory's hyaline ( $P < 0.04$ ), and pericellular fibrosis ( $P < 0.03$ ), than 10 patients receiving vitamin E alone. Conversely, in a full trial (247 patients) examining the effects of pioglitazone or vitamin E with placebo in non-diabetic patients (Sanyal et al. 2010), vitamin E therapy was associated with a significantly higher rate of improvement in NASH compared to placebo (43% vs 19%,  $P = 0.001$ ), but the rate of improvement with pioglitazone as compared with placebo was not significant (34% vs 19%,  $P = 0.04$ ), and pioglitazone did not demonstrate any significant improvement in fibrosis ( $P = 0.12$ ). Pioglitazone therapy did demonstrate significant reductions in serum alanine and aspartate aminotransferase levels ( $P < 0.001$ ), as well as in hepatic steatosis ( $P < 0.001$ ) and lobular

inflammation ( $P = 0.004$ ) compared to placebo, however; pioglitazone therapy was also accompanied by weight gain which may preclude its use in some patients. Though TZDs continue to be explored for use in the treatment of NASH, it should be noted that clinical studies have focused primarily on pioglitazone, most likely due to the cardiovascular concerns surrounding rosiglitazone therapy, and the fact that most NASH patients already have significant risk factors for cardiovascular disease such as obesity.

### *Polycystic ovary syndrome*

PCOS is a common endocrine disorder that affects approximately 5 to 10% of women of reproductive age and is a major cause of infertility (Lujan 2008). Increased androgen levels resulting from hyperinsulinemia are thought to play an important role in the pathogenesis of PCOS in women (Dunaif 1997) where inappropriate pituitary gonadotropin secretion leads to increases in circulating luteinizing hormone (LH) and normal or decreased follicle-stimulating hormone levels (Dereli et al. 2005; Khan et al. 2006). Because hyperinsulinemia is caused by the resistance of peripheral tissues to insulin, and obesity contributes to insulin resistance, PCOS is more often observed in obese women (Dunaif et al. 1987). It has been hypothesized that drugs used to treat hyperinsulinemia could also treat increased androgen levels in women with PCOS (Nestler & Jakubowicz 1996; Nestler et al. 1989): these drugs are often used (off-label) in women with PCOS with positive effects. For example, metformin has been used by many clinicians for several years to decrease serum levels of insulin and to improve clinical and laboratory outcomes in patients with PCOS (Goodman et al. 2015).

Over the past decade, TZDs have been investigated for their role in the treatment of PCOS. For example, in a study of 40 women with PCOS and impaired glucose tolerance that

were randomly assigned to treatment with rosiglitazone (2 or 4 mg/day) for 8 months, rosiglitazone was found to improve ovulatory dysfunction, hirsutism, hyperandrogenemia, and insulin resistance in a dose-dependent manner (Dereli et al. 2005). In a shorter study evaluating the effects of 2 months of pioglitazone treatment (30 mg/day) on insulin response, serum levels of androgens and sex hormone-binding globulin (SHBG), and pituitary gonadotropin response to gonadotropin-releasing hormone (GnRH) stimulation in 15 obese women with PCOS, Garmes et al. (2005) found a significant decrease in insulin response and total and free testosterone levels, an increase in SHBG, and a reduction in LH response to GnRH stimulation after pioglitazone treatment. TZDs have also been demonstrated to be as, or more effective than metformin (Ciaraldi et al. 2013; Li et al. 2011), with pioglitazone demonstrating the most positive effects. In a meta-analysis of ten clinical trials assessing the effectiveness and safety of metformin compared to pioglitazone and rosiglitazone in the treatment of PCOS, Li et al. (2011) found that TZDs were superior to metformin in reducing serum levels of free testosterone ( $P = 0.03$ ) and dehydroepiandrosterone sulfate ( $P = 0.002$ ) after 3 months treatment with fewer side effects. Decreases in body mass index were, however, greater with metformin treatment at 3 and 6 months ( $P < 0.00001$ ). In another meta-analysis of six trials that included 278 women (Du et al. 2012), pioglitazone was found to be significantly more effective than metformin in reducing fasting insulin levels ( $P = 0.002$ ) and insulin resistance index ( $P = 0.014$ ) but less effective than metformin in reducing body mass index ( $P = 0.038$ ). Pioglitazone has also been demonstrated to be more effective than metformin in reducing chronic low-grade inflammation in PCOS patients. In a study comparing the effects of both drugs on patients with PCOS and healthy patients of similar body mass index (Ciaraldi et al. 2013), markers of inflammation in skeletal muscle were improved with pioglitazone treatment, but not metformin treatment.

TZDs have also been shown to be more effective when used in combination with metformin than when metformin or TZDs are used alone since TZDs are superior to metformin in reducing insulin resistance and insulin levels, while metformin can reduce body weight in PCOS patients, or at least minimize TZD-related weight gain (Du et al. 2012). It should be noted that although these treatments are promising, neither metformin nor TZDs are approved for use in treating PCOS and rosiglitazone is generally not used off-label because of cardiovascular safety concerns. Though prescribed by some clinicians, pioglitazone is not routinely used in PCOS patients because of concerns related to its osteological and carcinogenic risks, whereas metformin is generally preferred due to its long-term safety record including its safety of use during pregnancy (Yau et al. 2013).

#### *Other effects*

In addition to the diseases and conditions described above, TZDs have also been proposed as treatments for a diverse variety of other conditions, from hormonal disorders such as Cushing's disease (Heaney et al. 2003) and Grave's disease (Zhang et al. 2014), polycystic kidney disease (Indiana University 2016; Nagao & Yamaguchi 2012), skin conditions, physiological and psychological disorders, to erectile dysfunction (Aliperti & Hellstrom 2014; Gholamine et al. 2008; Kovanecz et al. 2006; Kovanecz et al. 2007), in hopes of finding novel or more effective treatments. For example, TZDs may be candidates for the treatment of psoriasis as rosiglitazone has been demonstrated to significantly inhibit the proliferation, motility, and matrix metalloproteinase production of skin keratinocytes (Bhagavathula et al. 2004), and topical application of ciglitazone and troglitazone have been shown to significantly reduce epidermal keratinocyte proliferation in rodent models (Demerjian et al. 2006). However, only one study has

been conducted in humans to date (Pershadsingh et al. 2005) and, although improvements in psoriasis plaques were observed after 26 weeks of rosiglitazone therapy, the study included only two cases (one diabetic patient and one non-diabetic patient).

Another interesting but not widely investigated use for TZDs is in the treatment of psychological stress and mental health conditions. Physiological reactions to psychological stress have been positively associated with several chronic conditions including digestive, neurodegenerative, and cardiovascular diseases, in addition to T2DM itself, and stress reactions have also been linked to increased mortality. Rats treated with rosiglitazone have exhibited reductions in initial heart rate response to acute restraint stress and a blunted hormonal response (Ryan et al. 2012); in humans, however, the potential adverse cardiovascular effects associated with rosiglitazone may preclude its use in patients with existing cardiovascular disease or with cardiovascular or other risk factors. Patients with metabolic syndrome and major depressive disorder or bipolar disorder have also demonstrated improvements in their symptoms with pioglitazone treatment (Kemp et al. 2012; Kemp et al. 2014), as have patients without metabolic syndrome or T2DM (Zeinoddini et al. 2015); this could provide a novel treatment for disorders that are often difficult to treat and currently use drugs that are often not well-tolerated by patients.

Though these examples are not exhaustive, research into the applicability of TZD therapy to diseases other than T2DM continues, even with the continued concerns of adverse effects that have been described in this review. It remains to be seen whether the use of TZDs continues to be investigated, and whether new TZDs or TZD-like compounds that are currently under development are marketed in the future.

### 4.3 New drug development

TZDs were first investigated more than three decades ago when it was discovered that these compounds could lower circulating glucose, lipid, and insulin levels by increasing the sensitivity of peripheral tissues to insulin (Colca et al. 2014a; Fujita et al. 1983). The first TZD drug tested in clinical trials was ciglitazone, which is considered to be a prototype for subsequent TZD class drugs (but was never marketed because of hepatotoxicity), followed by pioglitazone, though troglitazone was the first drug to be approved for the market in 1997 followed by rosiglitazone and then pioglitazone in 1999 (Colca et al. 2014b). Since initial market authorization of these drugs, many new TZDs and TZD-like compounds have been investigated with most new drugs targeting PPARs through changes in the design and synthesis of analogs to activate or antagonize PPAR $\gamma$  or other nuclear receptors from the PPAR family including PPAR $\delta$ , PPAR $\gamma/\alpha$ , or PPAR $\gamma/\alpha/\delta$  (Kliwer et al. 2001). For example, PPAR $\alpha$  was the first subtype identified which led to the development and marketing of agonist drugs that improved lipid profiles such as clofibrate, fenofibrate, and gemfibrozil (Chang et al. 2007). However, the development of drugs targeting PPAR $\beta/\delta$  in hopes of developing similar treatments for atherosclerosis in addition to metabolic syndrome and T2DM were less successful as the only candidate that advanced to clinical trials (GW501516) was abandoned in 2007 because of undisclosed safety concerns (Billin 2008) that were later reported to be a result of cancer in animal models (Mackenzie & Lione 2013).

On the whole, the development of new TZD drugs for use in the treatment of T2DM has been unsuccessful. No new full or partial PPAR $\gamma$  agonists have been marketed since rosiglitazone or pioglitazone. The novel TZD drug rivoglitazone, which is currently under development and is considered to be more potent and have a longer half-life than rosiglitazone or

pioglitazone (Koffarnus et al. 2013), has been investigated in only three clinical trials to date. In the first, a 26-week randomized, double-blind, double-dummy, placebo and active comparator controlled study (Truitt et al. 2010) designed to evaluate its efficacy and safety in 441 subjects with T2DM, all doses of rivoglitazone (1, 2, or 3 mg/day) demonstrated A1C reductions similar or superior to those observed for pioglitazone (45 mg/day). However, the incidence of early discontinuations in the study was > 50%, with the highest number of patients discontinuing treatment in the rivoglitazone groups compared to the placebo or pioglitazone groups due to a lack of efficacy or because of adverse effects such as peripheral edema and weight gain (two patients in the rivoglitazone groups also reported peripheral fractures). In a second double-blind, randomized, placebo- and active-controlled study of 174 patients with poorly-controlled T2DM who were randomized into one of the five treatment arms for 12 weeks, patients taking a dose of 0.5 (n = 35), 1.0 (n = 35) or 1.5 mg/day (n = 34) of rivoglitazone demonstrated improvements in A1C comparable to patients taking 30 mg/day of pioglitazone (n = 37) and superior to patients taking placebo (n = 33) (Kong et al. 2011). Drug-related edema was reported less often in the three rivoglitazone groups than in the pioglitazone group, but more often than in the placebo group. In a third clinical trial evaluating the efficacy and safety of rivoglitazone in patients with T2DM who were drug treatment-naïve or who were being treated with non-TZD drugs, patients were randomized to placebo (n = 137), rivoglitazone treatment (1.0 or 1.5 mg/day [n = 274 and 750, respectively), or pioglitazone (45 mg/day [n = 751]) for 26 weeks (Chou et al. 2012). In subjects with poorly controlled T2DM 1.5 mg/day of rivoglitazone, but not 1 mg/day, was associated with a statistically significant improvement in glycemic control compared to pioglitazone (P = 0.0339), but also with a similar frequency of adverse reactions including edema and weight gain. Though these studies are promising they have been relatively short in duration,

have had small sample sizes, and one study had a high rate of discontinuation; studies of longer duration with larger patient populations are therefore needed to fully assess the potential benefits and risks associated with rivoglitazone.

Perhaps the most promising new area of development was thought to be that of dual PPAR $\alpha$ / $\gamma$  agonists and more recently pan PPAR $\alpha$  / $\gamma$  / $\delta$  agonists; however, the results of studies investigating new compounds targeting multiple PPAR receptors have been disappointing. As previously mentioned the glitazars, dual PPAR $\alpha$ / $\gamma$  agonists such as muraglitazar, were discontinued between 2004 and 2006 primarily because of cardiovascular risks and an increased demand for cardiovascular outcome studies, but also because of safety concerns including an increased incidence of cancer observed in rodents at doses relevant to humans (US FDA 2005; Conlon 2006). Though new glitazars have been developed since that time with different structures in an attempt to avoid the adverse effects of their predecessors, they have not proceeded to market authorization and many subsequent studies have been abandoned. For example, Roche pharmaceuticals was investigating the novel dual PPAR $\alpha$ / $\gamma$  agonist aleglitazar (Dietz et al. 2012), but discontinued the investigation in 2013 because of a lack of efficacy and safety issues in clinical trials including a failure to improve cardiovascular outcomes and increased rates of heart failure (3.4% for aleglitazar versus 2.8% for placebo,  $P = 0.14$ ), gastrointestinal hemorrhage (2.4% for aleglitazar versus 1.7% for placebo,  $P = 0.03$ ), and renal dysfunction (7.4% for aleglitazar versus 2.7% for placebo,  $P < 0.001$ ) (Lincoff et al. 2014). A new dual agonist, chiglitazar, is still under investigation in a phase III study (NCT02121717) to evaluate its efficacy and safety in patients with insufficient glycemic control with diet and exercise alone and is currently recruiting participants.



A number of pan PPAR $\alpha$  / $\gamma$  / $\delta$  agonists have also been investigated with similar results to those for dual agonists. For example, investigations of DRL 11605, indeglitazar (also referred to as DPM-204 and PLX-204), GW-625019, sipoglitazar, and sodelglitazar (also referred to as GW-677954) have all been discontinued due to serious safety concerns (Azhar 2010). It is unknown whether netoglitazone (also referred to as MCC-555 or RWJ-241947), which has been investigated *in vitro* and *in vivo* for its antidiabetic effects, higher potency than rosiglitazone (more than 50-fold more potent than in decreasing blood glucose levels in rodent models of type 2 diabetes), and less deleterious effects on bone than other agonists such as pioglitazone (Lazarenko et al. 2006), and that was in phase II testing (Azhar 2010), is still under investigation as the results of trials have not been reported.

Though their mechanism of action is still not completely understood, TZDs and TZD-like compounds have been developed based on the hypothesis that the activation of PPARs is both the cause of, and necessary for, the positive effects of insulin-sensitizers. This hypothesis has evolved over the past 10 years and new non-TZD PPAR $\gamma$  agonists such as selective carboxylic-acid-based agonists and benzylpyrazole acylsulfonamides are being explored (Rikimaru et al. 2011), presumably in an attempt to avoid the adverse reactions that may be associated with TZDs themselves and not necessarily their PPAR target(s). Although these new compounds show promise, research has still focused almost exclusively on nuclear receptors even as no marketable drugs have come from targeted nuclear receptor discovery programmes over the last 15 years (Colca et al. 2014a). This has lead other researchers to hypothesize that this sole focus on nuclear receptors may not be appropriate and that other mechanisms, such as direct effects on mitochondrial metabolism, may be more worthwhile lines of investigation (Colca 2006; Colca et al. 2014b).

## 5. CONCLUSIONS

Although some clinicians and researchers continue to provide a rationale for the use of TZDs in the treatment of T2DM, the clinical trials, observational studies, and meta-analyses described in this review have demonstrated conflicting results with regards to their safety. Current treatment guidelines (ADA 2014) recommend that TZDs be used cautiously, if used at all, in patients who are at risk for CHF, other adverse cardiovascular effects, fractures, or bladder cancer. It remains to be seen how long TZDs continue to be prescribed and whether they will be replaced with alternative antihyperglycemic agents, such as the newer incretin-based therapies that target  $\beta$ -cell function that have less controversial treatment profiles. Studies of more effective PPAR agonists, dual agonists, and antagonists continue to be conducted, and the combination of PPAR $\gamma$  agonists with other cardiovascular drugs may address some of the cardiovascular safety concerns associated with the TZD class (Abbas et al. 2012). As well, the repurposing of TZD drugs and the development of new PPAR-targeting medications for the treatment of cancer, PCOS, and other inflammatory diseases may lead to further shifts in drug utilization patterns, if they do continue to be used, and in which patient populations. The therapeutic future of TZDs remains to be seen.

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## **DISCLOSURE OF INTEREST**

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### **CHAPTER 3: DATA ARTICLE 1 - Myocardial infarction, congestive heart failure, and thiazolidinedione drugs: a case-control study using hospital-based data**

Davidson MA, Gravel C, McNair D, Mattison DR, Krewski, D. Myocardial infarction, congestive heart failure, and thiazolidinedione drugs: a cohort study using hospital-based data. Unpublished manuscript;2018.

### **PREFACE**

This manuscript presents the results of a pharmacoepidemiological study of the cardiovascular risks associated with thiazolidinedione drugs. Specifically, a nested case-control study was designed and conducted to investigate associations between thiazolidinedione use and risk of myocardial infarction and congestive heart failure in a population of Type 2 diabetics. The study accounts for the potential confounding effects of a variety of demographic factors, health care facility characteristics, concomitant therapies, and comorbidities. The statement of contributions of collaborators and co-authors, including the student's individual contribution, can be found in the acknowledgements at the end of this manuscript.

## **Myocardial infarction, congestive heart failure, and thiazolidinedione drugs: a case-control study using hospital-based data**

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of Ottawa Canada.

**Keywords:** Thiazolidinedione, pioglitazone, rosiglitazone, cardiovascular, myocardial infarction, heart failure.

The data used in this study were provided to the University of Ottawa by Cerner Corporation under a Material Transfer Agreement allowing for the data to be used for research purposes. Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this manuscript.

## ABSTRACT

**Objective:** To determine if use of thiazolidinedione (TZD) drugs is associated with an increased risk of myocardial infarction (MI) and congestive heart failure (CHF) in a cohort of Type 2 diabetics.

**Design:** A nested case-control analysis.

**Setting:** Hospitals in the United States contributing to the Cerner HealthFacts® datawarehouse.

**Participants:** A MI cohort of 11,611 patients and a CHF cohort of 9,229 patients with Type 2 diabetes who initiated treatment with metformin or sulphonylurea monotherapy between January 1, 2000 and December 31, 2012 who then switched to or added-on another antidiabetic drug.

**Main outcome measures:** Within each cohort (MI and CHF) we conducted nested case-control analyses where incident cases of MI and CHF were matched to up to 10 controls on sex, race, age, year of study cohort entry, and duration of follow-up. Odds ratios (ORs) and 95% confidence intervals (CIs) for incident MI and CHF were estimated comparing use of TZDs with use of other antidiabetic drugs.

**Results:** During 19,838 person years of follow-up (median follow-up ranging from 0.2 to 2.6 years; maximum 11.9 years), 432 patients were newly diagnosed as having had a MI (crude incidence rate 21.8 per 1000 person years) and 1,176 patients were newly diagnosed with CHF (crude incidence rate 72.5 per 1000 person years) during 16,219 person years of follow-up (median follow-up ranging from 0.2 to 2.7 years; maximum 11.9 years). The populations of both study cohorts were older in age with a mean age of 73.5 years for cases with MI and 72.1 years for cases with CHF. Overall, both exclusive ever use of pioglitazone and exclusive ever use of rosiglitazone were significantly associated with an increased risk of adverse cardiovascular

events. Compared with use of other antidiabetic drugs, pioglitazone (OR: 3.87, 95% CI: 2.52-5.94) and rosiglitazone (OR: 3.68, 95% CI: 2.18-6.21) were associated with a comparable risk of MI. For CHF, pioglitazone (OR: 4.15, 95% CI: 3.21-5.37) was associated with a greater risk than rosiglitazone (OR: 2.69, 95% CI: 1.91-3.80).

**Conclusions:** In this hospital-based cohort of older patients, TZD use was associated with an increased risk of MI and CHF.

## INTRODUCTION

Cardiovascular safety concerns related to weight gain, edema, congestive heart failure (CHF), myocardial infarction (MI), and increased mortality have been raised for thiazolidinedione (TZD) class drugs for over ten years. Some studies have implicated rosiglitazone [1-3] but not pioglitazone in clinical trials [4-8] or observational studies where both rosiglitazone and pioglitazone were compared [9-13]. Other observational studies and meta-analyses have implicated both rosiglitazone and pioglitazone equally [14, 15] or have found negative associations with pioglitazone [16, 17] or rosiglitazone [18-19] alone. Others still have found no adverse cardiovascular effects associated with rosiglitazone use [20-21] or use of either TZD drug [22]. Though the focus of investigation in recent years has been primarily on rosiglitazone and its associations with MI and CHF, mainly because of a lack of association with pioglitazone observed in clinical trials, to date there is still no consensus in the research, medical, or regulatory communities on the adverse cardiovascular effects of TZDs, as demonstrated by continued conflicting evidence.

Attention was first drawn to the potential adverse cardiovascular effects of TZDs when an early meta-analysis of 42 short-term clinical studies reported that rosiglitazone was associated with a 43% higher risk of MI [18]. A patient-level analysis performed by the manufacturer of rosiglitazone [23] confirmed these findings, as did a meta-analysis conducted by Singh et al. [19] that found that rosiglitazone increased the risk of MI by 42% (relative risk [RR]: 1.42, 95% confidence interval [CI]: 1.06-1.91) compared with other oral hypoglycaemic agents, but without an increased risk of cardiovascular death (RR: 0.90, 95% CI: 0.63-1.26,  $P = 0.53$ ). A case-control study by Lipscombe et al. [9] also found an increased risk of CHF (RR: 1.60, 95% CI: 1.21-2.10,  $P < 0.001$ ), MI (RR: 1.40, 95% CI: 1.05-1.86,  $P = 0.02$ ), and death (RR: 1.29,

95% CI: 1.02-1.62,  $P = 0.03$ ) for TZD monotherapy in older patients with T2DM (mean age 74.7 years) with associations primarily occurring with rosiglitazone. By contrast for pioglitazone, a meta-analysis of 19 trials [24] suggested that even though it appeared to increase the risk of CHF, pioglitazone may actually reduce the risk of MI, stroke, or death. Subsequent studies have also found increased risks of CHF in pioglitazone-treated patients [16, 17].

The publication of the initial meta-analysis [18] that reported an increased risk of MI led to an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial. RECORD, a noninferiority open-label trial of rosiglitazone in 4,447 T2DM patients, was originally a 6-year randomized study of patients with inadequate glycaemic control when using metformin or a sulphonylurea alone, who added-on rosiglitazone, metformin, or a sulphonylurea with a goal of reducing glycated hemoglobin (A1C) to 7% or less [1]. The primary study end point was hospitalization for acute MI, CHF, stroke, unstable angina, transient ischemic attack, unplanned revascularisation, amputation of extremities, or any other definitive cardiovascular reason, or cardiovascular mortality. Interim analysis after 3.7 years of follow-up demonstrated an increased risk of CHF with rosiglitazone (hazard ratio [HR]: 2.15, 95% CI: 1.30-3.57), but no increase in death from cardiac causes or all-cause mortality [1]. The data were insufficient to determine whether rosiglitazone was associated with an increased risk of MI but possible associations could not be ruled out. Subsequent analysis of the trial at 5.5 years of follow-up [2] also found a similarly increased risk of CHF with rosiglitazone (HR: 2.10, 95% CI: 1.35-3.27) but no statistically significant differences between the rosiglitazone group and the control group for MI, stroke, or death. In reaction to the results of the aforementioned studies and others, rosiglitazone access was restricted in the United States (US) in September 2010 and rosiglitazone was removed from the market in Europe.

Since that time some, but not all studies have found increased risks of MI and CHF with TZD use. For example, in the most recent re-evaluation of the RECORD trial [25] the HR for rosiglitazone compared to metformin and sulphonylureas for a composite of cardiovascular mortality, stroke, and MI was 0.95 (95% CI: 0.78-1.17) compared with 0.93 (95% CI: 0.74-1.15) from the original RECORD results. Treatment comparisons for MI (HR: 1.13, 95% CI: 0.80-1.59) and mortality (HR: 0.86, 95% CI: 0.68-1.08) were also the same compared with the original results (HR: 1.14, 95% CI: 0.80-1.63 for MI; HR: 0.86, 95% CI: 0.68-1.08 for mortality) suggesting that the cardiovascular risks for rosiglitazone were similar to metformin and sulphonylureas. In reaction to the results of this study the US Food and Drug Administration (US FDA) conducted a risk re-evaluation leading to the removal of restrictions for rosiglitazone in November 2013 even though many in the pharmacovigilance community were not in agreement with the risk re-evaluation itself or with the final decision to remove the restrictions [26].

Today, controversy still exists as to whether the increased risks seen with TZD therapy in some studies is justified, or if the reporting of adverse events with low baseline risks has exaggerated the risk of cardiovascular events. The continued lack of concurrence of research findings, and the differing approaches taken by regulatory agencies globally with regards to rosiglitazone demonstrate that more research is needed to further clarify associations between TZD use and cardiovascular risk. Further research is also needed to inform decisions related to the use and long-term safety of TZD drugs as other adverse effects such as bone fractures and bladder cancer continue to be investigated and these drugs are being used off-label in the treatment of other diseases and conditions such as cancer [27]. To this end, we conducted nested case-control studies to determine if rosiglitazone or pioglitazone are associated with an increased risk of incident MI and CHF in people with T2DM.

## **METHODS**

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, ON, Canada.

### **Data source**

This study was carried out using the Cerner Health Facts® datawarehouse (Kansas City, MO, US), a longitudinal database of electronic health record data from over 480 contributing hospitals throughout the US. Health Facts® contains anonymized data of encounters for over 41 million people and includes demographics, diagnoses, prescriptions, procedures, laboratory testing, hospital information, service location, and billing data. At the time of analysis this datawarehouse contained encrypted and time-stamped information on distinct inpatient admissions and discharges, emergency department encounters, and outpatient encounters. Each patient encounter within the datawarehouse is linked by unique patient and encounter identifiers to permit the assessment of treatments over time including diagnostics and procedures, and medications prescribed and dispensed. Information contained in the datawarehouse used for the analyses consisted of patient demographics, hospital or clinic characteristics, prescribed and dispensed medications (orders, dispensing events, billing information, National Drug Code number, quantity, and date of administration), and medical events, procedures, and diagnoses (International Classification of Diseases, 9th Edition [ICD-9] codes).

### **Study population**

Type 2 diabetics often receive antidiabetic drug prescriptions from a general practitioner outside of a hospital or outpatient setting. This introduces the possibility of capturing prevalent



users in hospital-based administrative data [28]. To address potential prevalent user bias in this study, a design [29] was employed that first assembled a base cohort population of patients who had a similar level of T2DM disease severity, and from that base cohort, two study cohorts of patients who intensified or progressed their treatment regime by switching to, or adding-on another oral antihyperglycaemic agent (OHA) or insulin to establish study populations that are more likely to contain incident drug users (**Figures 1-2**).

### *Base cohort*

A base cohort was assembled consisting of all patients who commenced treatment for T2DM with a first ever antidiabetic drug prescription of metformin or sulphonylurea monotherapy between January 1, 2000 and December 31, 2012. Patients initiating treatment with these drugs were selected to establish a patient population with a comparable level of T2DM severity, to the extent possible, from which to sample from for the study cohorts. The date of each patient's first metformin or sulphonylurea monotherapy prescription defined entry into the base cohort. Patients were then excluded if they had any of the following characteristics at entry to the base cohort: age less than 18 years and women with a history of diagnosed polycystic ovarian syndrome or a diagnosis of gestational diabetes before entry into the base cohort, as these conditions are other possible indications for metformin.

### *Study cohorts*

Within the base cohort, two study cohorts (MI: **Figure 1**; CHF: **Figure 2**) were established consisting of all patients who added on or switched to an OHA drug class not previously identified in their drug history, or insulin, on or after March 30, 2000 (the year where

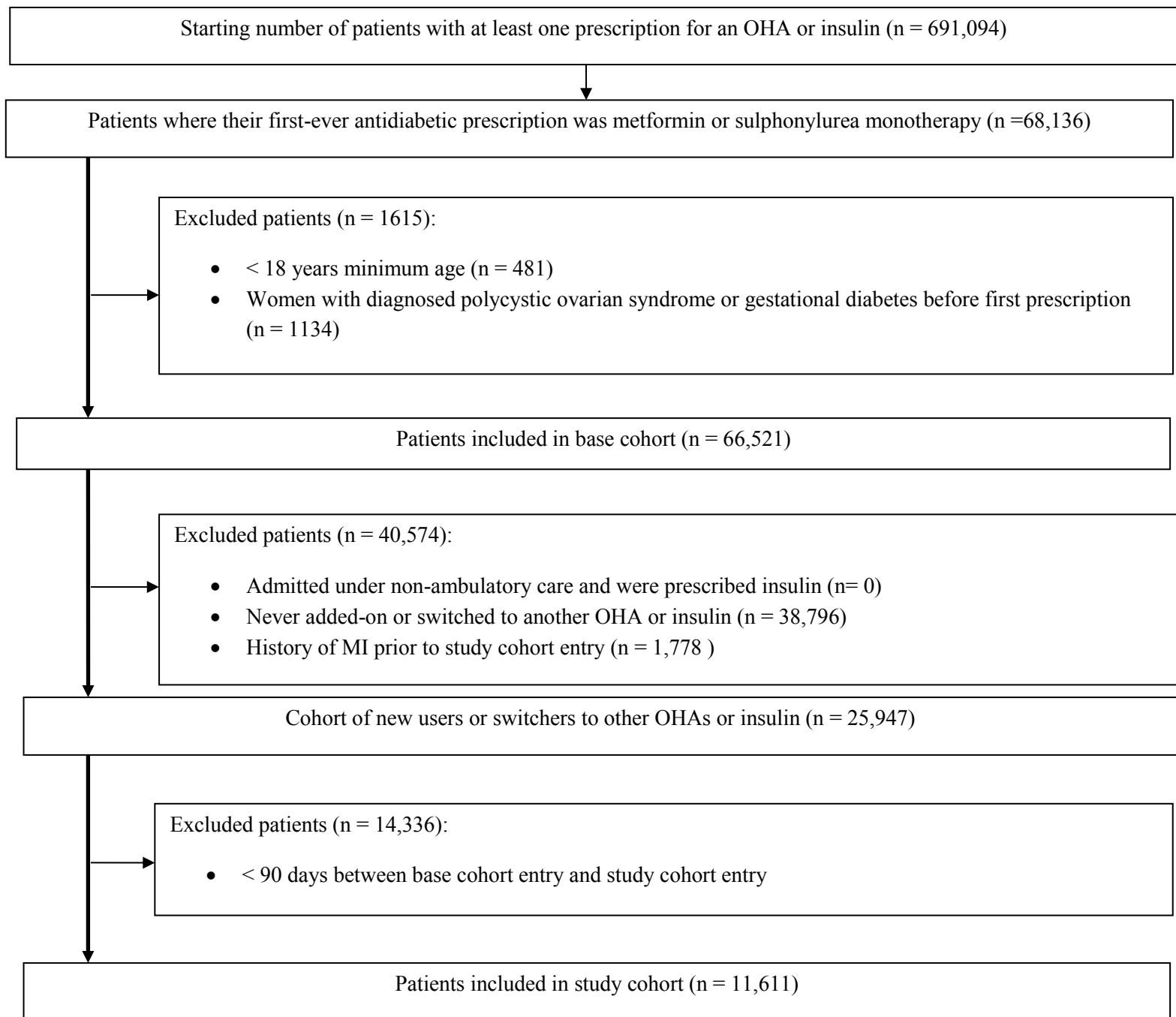


**Figure 1.** Establishment of base and study cohorts and flow of participants in the cardiovascular study design for MI.

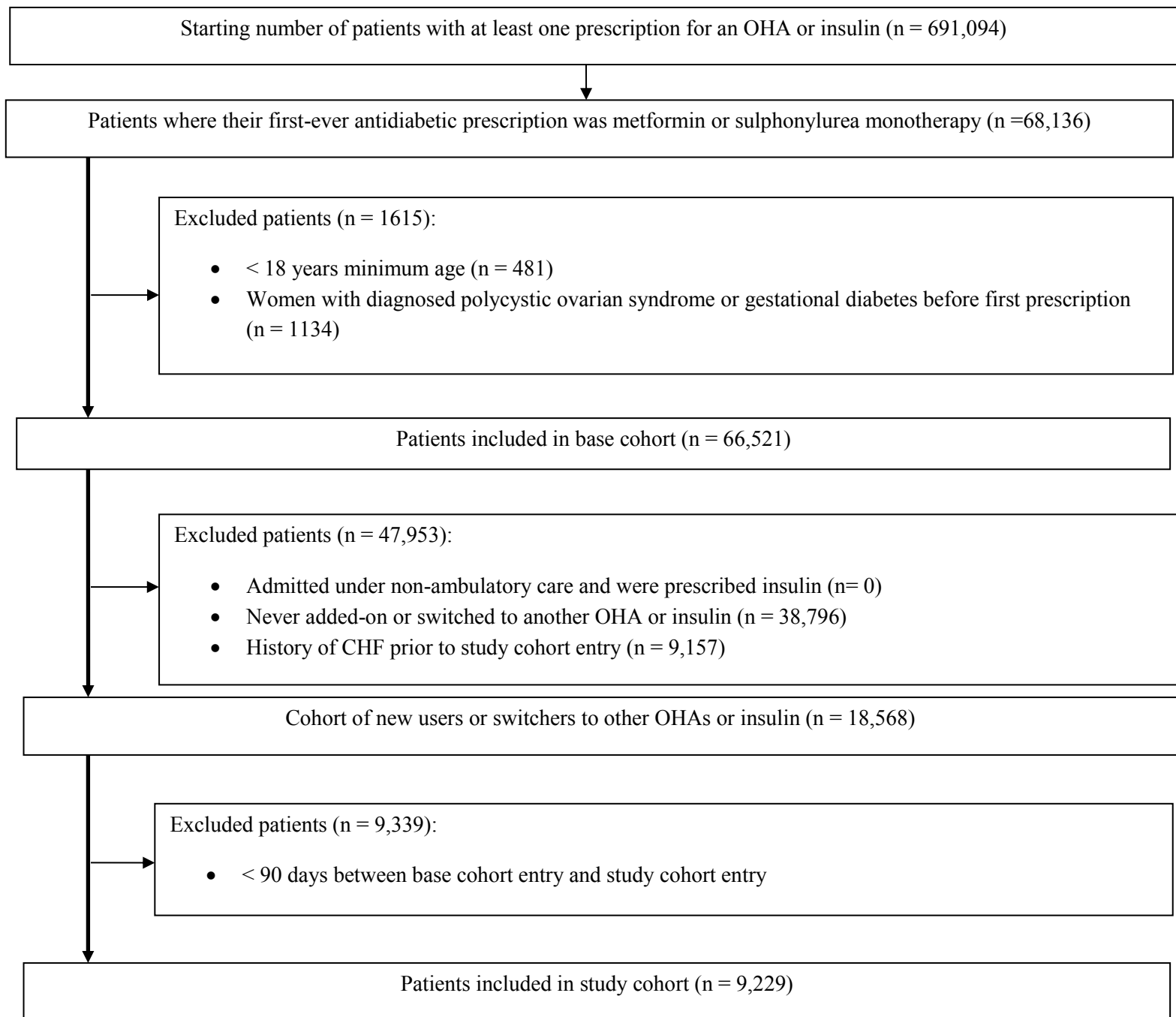


**Figure 2.** Establishment of base and study cohorts and flow of participants in the cardiovascular study design for CHF.

rosiglitazone and pioglitazone first appeared in the dataset and the year immediately following the approval of rosiglitazone and pioglitazone for the US market) until December 31, 2012. The date of this new prescription defined entry to each study cohort. Patient encounters where the first new antidiabetic prescription was for insulin and where that patient was not in an ambulatory state (i.e. being treated in an intensive care unit) were censored to account for situations where insulin may be administered in-hospital to non-ambulatory patients instead of their normal course of antidiabetic therapy (e.g. an OHA). However, these patients were permitted to re-enter the cohort at the time of their next antidiabetic prescription where they were in an ambulatory state. Patients were then excluded from the MI study cohort if they had a history of MI prior to study cohort entry and the CHF study cohort if they had a history of CHF prior to study cohort entry. Patients were excluded from both cohorts if they had less than 90 days between base cohort entry and study cohort entry to take into account a timeframe within which other antidiabetic drug prescriptions would reasonably be expected to appear in their medical records.

### **Follow-up**

Patients meeting the study inclusion criteria were followed from the date of study cohort entry until a diagnosis of MI (ICD-9 diagnostic codes 410, 410.x, and 410.xx), CHF (ICD-9 codes 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, and 428.x), death from any cause, their last encounter in the dataset, or end of the study period (December 31, 2012), whichever occurred first.

## **Selection of cases and controls**

To investigate associations between TZD pharmacotherapy, MI, and CHF we carried out nested case-control analyses. As described by Azoulay et al. [30], this approach was used because of the time varying nature of drug use, the size of the cohorts, and the long duration of follow-up in the dataset [31]. Compared with a full cohort approach, using a nested case-control analysis is computationally more efficient [32-33]. We used risk set sampling for the matching of controls to cases as this method produces odds ratios (ORs) that are unbiased estimators of HRs [31, 33-34].

All incident cases of MI and CHF were identified during follow-up. For each case, the first hospital admission with a diagnosis of MI or CHF, respectively, was used to define the index date. Up to 10 controls were randomly selected from the case's risk set after matching on age ( $\pm 1$  year), sex, race, year of cohort entry ( $\pm 1$  year), and duration of follow-up ( $\pm 1$  year). Matched controls were assigned the index date of their respective cases.

## **Drug exposure and use of thiazolidinediones**

All OHAs and insulin approved by the US FDA for use during the study period (including those under restricted access, i.e. rosiglitazone) were identified in the dataset. For cases and controls we obtained prescription information for drugs prescribed at any time before the index date using time and date-stamped pharmacy orders, dispensing events, and National Drug Code numbers within the dataset. Antidiabetic drug exposure was defined as receiving at least one prescription preceding the index date.

Use of TZDs was classified into one of the four mutually exclusive categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and rosiglitazone use (mainly switchers from one drug to the other), and 4) never use of any TZD. Never users of any TZD were used as the reference group. Patients were considered unexposed to TZDs until the time of their first TZD prescription.

### **Statistical analysis**

Descriptive statistics were used to summarise the baseline characteristics of matched cases and controls at cohort entry. Conditional logistic regression was used to estimate ORs and corresponding 95% CIs for associations between TZD use and risk of MI and CHF.

In addition to age, sex, race, year of cohort entry, and duration of follow-up (on which the logistic regression models were conditioned) models were adjusted for several potential confounders if their inclusion changed the estimate of risk by 10% or more. Potential confounders measured at entry to the study cohort included: payer class (as a surrogate for socioeconomic status), census region, region type (urban/rural), treatment center size (number of hospital beds), and treatment center type (teaching/non-teaching, acute care/non-acute care). Known risk factors for cardiovascular events and related medications [35-36] measured at any time before study cohort entry included: angina, atrial fibrillation or flutter, previous cancer (other than non-melanoma skin cancer), CHF (only in the MI study cohort), chronic obstructive pulmonary disease (COPD), coronary artery/heart disease (CAD), dyslipidemia, hypertension, MI (only in the CHF study cohort), peripheral vascular disease (PVD), ischemic stroke, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, and nonsteroidal

anti-inflammatory drugs (NSAIDs). Models were also adjusted for excessive alcohol use (based on alcohol related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), obesity (treatment for obesity or body mass index greater than 30 kg/m<sup>2</sup>), and smoking (ever/never) measured at any time prior to, or after study cohort entry. Finally, models were adjusted for total number of hospital admissions and total number of unique non-diabetic drugs prescribed, both measured in the 90 days prior to, and after cohort entry, and entered as four level ordered categorical variables, as general measures of comorbidity [37].

The primary analyses evaluated whether exclusive ever use of pioglitazone, exclusive ever use rosiglitazone, or use of pioglitazone and rosiglitazone, when compared with never use of any TZD (the reference group), were associated with an increased risk of MI and CHF. Due to the hospital-based nature of the data, analyses investigating potential dose-response relationships could not be reliably conducted as it could not be determined with certainty if patients received other prescriptions outside of the Cerner network (e.g. by a general practitioner).

### *Sensitivity Analyses*

To assess the robustness of the findings of this study, four sensitivity analyses were conducted. In the first, we contrasted the use of rosiglitazone with the use of pioglitazone by repeating our primary analysis with the latter as the reference category to further assess drug-specific versus class effects. In the second, the primary analyses were repeated with a lag period of less than one year between study cohort entry and the index date to investigate potential early treatment effects. In the third, the primary analyses were repeated with a lag period of at least one year between study cohort entry and the index date to account for uncertainty in the length of

a possible latency period. Finally, the primary analyses were repeated with a lag period of at least two years between study cohort entry and the index date to further account for uncertainty in the length of a possible latency period. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Results are not presented where the number of cases is less than five to account for where the effect estimate is highly uncertain because of small sample size.

## RESULTS

Of the 68,136 patients with a first prescription that was metformin or sulphonylurea monotherapy, 11,611 met the study inclusion criteria for MI (**Figure 1**) and 9,229 patients met the study inclusion criteria for CHF (**Figure 2**). In the MI study cohort, mean age at cohort entry was 68.7 years, 46.9% were men, and the median duration of follow-up across participating facilities in the Cerner network ranged from 0.2 to 2.6 years with a maximum of 11.9 years. Overall, the study cohort generated 19,838 person years of follow-up. During this time 432 patients were newly diagnosed as having an MI, generating a crude incidence rate of 21.8 per 1,000 person years (95% CI: 19.7-23.8). In the CHF study cohort, mean age at cohort entry was 67.2 years, 46.3% were men, and the median duration of follow-up across participating facilities in the Cerner network ranged from 0.2 to 2.7 years with a maximum of 11.9 years. Overall, the study cohort generated 16,219 person years of follow-up. During this time 1,176 patients were newly diagnosed with CHF, generating a crude incidence rate of 72.5 per 1,000 person years (95% CI: 68.4-76.7).

### *Baseline characteristics*

The baseline characteristics of 418 cases of MI and 3,816 matched controls, and 1,134 cases of CHF and 9,636 matched controls are presented in **Table 1**. Of the initial unmatched



**Table 1.** Baseline characteristics of cases and matched controls for MI and CHF. Values are numbers (percentages) unless stated otherwise.

| Characteristic                                  | MI                 |                         | CHF                  |                         |
|-------------------------------------------------|--------------------|-------------------------|----------------------|-------------------------|
|                                                 | Cases<br>(n = 418) | Controls<br>(n = 3,816) | Cases<br>(n = 1,134) | Controls<br>(n = 9,636) |
| <b>Mean (SD) age (years)*</b>                   | <b>73.5 (11.3)</b> | <b>74.4 (10.9)</b>      | <b>72.1 (11.6)</b>   | <b>73.2 (11.0)</b>      |
| 18-25                                           | 1 (0.2)            | 9 (0.2)                 | 1 (0.1)              | 33 (0.3)                |
| 26-35                                           | 3 (0.7)            | 46 (1.2)                | 18 (1.6)             | 145 (1.5)               |
| 36-45                                           | 13 (3.1)           | 168 (4.4)               | 59 (5.2)             | 518 (5.4)               |
| 46-55                                           | 58 (13.9)          | 459 (12.0)              | 151 (13.3)           | 1,318 (13.7)            |
| 56-65                                           | 73 (17.5)          | 751 (19.7)              | 254 (22.4)           | 1,958 (20.3)            |
| 66-75                                           | 108 (25.8)         | 951 (24.9)              | 254 (22.4)           | 2,475 (25.7)            |
| 76-85                                           | 125 (29.9)         | 1,054 (27.6)            | 301 (26.5)           | 2,383 (24.7)            |
| >85                                             | 37 (8.9)           | 378 (9.9)               | 96 (8.5)             | 806 (8.4)               |
| <b>Men*</b>                                     | <b>217 (51.9)</b>  | <b>1,835 (48.1)</b>     | <b>510 (45.0)</b>    | <b>4,564 (47.4)</b>     |
| <b>Year of study cohort entry*</b>              |                    |                         |                      |                         |
| 2000                                            | 2 (0.5)            | 5 (0.1)                 | 9 (0.8)              | 19 (0.2)                |
| 2001                                            | 27 (6.5)           | 161 (4.2)               | 42 (3.7)             | 163 (1.7)               |
| 2002                                            | 26 (6.2)           | 215 (5.6)               | 89 (7.9)             | 541 (5.6)               |
| 2003                                            | 28 (6.7)           | 240 (6.3)               | 68 (6.0)             | 490 (5.1)               |
| 2004                                            | 35 (8.4)           | 326 (8.5)               | 93 (8.2)             | 743 (7.7)               |
| 2005                                            | 28 (6.7)           | 275 (7.2)               | 82 (7.2)             | 666 (6.9)               |
| 2006                                            | 37 (8.9)           | 361 (9.5)               | 93 (8.2)             | 804 (8.3)               |
| 2007                                            | 30 (7.2)           | 268 (7.0)               | 80 (7.1)             | 684 (7.1)               |
| 2008                                            | 55 (13.2)          | 525 (13.8)              | 138 (12.2)           | 1,294 (13.4)            |
| 2009                                            | 46 (11.0)          | 442 (11.6)              | 148 (13.1)           | 1,411 (14.6)            |
| 2010                                            | 47 (11.2)          | 443 (11.6)              | 127 (11.2)           | 1,232 (12.8)            |
| 2011                                            | 45 (10.8)          | 435 (11.4)              | 123 (10.9)           | 1,179 (12.2)            |
| 2012                                            | 12 (2.9)           | 120 (3.1)               | 42 (3.7)             | 410 (4.3)               |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.7 (2.1)</b>   | <b>1.7 (2.2)</b>        | <b>1.6 (1.9)</b>     | <b>1.7 (1.9)</b>        |
| <b>Race*</b>                                    |                    |                         |                      |                         |
| Caucasian                                       | 350 (83.7)         | 3,168 (83.0)            | 891 (78.6)           | 7,663 (79.5)            |
| African-American                                | 60 (14.4)          | 562 (14.7)              | 200 (17.6)           | 1,603 (16.6)            |
| Other                                           | 8 (1.9)            | 86 (2.3)                | 43 (3.8)             | 370 (3.8)               |
| <b>Payer class</b>                              |                    |                         |                      |                         |
| Medicare                                        | 105 (25.1)         | 1,009 (26.4)            | 292 (25.8)           | 2,653 (27.5)            |
| Other                                           | 45 (10.8)          | 503 (13.2)              | 216 (19.1)           | 1,807 (18.8)            |
| Unknown                                         | 268 (64.1)         | 2,304 (60.4)            | 626 (55.2)           | 5,176 (53.7)            |
| <b>Census region</b>                            |                    |                         |                      |                         |
| Northeast                                       | 177 (42.3)         | 1,617 (42.4)            | 489 (43.1)           | 4,220 (43.8)            |
| Midwest                                         | 78 (18.7)          | 691 (18.1)              | 232 (20.5)           | 1,894 (19.7)            |
| West                                            | 15 (3.6)           | 153 (4.0)               | 59 (5.2)             | 505 (5.2)               |
| South                                           | 148 (35.4)         | 1,355 (35.5)            | 354 (31.2)           | 3,017 (31.3)            |

Table 1. *Continued.*

| Characteristic                                             | MI                 |                         | CHF                  |                         |
|------------------------------------------------------------|--------------------|-------------------------|----------------------|-------------------------|
|                                                            | Cases<br>(n = 418) | Controls<br>(n = 3,816) | Cases<br>(n = 1,134) | Controls<br>(n = 9,636) |
| <b>Region type</b>                                         |                    |                         |                      |                         |
| Urban                                                      | 418 (100.0)        | 3,807 (99.8)            | 1,130 (99.7)         | 9,615 (99.8)            |
| Rural                                                      | 0 (0.0)            | 9 (0.2)                 | 4 (0.4)              | 21 (0.2)                |
| <b>Treatment center type</b>                               |                    |                         |                      |                         |
| Acute care                                                 | 388 (92.8)         | 3,596 (94.2)            | 1,102 (97.2)         | 9,378 (97.3)            |
| Non-acute care                                             | 30 (7.2)           | 214 (5.6)               | 31 (2.7)             | 249 (2.6)               |
| Missing                                                    | 0 (0.0)            | 6 (0.2)                 | 1 (0.1)              | 9 (0.1)                 |
| <b>Treatment center teaching status</b>                    |                    |                         |                      |                         |
| Teaching                                                   | 228 (54.6)         | 2,178 (57.1)            | 707 (62.4)           | 6,018 (62.5)            |
| Non-teaching                                               | 190 (45.5)         | 1,638 (42.9)            | 427 (37.7)           | 3,618 (37.6)            |
| <b>Treatment center beds</b>                               |                    |                         |                      |                         |
| 1-199                                                      | 61 (14.6)          | 508 (13.3)              | 99 (8.7)             | 780 (8.1)               |
| 100-199                                                    | 61 (14.6)          | 629 (16.5)              | 126 (11.1)           | 1,173 (12.2)            |
| 200-299                                                    | 99 (23.7)          | 918 (24.1)              | 320 (28.2)           | 2,804 (29.1)            |
| 300-499                                                    | 68 (16.3)          | 648 (17.0)              | 232 (20.5)           | 1,791 (18.6)            |
| ≥ 500                                                      | 129 (30.9)         | 1,113 (29.2)            | 357 (31.5)           | 3,088 (32.1)            |
| Ever smoker†                                               | 35 (8.4)           | 386 (10.1)              | 143 (12.6)           | 1,209 (12.6)            |
| Ever diagnosis or treatment for obesity‡                   | 116 (27.8)         | 1,320 (34.6)            | 497 (43.8)           | 4,329 (44.9)            |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 21 (5.0)           | 142 (3.7)               | 62 (5.5)             | 452 (4.7)               |
| <b>Comorbidities</b>                                       |                    |                         |                      |                         |
| Angina                                                     | 9 (2.2)            | 153 (4.0)               | 56 (4.9)             | 427 (4.4)               |
| Atrial fibrillation                                        | 35 (8.4)           | 451 (11.8)              | 93 (8.2)             | 777 (8.1)               |
| Previous cancer                                            | 23 (5.5)           | 231 (6.1)               | 94 (8.3)             | 744 (7.7)               |
| Chronic obstructive pulmonary disease                      | 46 (11.0)          | 520 (13.6)              | 145 (12.8)           | 1,203 (12.5)            |
| CHF                                                        | 42 (10.1)          | 513 (13.5)              | -                    | -                       |
| Coronary artery/heart disease                              | 100 (23.9)         | 1,006 (26.4)            | 317 (28.0)           | 2,522 (26.2)            |
| Dyslipidemia                                               | 111 (26.6)         | 1,238 (32.4)            | 429 (37.8)           | 3,716 (38.6)            |
| Hypertension                                               | 169 (40.4)         | 1,749 (45.8)            | 606 (53.4)           | 5,154 (53.5)            |
| MI                                                         | -                  | -                       | 29 (2.6)             | 217 (2.3)               |
| Peripheral vascular disease                                | 21 (5.0)           | 144 (3.8)               | 62 (5.5)             | 436 (4.5)               |
| Ischemic stroke                                            | 11 (2.6)           | 94 (2.5)                | 37 (3.3)             | 244 (2.5)               |

Table 1. *Continued.*

| Characteristic                                 | MI                 |                         | CHF                  |                         |
|------------------------------------------------|--------------------|-------------------------|----------------------|-------------------------|
|                                                | Cases<br>(n = 418) | Controls<br>(n = 3,816) | Cases<br>(n = 1,134) | Controls<br>(n = 9,636) |
| <b>Concomitant medications</b>                 |                    |                         |                      |                         |
| Angiotensin-converting enzyme inhibitors       | 201 (48.1)         | 1,739 (45.6)            | 513 (45.2)           | 4,307 (44.7)            |
| Angiotensin II receptor antagonists            | 62 (14.8)          | 656 (17.2)              | 183 (16.1)           | 1,547 (16.1)            |
| Beta-blockers                                  | 191 (45.7)         | 2,015 (52.8)            | 593 (52.3)           | 4,875 (50.6)            |
| Calcium channel blockers                       | 132 (31.6)         | 1,215 (31.8)            | 370 (32.6)           | 3,010 (31.2)            |
| Diuretics                                      | 190 (45.5)         | 1,856 (48.6)            | 442 (39.0)           | 3,820 (39.6)            |
| Digoxin                                        | 60 (14.4)          | 534 (14.0)              | 90 (70.9)            | 745 (70.7)              |
| Spironolactone                                 | 17 (4.1)           | 206 (5.4)               | 39 (3.4)             | 299 (3.1)               |
| Statins                                        | 200 (47.9)         | 1,818 (47.6)            | 555 (48.9)           | 4,695 (48.7)            |
| Nonsteroidal anti-inflammatory drugs           | 236 (56.5)         | 2,248 (58.9)            | 711 (62.7)           | 5,860 (60.8)            |
| Mean number hospital admissions (SD)           | 2.7 (2.5)          | 2.8 (2.8)               | 2.9 (2.9)            | 2.8 (2.8)               |
| <b>Number of hospital admissions</b>           |                    |                         |                      |                         |
| 1                                              | 176 (42.1)         | 1,630 (42.7)            | 450 (39.7)           | 3,951 (41.0)            |
| 2                                              | 96 (23.0)          | 801 (21.0)              | 245 (21.6)           | 2,082 (21.6)            |
| 3                                              | 48 (11.5)          | 475 (12.5)              | 153 (13.5)           | 1,209 (12.6)            |
| ≥ 4                                            | 98 (23.4)          | 910 (23.9)              | 286 (25.2)           | 2,394 (24.8)            |
| Mean number unique non-diabetic drugs (SD)     | 4.1 (1.6)          | 4.1 (1.7)               | 4.1 (1.7)            | 4.1 (1.7)               |
| <b>Number of unique non-antidiabetic drugs</b> |                    |                         |                      |                         |
| 0                                              | 8 (1.9)            | 75 (2.0)                | 24 (2.1)             | 182 (1.9)               |
| 1                                              | 11 (2.6)           | 142 (3.7)               | 43 (3.8)             | 381 (4.0)               |
| 2                                              | 37 (8.9)           | 375 (9.8)               | 117 (10.3)           | 988 (10.3)              |
| 3                                              | 92 (22.0)          | 787 (20.6)              | 231 (20.4)           | 2,022 (21.0)            |
| ≥ 4                                            | 270 (64.6)         | 2,437 (63.9)            | 719 (63.4)           | 6,063 (62.9)            |
| <b>Antidiabetic drug use<sup>a</sup></b>       |                    |                         |                      |                         |
| Metformin                                      | 203 (48.6)         | 2,037 (46.6)            | 637 (56.2)           | 5,660 (58.7)            |
| Sulphonylureas                                 | 347 (83.0)         | 2,794 (73.2)            | 873 (77.0)           | 6,767 (70.2)            |
| Pioglitazone                                   | 39 (9.3)           | 98 (2.6)                | 108 (9.5)            | 254 (2.6)               |
| Rosiglitazone                                  | 27 (6.5)           | 70 (1.8)                | 58 (5.1)             | 181 (1.2)               |
| DPP-4 inhibitors                               | 28 (6.7)           | 219 (5.7)               | 86 (7.6)             | 583 (6.1)               |
| α-glucosidase inhibitors                       | 5 (1.2)            | 17 (0.5)                | 10 (0.9)             | 53 (0.6)                |
| Meglitinides                                   | 18 (4.3)           | 144 (3.8)               | 60 (5.3)             | 336 (3.5)               |
| Insulins                                       | 410 (98.1)         | 3,533 (92.6)            | 1,102 (97.2)         | 8,851 (91.9)            |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

cases, 14 cases of MI and 42 cases of CHF were removed based on the matching criteria and a lack of controls meeting the same criteria as these cases. In general, when compared to CHF cases, MI cases were slightly older (73.5 years versus 72.1 years, respectively), more likely to be male (51.9% versus 45.0%, respectively), and Caucasian (83.7% versus 78.6 %, respectively). A greater percentage of MI cases were also prescribed rosiglitazone compared to CHF cases (6.5% versus 5.1%, respectively). However, CHF cases were more likely to have a history of smoking, obesity, alcohol abuse, and cardiovascular risk factors, and were more likely than MI cases to be treated in an acute care or teaching facility.

When compared with their matched controls, MI cases were more likely to be located in the Midwest, have a history of treatment for alcohol related disorders and PVD, and have a record of being prescribed ACE inhibitors, digoxin, and statins. Cases were less likely to have health coverage through Medicare, to have received treatment at an acute care or teaching facility, and less likely to have a history of smoking, obesity, and other cardiovascular risk factors. Overall, the number of different antidiabetic drugs prescribed to cases was greater than for controls (i.e. a greater number of cases were prescribed combination therapy) and the number of cases with a prescription for a TZD drug was also higher than for controls (9.3% of MI cases were prescribed pioglitazone compared to 2.6% of controls and 6.5% of cases were prescribed rosiglitazone compared to 1.8% of controls), as was insulin use (98.1% of cases compared to

92.6% of controls). The cases and matched controls were similar for other characteristics including total number of hospital admissions and total number of unique non-diabetic drugs.

Cases of CHF were more likely to be located in the Midwest, have a history of treatment for alcohol related disorders, angina, cancer, CAD, MI, PVD, and stroke, and were more likely to have been prescribed a drug associated with cardiovascular risk factors compared to their matched controls. Cases were less likely to have health coverage through Medicare and have a history of obesity and dyslipidemia. Similar to cases of MI, the number of different antidiabetic drugs prescribed to CHF cases was greater than for controls and the number of cases with a prescription for a TZD drug was also higher than for controls (9.5% of CHF cases were prescribed pioglitazone compared to 2.6% of controls and 5.1% of cases were prescribed rosiglitazone compared to 1.2% of controls), as was the percentage of cases prescribed insulin (97.2% of cases compared to 91.9% of controls). The cases and matched controls were similar for other characteristics including total number of hospital admissions and total number of unique non-diabetic drugs.

### *MI*

The results of the primary analysis for MI are presented in **Table 2**. Compared with never use of any TZD drug, exclusive ever use of either pioglitazone (OR: 3.87, 95% CI: 2.52-5.94) or rosiglitazone (OR: 3.68, 95% CI: 2.18-6.21) were associated with a statistically significant increased risk of MI that was comparable for both drugs. There were an insufficient number of cases to reliably assess whether ever use of both pioglitazone and rosiglitazone was associated with an increased risk of MI (results not shown).

**Table 2.** Thiazolidinedione use and risk of MI among cases and matched controls\*

| Thiazolidinedione use**                        | Cases<br>(n = 418)<br>n (%) | Controls<br>(n = 3,816)<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|-----------------------------|----------------------------------|-------------------------|-------------------------------------|-------------------------------------|
| Never use of any thiazolidinedione (reference) | 354<br>(84.7)               | 3,651<br>(95.7)                  | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 37<br>(8.9)                 | 95<br>(2.5)                      | 3.64<br>(2.41-5.49)     | 4.00<br>(2.62-6.10)                 | 3.87<br>(2.52-5.94)                 |
| Exclusive ever use of rosiglitazone            | 25<br>(6.0)                 | 67<br>(1.8)                      | 3.47<br>(2.10-5.72)     | 3.63<br>(2.16-6.09)                 | 3.68<br>(2.18-6.21)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for payer class, census region, hospital size, and total number of hospital admissions.

In sensitivity analyses, when rosiglitazone use was directly compared to pioglitazone use (i.e. pioglitazone was included in the reference group), rosiglitazone use was associated with a lower risk of MI but this risk was not statistically significant (OR: 0.59, 95% CI: 0.19-1.78). When exploring the effects of adding a lag period between study cohort entry and index date, less than one year (**Table 3**), one year or more (**Table 4**), and two years or more (**Table 5**) of lag time were associated with an increased risk of MI. When the lag period was less than one year, the OR for exclusive ever use of pioglitazone greatly increased (OR: 5.52, 95% CI: 1.70-17.96) however, the number of cases in this analysis was relatively low (six cases) which may in part explain this increase. For rosiglitazone, there was an insufficient number of cases to assess associations with risk of MI when the lag period was less than a year (results not shown). When the lag period was increased to one year or more and two years or more, both exclusive ever use of pioglitazone ( $\geq 1$  year OR: 3.10, 95% CI: 1.96-4.89;  $\geq 2$  years OR: 3.72, 95% CI: 2.19-6.31) and exclusive ever use of rosiglitazone ( $\geq 1$  year OR: 3.46, 95% CI: 1.98-6.03;  $\geq 2$  years OR: 2.40, 95% CI: 1.20-4.78) remained significantly associated with an increased risk of MI. This association decreased slightly for pioglitazone when the lag period was a year or more, however, when the lag period was two years or more the result was comparable to the primary analysis. For rosiglitazone, the association when the lag period was a year or more was comparable to the primary analysis but decreased when the lag period was two years or more. However, the association between rosiglitazone and increased risk of MI remained statistically significant.

**Table 3.** Thiazolidinedione use and risk of MI among cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|-------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                         |                                     |                                     |
| Never use of any thiazolidinedione (reference) | 91<br>(91.0)   | 941<br>(98.3)     | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 6<br>(6.0)     | 10<br>(1.0)       | 5.67<br>(1.99-16.18)    | 5.88<br>(1.92-18.03)                | 5.52<br>(1.70-17.96)                |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone and ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for payer class, census region, hospital size, and total number of hospital admissions.



**Table 4.** Thiazolidinedione use and risk of MI among cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|-------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                     |
| Never use of any thiazolidinedione (reference) | 263<br>(82.7)  | 2,663<br>(94.2)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 31<br>(9.7)    | 98<br>(3.5)       | 2.87<br>(1.85-4.44)     | 3.09<br>(1.97-4.86)                 | 3.10<br>(1.96-4.89)                 |
| Exclusive ever use of rosiglitazone            | 22<br>(6.9)    | 63<br>(2.2)       | 3.08<br>(1.81-5.25)     | 3.20<br>(1.85-5.53)                 | 3.46<br>(1.98-6.03)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for payer class, census region, hospital size, and total number of hospital admissions.

**Table 5.** Thiazolidinedione use and risk of MI among cases and matched controls based on a lag period of two years or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|-------------------------------------|
| <b>≥ 2 year lag period</b>                     |                |                   |                         |                                     |                                     |
| Never use of any thiazolidinedione (reference) | 186<br>(81.6)  | 1,853<br>(94.2)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 26<br>(11.4)   | 62<br>(3.2)       | 3.80<br>(2.31-6.25)     | 3.99<br>(2.38-6.70)                 | 3.72<br>(2.19-6.31)                 |
| Exclusive ever use of rosiglitazone            | 14<br>(6.1)    | 52<br>(2.6)       | 2.20<br>(1.15-4.23)     | 2.22<br>(1.13-4.35)                 | 2.40<br>(1.20-4.78)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for payer class, census region, hospital size, and total number of hospital admissions.

## *CHF*

The results of the primary analysis for CHF are presented in **Table 6**. Compared with never use of any TZD drug, exclusive ever use of either pioglitazone (OR: 4.15, 95% CI: 3.21-5.37) or rosiglitazone (OR: 2.69, 95% CI: 1.91-3.80) were associated with a statistically significant increased risk of CHF with pioglitazone demonstrating a greater association than rosiglitazone. There were an insufficient number of cases to reliably assess whether ever use of both pioglitazone and rosiglitazone was associated with an increased risk of CHF (results not shown).

In the first sensitivity analysis, rosiglitazone use compared with pioglitazone use was not associated with a decreased risk of CHF (OR: 0.97, 95% CI: 0.30-3.20). In the other sensitivity analyses investigating the effects of a lag period on CHF risk, all lag periods were associated with an increased risk of CHF that were statistically significant. When the lag period was less than one year (**Table 7**), the OR for exclusive ever use of pioglitazone was greatly increased (OR: 6.29, 95% CI: 3.25-12.18) and the OR for exclusive ever use of rosiglitazone was increased (OR: 3.25, 95% CI: 1.14-9.28). When the lag period was increased to one year or more (**Table 8**) and two years or more (**Table 9**) the results were comparable to the primary analyses. Both exclusive ever use of pioglitazone ( $\geq 1$  year OR: 3.86, 95% CI: 2.91-5.12;  $\geq 2$  years OR: 3.84, 95% CI: 2.82-5.24) and exclusive ever use of rosiglitazone ( $\geq 1$  year OR: 2.86, 95% CI: 1.96-4.17;  $\geq 2$  years OR: 2.81, 95% CI: 1.85-4.27) remained significantly associated with an increased risk of CHF with the ORs for pioglitazone slightly lower than the primary analysis and the ORs for rosiglitazone slightly higher.

**Table 6.** Thiazolidinedione use and risk of CHF among cases and matched controls\*

| Thiazolidinedione use**                        | Cases<br>(n =<br>1,134)<br>n (%) | Controls<br>(n<br>=9,636)<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------------------------|------------------------------------|-------------------------|-------------------------------------|-------------------------------------|
| Never use of any thiazolidinedione (reference) | 972<br>(85.7)                    | 9,204<br>(95.5)                    | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 104<br>(9.2)                     | 251<br>(2.6)                       | 3.71<br>(2.90-4.75)     | 4.13<br>(3.20-5.35)                 | 4.15<br>(3.21-5.37)                 |
| Exclusive ever use of rosiglitazone            | 54<br>(4.8)                      | 178<br>(1.8)                       | 2.30<br>(1.65-3.20)     | 2.67<br>(1.89-3.77)                 | 2.69<br>(1.91-3.80)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin,

‡Further adjusted for total number of distinct non-diabetic drugs.

**Table 7.** Thiazolidinedione use and risk of CHF among cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-----------------------------------|-------------------------------------|-------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                                   |                                     |                                     |
| Never use of any thiazolidinedione (reference) | 220<br>(90.5)  | 2,190<br>(97.6)   | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 17<br>(7.0)    | 31<br>(1.4)       | 5.18<br>(2.80-9.58)               | 6.28<br>(3.25-12.13)                | 6.29<br>(3.25-12.18)                |
| Exclusive ever use of rosiglitazone            | 5<br>(2.1)     | 20<br>(0.9)       | 2.34 <sup>NS</sup><br>(0.86-6.36) | 3.17<br>(1.11-9.03)                 | 3.25<br>(1.14-9.28)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for total number of distinct non-diabetic drugs.

<sup>NS</sup>Not statistically significant.

**Table 8.** Thiazolidinedione use and risk of CHF among cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted<br>OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|----------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                        |
| Never use of any thiazolidinedione (reference) | 748<br>(84.2)  | 6,865<br>(95.0)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                    |
| Exclusive ever use of pioglitazone             | 88<br>(9.9)    | 222<br>(3.1)      | 3.45<br>(2.64-4.51)     | 3.84<br>(2.90-5.09)                 | 3.86<br>(2.91-5.12)                    |
| Exclusive ever use of rosiglitazone            | 49<br>(5.5)    | 140<br>(1.9)      | 2.45<br>(1.71-3.51)     | 2.86<br>(1.96-4.17)                 | 2.86<br>(1.96-4.17)                    |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for total number of distinct non-diabetic drugs.

**Table 9.** Thiazolidinedione use and risk of CHF among cases and matched controls based on a lag period of two years or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|-------------------------------------|
| <b>≥ 2 year lag period</b>                     |                |                   |                         |                                     |                                     |
| Never use of any thiazolidinedione (reference) | 546<br>(82.4)  | 4,863<br>(94.4)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 73<br>(11.0)   | 180<br>(3.5)      | 3.52<br>(2.61-4.74)     | 3.84<br>(2.82-5.23)                 | 3.84<br>(2.82-5.24)                 |
| Exclusive ever use of rosiglitazone            | 41<br>(6.2)    | 105<br>(2.0)      | 2.64<br>(1.77-3.94)     | 2.82<br>(1.86-4.27)                 | 2.81<br>(1.85-4.27)                 |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, CAD, hypertension, PVD, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Further adjusted for total number of distinct non-diabetic drugs.

## **DISCUSSION**

In this hospital-based study we investigated associations between use of TZD drugs and risk of MI and CHF. The findings of this study, comprising cohorts of more than 11,000 and 9,000 people with T2DM, respectively, suggest that use of TZD drugs is associated with an increased risk of adverse cardiovascular events when compared with never use of TZD drugs. These results remained consistent in several sensitivity analyses which considered TZD class effect and latency period.

### **Comparison with previous studies**

Numerous observational studies have investigated associations between TZD use and risks of MI [9-12, 15, 20-22, 38-49] and CHF [9, 10, 21-22, 39, 42-43, 45-46, 50-52]. Of these studies, nearly half have found significant associations between pharmacotherapy with at least one TZD drug type and an increased risk of MI and half have found associations with an increased risk of CHF. However, the associations in these studies have, for the most part, been lower than those found in the present study, and the remaining half of the studies conducted to date have not found associations between TZDs and adverse cardiovascular events indicating that evidence is still conflicting.

Our results demonstrate a comparable association for either rosiglitazone (OR: 3.68, 95% CI: 2.18-6.21) or pioglitazone (OR: 3.87, 95% CI: 2.52-5.94) and an increased risk of MI. Similarly, a study by Koro et al. [15] also demonstrated associations with both drugs with rosiglitazone use associated with a 15% increased risk of MI (OR 1.15, 95% CI: 1.04-1.27) and pioglitazone use associated with a 13% increased risk (OR 1.13, 95% CI: 1.02-1.26) after at least one year of exposure when compared to patients not exposed to TZDs. Our ORs were higher



than in the Koro et al. [15] study; however, their study was conducted in a non-elderly population where the mean age for cases and controls was approximately 63 years of age versus our population that had mean ages of 73.5 years for MI cases and 72.1 years for CHF cases. Therefore, our higher estimates may in part be a reflection of an older and less healthy population. In addition, the nature of the dataset used, a managed care database, most likely captured prevalent users in their cohort that may have influenced the OR estimates as they did not control for prevalent users or severity of disease. To our knowledge, ours is one of few observational studies [53 , 54] investigating associations between TZDs, MI, and CHF that has controlled for prevalent users that are inherent in administrative hospital-based datasets.

In one study that included an older patient population (mean age 73.0 years) and that also accounted for diabetes severity, Stockl et al. [44] found that when recently exposed TZD patients (i.e. their last prescription overlapped the index date) were compared to patients of a similar level of diabetes severity (exposed to TZDs more than 60 days prior to the index date, but not recently), patients with a recent exposure to rosiglitazone, but not pioglitazone, demonstrated a statistically significant association with an increased risk of MI (OR: 3.12, 95% CI: 1.67-5.83). This result is similar to our primary analysis for rosiglitazone and also reflects the trends observed in our sensitivity analyses where associations between rosiglitazone exposure and risk of MI decreased over time ( $\geq 2$  year lag period OR: 2.40, 95% CI: 1.20-4.78) implying that there could be an early treatment effect for rosiglitazone (pioglitazone demonstrated a similar trend in our study with the OR increasing significantly within a year of cohort entry and then decreasing with a year or more of lag time). When compared to never users of TZDs, the same study [44] found that risk of MI was increased 1.69-fold for patients with recent rosiglitazone exposure (OR: 1.69, 95% CI: 1.18-2.44), but not with recent pioglitazone exposure (OR: 1.18, 95%CI:

0.61-2.28), however, these analyses compared diabetics of differing levels of disease severity. Therefore, our higher ORs may have also in part resulted from comparing patients with a similar level of diabetes severity that may better estimate the level of associated risk.

For CHF, the observational studies conducted to date have primarily found associations with rosiglitazone and not pioglitazone therapy when stratified by TZD drug type. In our study, we found a significantly increased risk of CHF with either pioglitazone (OR: 4.15, 95% CI: 3.21-5.37) or rosiglitazone use (OR: 2.69, 95% CI: 1.91-3.80) and we could not exclude a TZD class effect in sensitivity analyses. This may in part be a result of the greater degree of pre-existing cardiovascular disease in the cases in our study cohort compared to controls including a greater proportion of patients with angina and CAD that may have predisposed TZD-treated patients towards heart failure compared to non-TZD treated patients, even when these factors were controlled for in our analyses. This association has been observed in clinical trials for pioglitazone. For example, in a randomized control trial comparing pioglitazone use with glyburide use in patients with mild cardiac disease or symptomatic CHF [17], an increased incidence of CHF (10 versus seven patients) and hospitalization for CHF (four versus zero patients) was observed in pioglitazone-treated patients after six months and one year of therapy. Similarly, in the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) investigating the effects of pioglitazone in patients with or without a previous history of stroke [16], 5.7% of pioglitazone-treated patients developed heart failure leading to hospitalization compared with 4.1% of placebo-treated patients.

For rosiglitazone several observational studies have found statistically significant associations with an increased risk of CHF. In a retrospective cohort study using a large vertically integrated health system in southeast Michigan, Habib et al. [42] found that

rosiglitazone was associated with an increased risk of hospitalization for CHF (HR: 1.65, 95%CI: 1.25-2.19) compared with patients that had not used rosiglitazone. However, it should be noted that this study was also conducted in a much younger population (mean age of patients 58.3 years) which may have underestimated the risk compared to older patients. In a population of Medicaid beneficiaries aged 65 years and older (mean age 74.4 years), Graham et al. [46] found that rosiglitazone use was associated with a 25% increased risk of hospitalization for CHF (HR: 1.25, 95% CI: 1.16-1.34) when compared to pioglitazone use. However, TZD use was not directly compared to users of other OHAs or insulin.

Of the clinical trials conducted to date, several have also found associations between rosiglitazone therapy and CHF. For example, in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) study [55] there were a higher number of a composite of cardiovascular events (MI, stroke, cardiovascular death, CHF, angina, and revascularisation) in the rosiglitazone group (2.9% versus 2.1% in the placebo group; HR 1.37; 95% CI 0.97-1.94; P = 0.08) in a population of 5,269 patients with impaired glucose tolerance and/or impaired fasting glucose. This was primarily a result of a high rate of CHF in the rosiglitazone group (0.5%; n = 14) compared to the placebo group (0.1%, n = 2; HR 7.03; 95% CI 1.60-30.9; P = 0.01). As well, in the RECORD trial [2] both interim analysis after 3.7 years [1] and subsequent analysis after 5.5 years of follow-up demonstrated increased risks of CHF with rosiglitazone use (HR: 2.15, 95% CI: 1.30-3.57 and HR: 2.10, 95% CI: 1.35-3.27, respectively), that are more comparable to the results obtained in our study for associations between rosiglitazone and risk of CHF.

## Biological mechanisms

The mechanism(s) behind the adverse cardiovascular effects seen in some of the TZD studies described above is thought to occur as a result of peroxisome proliferator-activated receptor (PPAR) activation. As agonists of PPARs, TZD drugs primarily activate the  $\gamma$  PPAR subtype that is most abundant in adipose tissues with pioglitazone also showing a weak affinity for the  $\alpha$  subtype [27]. As described by Davidson et al. [27], the most commonly reported and well-recognized adverse effects of TZD therapy are weight gain, fluid retention, and edema which can sometimes precipitate or exacerbate heart failure. For example, it is estimated that peripheral edema occurs in approximately 5% of patients undergoing TZD therapy and that this adverse effect increases to approximately 15% in patients combining TZDs with insulin [56]. Because fluid retention is a known class effect of PPAR $\gamma$  medications that appeared in initial trials prior to TZDs being marketed, CHF was listed as a contraindication of TZD use at the time of licensing [57].

The mechanisms behind fluid retention and edema resulting from TZD pharmacotherapy are not completely understood but it is hypothesized that these effects may result, at least in part, from stimulation of PPARs. In heart failure, the heart preferentially switches its substrate preference from fatty acids to glucose [58]. Because gene products downstream of PPAR $\gamma$  are critical in the regulation of glucose and lipid metabolism in the heart, PPAR $\gamma$  activation may modulate nutrient metabolism or expand intravascular volume in a manner that results in cardiac hypertrophy [59]. Though the heart initially compensates through this enlargement of the heart muscle, cardiomyopathy and CHF then follow [60]. Since adverse events have been reported more frequently with rosiglitazone in some studies, the absence of PPAR $\alpha$  activity observed with rosiglitazone compared to pioglitazone has been thought to contribute more significant fluid

retention [61]. However, the increased mortality associated with dual PPAR $\alpha/\gamma$  agonists such as muraglitazar may disprove this mechanism [62] and the numerous studies demonstrating adverse cardiovascular events associated with pioglitazone therapy, including associations between pioglitazone and an increased risk of CHF demonstrated in our study, do not support this hypothesis.

### **Strengths and limitations**

This population-based study has several strengths. Firstly, this study had two cohorts of 11,611 and 9,229 patients with T2DM who were followed for up to 11.9 years. The size and long term follow-up of patients enabled the identification of a large number of cardiovascular events. Secondly, because the Cerner Health Facts® database contains pre-recorded information on prescriptions, and these prescriptions are filled in-hospital, the possibility of recall bias was eliminated. Thirdly, the study was specifically designed to increase the likelihood that patients entering the base and study cohorts were new users of antidiabetic drugs, therefore, this addressed biases related to the inclusion of prevalent users, and meant that patients included in the study cohort were more likely to have a similar level of diabetes severity [29]. Fourthly, the inclusion of a lag period in the sensitivity analyses provided an approximation of latency and findings were generally consistent in sensitivity analyses in which the duration of the lag period was varied. Finally, the use of EMR data from more than 480 contributing hospitals throughout the US strengthens the generalisability of our findings.

Our study also has certain limitations. Firstly, as previously discussed, we acknowledge that our ORs were in most cases higher than in the literature and that this may be a function of differences in study design and the inclusion of prevalent users in previous studies. However,

this is also likely caused by the greater proportion of cases that received TZD drugs in both cohorts compared to controls which may be a function of different prescribing practices when treating diabetic patients in-hospital (refer to **Chapter 6** of this thesis for a general discussion related to this observation in the dataset). We also acknowledge limitations in the secondary analyses where the lag period was less than one year as there were an insufficient number of cases to assess associations between rosiglitazone and risk and MI. Therefore, the results should be interpreted with caution though they do imply that there could be a trend towards an early treatment effect with pioglitazone. To date, the literature remains inconsistent on associations between TZDs and adverse cardiovascular events within a year of treatment with some observational studies ([50]: increased risk of hospitalization for CHF within 60 days of beginning TZD treatment; [44]: increased risk of MI within 1-60 days of exposure to rosiglitazone), but not all ([15]: increased risk of MI after  $\geq 12$  months of therapy only for both rosiglitazone and pioglitazone), reporting statistically significant associations within 12 months of treatment.

Secondly, there were an insufficient number of cases to determine associations between ever use of both pioglitazone and rosiglitazone (i.e. mostly patients who switched from one drug to the other) and risk of both MI and CHF. However, associations remained consistent with the primary analyses when rosiglitazone use was directly compared to pioglitazone use and a class effect could not be excluded. Thirdly, drug information in the database represents prescriptions written only by hospital physicians. As such, it is unknown whether additional prescriptions were provided to patients from other health care providers, such as general practitioners, outside of the Cerner network. Because many diabetic patients are primarily under the care of general practitioners and would be assumed to have received prescriptions for antihyperglycaemic drugs

from these practitioners, this does introduce exposure misclassification into the study and also meant that it was not possible to assess the dose-specific effects of TZDs. However, our study was designed to increase the likelihood of capturing incident users, to the extent possible, and thus minimizes this bias. Though it does not preclude TZD patients adding-on or substituting other medications after study cohort entry, such as insulin, to intensify or adjust their treatment regimes that may have contributed to increased cardiovascular risk. This is especially possible in a hospital-based population and although we censored patients entering the study cohort who were taking insulin while in a non-ambulatory state, such patients were not censored for this reason after entry to the study cohort.

Fourthly, when working with administrative hospital data there is always the possibility that coding errors or omissions may have occurred, and that ICD-9 codes may not accurately or completely reflect the patient's diagnosis. This also includes the possibility that cardiovascular outcomes may have been misclassified. Given the hospital-based setting of the database, and the fact that serious cardiovascular events such as MI and CHF are treated in-hospital, this is unlikely. Our overall crude incidence rates of MI (21.8 per 1000 person years) and CHF (72.5 per 1000 person years) were comparable to others obtained using US administrative health care data investigating MI (26.8 per 1000 person years in a cohort using the HealthCore Integrated Research Environment [63]) and CHF (68.0 per 1000 person years in a cohort using Kaiser Permanente Northwest Division data [64]) in diabetics.

Finally, given the observational nature of the study, and the use of hospital-based versus general practice data, it is possible that there may have been residual confounding by disease severity as we had no information on the duration of treated diabetes prior to a patient's first recorded encounter in the dataset. This is especially true given the strong link between T2DM

and cardiovascular disease. However, the design of this study attempted to control for this through the criteria for entry to the base cohort and by matching cases and controls on duration of follow-up which has been shown to be a good proxy for disease severity [65]. In addition, our analyses adjusted for known cardiovascular risk factors and related medications, including medications that themselves have been shown to be associated with an increased risk of adverse cardiovascular events (e.g. NSAIDs).

## CONCLUSIONS AND IMPLICATIONS

It is well established that cardiovascular disease is a complication of T2DM [66]: it has been estimated that in the US, at least 68% of people aged 65 years or older with diabetes will die from some form of heart disease [67]. As such, this has made it difficult to determine associations between the cardiovascular effects of antidiabetic pharmacotherapy and cardiovascular disease in diabetics, and most likely plays a role in the conflicting evidence related to the cardiovascular safety of TZD drugs. In this hospital-based study, we found that use of TZD drugs was associated with an increased risk of MI and CHF compared with never use of TZD drugs in patients followed for up to 11.9 years (median 0.2-2.7 years). These findings generally remained consistent when latency was varied and within the TZD class, though pioglitazone was more strongly associated with CHF than rosiglitazone. Our study provides support for the existing body of literature that has found that both pioglitazone and rosiglitazone are associated with adverse cardiovascular events.

Prescribing rates for TZD drugs have steadily decreased over time since the first warnings of adverse cardiovascular events in 2007 [27] (also refer to **Chapter 6** for an overview of TZD prescriptions over time within the diabetes cohort) and because new OHAs with less



controversial side effect profiles have been marketed since the introduction of TZD drugs into clinical practice. Nevertheless, TZDs continue to be used as second or third-line treatments for T2DM. They are also increasingly being repurposed and used off-label for the treatment of other diseases and conditions such as some cancers, neurodegenerative disorders, and PCOS in non-diabetic populations [68]. Given the trend of increased cardiovascular risk that we observed, this study reiterates a need for regular monitoring of cardiovascular health indicators in both diabetics and non-diabetics prescribed TZD drugs, and the continued need for a cautious approach in prescribing TZDs to patients with pre-existing cardiovascular risk factors.

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### **Author's roles**

M.A. Davidson formulated the hypothesis and design for this study and performed the SAS coding, statistical analyses, and literature review required for the manuscript under the guidance of D. Krewski and with advice from C. Gravel, D. Mattison, and D. McNair. C. Gravel provided assistance in validating the accuracy of the SAS code. M.A. Davidson drafted all text, figures, and tables with editorial input from the co-authors. All contributors were involved in the evaluation and interpretation of the study findings.

### **Authors' disclosures of potential conflicts of interest**

M.A. Davidson, C. Gravel, D. Mattison, and D. Krewski have no actual or potential competing financial interest. D. Krewski is the Natural Sciences and Engineering Research

Council of Canada Chair in Risk Science at the University of Ottawa. He also serves as Chief Risk Scientist and CEO for Risk Sciences International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa to provide consulting services in risk science to both public and private sector clients. To date, RSI has not conducted work on antihyperglycaemics, the subject of the present paper. D. Mattison was supported by RSI. D. McNair is the President of Cerner Math Inc. and has ownership interest in Cerner Corporation.

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## **CHAPTER 4: DATA ARTICLE 2 - Thiazolidinedione use and fracture risk in a cohort of Type 2 diabetics**

Davidson MA, Gravel C, McNair D, Mattison D, Krewski D. Thiazolidinedione use and fracture risk in a cohort of Type 2 diabetics. Unpublished manuscript;2018.

### **PREFACE**

This manuscript presents the results of a pharmacoepidemiological study of the osteological risks associated with thiazolidinedione drugs. Specifically, a nested case-control study was designed and conducted to investigate associations between thiazolidinedione use and risk of closed bone fractures in a population of Type 2 diabetics. Secondary analyses investigated if associations varied by fracture site or by patient sex. All analyses in this study account for the potential confounding effects of a variety of demographic factors, health care facility characteristics, concomitant therapies, and comorbidities. The statement of contributions of collaborators and co-authors, including the student's individual contribution, can be found in the acknowledgements at the end of this manuscript.

## **Thiazolidinedione use and fracture risk in a cohort of Type 2 diabetics**

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of Ottawa Canada.

Keywords: Thiazolidinedione, pioglitazone, rosiglitazone, closed fracture, peripheral fracture, osteoporotic fracture.

The data used in this study were provided to the University of Ottawa by Cerner Corporation under a Material Transfer Agreement allowing for the data to be used for research purposes.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this manuscript.

## ABSTRACT

**Objective:** To determine if use of thiazolidinedione (TZD) drugs is associated with an increased risk of bone fracture.

**Design:** A nested case-control analysis.

**Setting:** Hospitals in the United States contributing to the Cerner HealthFacts® datawarehouse.

**Participants:** A cohort of 12,462 patients with Type 2 diabetes who initiated treatment with metformin or sulphonylurea monotherapy between January 1, 2000 and December 31, 2012 who then switched to or added-on another antidiabetic drug.

**Main outcome measures:** Incident cases of closed bone fracture were matched to up to 10 controls on sex, age, race, year of study cohort entry, and duration of follow-up. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated comparing use of TZDs with use of other antidiabetic drugs.

**Results:** In the study cohort, 749 patients were newly diagnosed as having any closed fracture. Compared with use of other antidiabetic drugs, exclusive ever use of pioglitazone (OR: 2.66, 95% CI: 1.93-3.66) or rosiglitazone (OR: 3.23, 95% CI: 2.08-5.02) were associated with an increased risk of any closed fracture. When stratified by fracture site, use of pioglitazone or rosiglitazone (respectively), were significantly associated with an increased risk of peripheral fracture (OR: 2.58, 95% CI: 1.77-3.78; OR: 3.33, 95% CI: 2.02-5.50). Use of pioglitazone (OR: 1.95, 95% CI: 1.27-2.99) but not rosiglitazone (OR: 1.78, 95% CI: 0.91-3.49) was significantly associated with an increased risk of osteoporotic fracture, but not in patients with less than one year between study cohort entry and the index date. In women, use of either pioglitazone or rosiglitazone was associated with an increased risk of any closed fracture (OR: 4.40, 95% CI:

2.97-6.52; OR: 4.06, 95% CI: 2.30-7.18, respectively) and peripheral fracture (OR: 3.35, 95% CI: 2.12-5.30; OR: 3.68, 95% CI: 2.01-6.75). Use of pioglitazone (OR: 2.71, 95% CI: 1.60-4.60), but not rosiglitazone (OR: 2.14, 95% CI: 0.93-4.93), was also significantly associated with an increased risk of osteoporotic fracture in women. In men, use of rosiglitazone but not pioglitazone was significantly associated with an increased risk of any closed fracture (rosiglitazone: OR: 2.54, 95% CI: 1.23-5.22; pioglitazone: OR: 1.47, 95% CI: 0.79-2.72) and peripheral fracture (rosiglitazone: OR: 2.97, 95% CI: 1.20-7.33; pioglitazone: OR: 1.58, 95% CI: 0.78-3.22), but not osteoporotic fracture (pioglitazone: OR: 1.56, 95% CI: 0.71-3.44; rosiglitazone: less than 5 cases).

**Conclusions:** In this hospital-based cohort, TZD use was associated with an increased risk of closed bone fracture among Type 2 diabetics. In women, use of pioglitazone or rosiglitazone were associated with an increased risk of fracture across multiple sites but only rosiglitazone was associated with a statistically significant increased risk of fracture in men, and only peripheral fractures when stratified by site, though odds ratios remained high. These findings support previous studies that have found associations between TZD therapy and increased risk of bone fracture in women, and provide additional evidence for potential associations between TZD therapy and fracture risk in men.

## INTRODUCTION

Thiazolidinedione (TZD) class drugs are peroxisome proliferator-activated receptor (PPAR) agonists used in the treatment of Type 2 diabetes mellitus (T2DM) that act as insulin sensitizers. First marketed in the 1990s, drugs in this class have been associated with several adverse health effects, including bone fractures. Epidemiological evidence of the association between TZDs and fractures is however, unclear. In recent years there has been accumulating evidence that treatment choice for T2DM may affect bone health and that TZD pharmacotherapy may be associated with decreased bone density [1-12] and increased fracture risk, particularly in women, and in some clinical trials [13-17].

Associations between bone fractures and TZDs first attracted attention after a review of the A Diabetes Outcome Progression Trial (ADOPT) data for adverse events of interest detected a higher rate of fracture in women [16]. ADOPT was conducted to investigate the effects of 4 years of randomly-assigned rosiglitazone treatment versus metformin or glyburide treatment on glycaemic control in newly-diagnosed diabetic patients [15]. When adverse events in the trial were reviewed, an increased occurrence of upper limb (22 patients versus 10 in the metformin group and nine in the glyburide group) and lower limb (36 patients versus 18 in the metformin group and eight in the glyburide group) fractures, but not fractures of the hip or vertebrae, were observed in women assigned to the rosiglitazone treatment group. In response to these findings, the manufacturer of rosiglitazone released a letter to healthcare providers in February 2007 [18], followed by a letter from the manufacturer of pioglitazone in March of the same year reporting that an analysis of its clinical trials database found an increase in fractures in women, but not in men [19]. A subsequent detailed report of the ADOPT findings [16] found that though fracture rates did not differ between treatment groups in men (1.16 per 100 patient-years for

rosiglitazone, 0.98 per 100 patient-years for metformin, and 1.07 per 100 patient-years with glyburide [hazard ratio {HR}: 1.18, 95% confidence interval {CI}: 0.72-1.96 versus metformin and HR: 1.08, 95% CI: 0.65-1.79 versus glyburide]), in women the incidence was 2.74 per 100 patient-years with rosiglitazone (a cumulative incidence of 15.1% at 5 years) versus 1.54 per 100 patient-years for metformin (7.3% cumulative incidence), and 1.29 per 100 patient-years for glyburide (7.7% cumulative incidence); a doubled risk of fractures with rosiglitazone treatment that appeared approximately one year after exposure. Compared to metformin (HR: 1.81, 95% CI: 1.17-2.80) and glyburide (HR: 2.13, 95% CI: 1.30-3.51), fractures were more likely to occur in post-menopausal women treated with rosiglitazone who were greater than 50 years of age.

Data from other [13-14, 17], but not all [20] clinical trials have also corroborated an increased risk of fracture with rosiglitazone or pioglitazone primarily at peripheral sites. For example, the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial [17] investigating the effects of 18 months of pioglitazone or glimepiride use on the progression of coronary atherosclerosis in 543 patients with T2DM reported fractures only in the pioglitazone group. Fractures, primarily at peripheral sites, occurred in 3% of pioglitazone-treated patients (six women and two men; average age of patients in the pioglitazone group was 60 years) compared to none of the glimepiride-treated patients [17] which indicates that these occurrences most likely cannot be attributed to the age and gender of the patients in the pioglitazone group alone (mean age was 59.7 in the glimepiride group and patients were 65.9% male versus 68.9% male in the pioglitazone group). In the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) [13], a randomized, double-blind, placebo-controlled cardiovascular outcomes study in high risk patients with T2DM assigned to receive pioglitazone as an add-on to another

antihyperglycaemic drug, 5.1% of pioglitazone-treated women experienced fractures (1.0 per 100 patient-years) compared to 2.5% treated with placebo (0.5 per 100 patient-years). No increase in fracture rates was observed in men treated with pioglitazone (1.7%) compared to placebo (2.1%). Similar to the rosiglitazone findings in ADOPT, the majority of fractures were seen in post-menopausal women (mean age was approximately 62 years of age), and only after approximately one year of exposure. Not all studies however, have found increased risks. For example, Perez et al. [20] saw no increased risk of fractures in T2DM patients who were previously not taking antihyperglycaemic drugs who were prescribed a combination of pioglitazone and metformin versus patients prescribed pioglitazone or metformin alone in a twice-daily regimen over 24 weeks. The early stage of diabetes, lower average age of patients (approximately 54 years in the pioglitazone/metformin and pioglitazone groups), and the short six month treatment could explain why effects were not observed in this study.

In observational studies and meta-analyses (also see Davidson et al. [21] - **Chapter 2** of this thesis), rosiglitazone and pioglitazone have been associated with comparable risk in some studies [e.g. 22-26], whereas others have found that rosiglitazone [e.g. 27-28], or that pioglitazone treatment [e.g. 29] may be more strongly associated with fractures. Some have found fractures primarily in women, especially post-menopausal women [e.g. 24, 30-35 {pelvis}, 36-37], others have found comparable risk between the sexes [e.g. 22-23, 25, 29, 35 {upper and lower limb}, 38 {only in men also taking loop diuretics}, 39-40], and few have investigated or found increased risk in men alone [e.g. 41].

The continued lack of concurrence of the aforementioned findings demonstrates that more research is needed to further clarify associations between TZD use and fracture risk. Further research is also needed to inform decisions related to the use and long-term safety of

TZD drugs as these drugs are increasingly being investigated for, or used in, the treatment of other diseases and conditions such as polycystic ovary syndrome (PCOS) and some cancers (see Davidson et al. [21] - **Chapter 2** of this thesis for more detailed information). To this end, we conducted a nested case-control study to determine if TZD drugs, including rosiglitazone or pioglitazone alone, are associated with an increased risk of closed fracture in people with T2DM, and if risk varied by fracture site and sex.

## **METHODS**

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, ON, Canada.

### **Data source**

This study was carried out using the Cerner Health Facts® datawarehouse (Kansas City, MO, US), a longitudinal database of electronic health record data from over 480 contributing hospitals throughout the United States (US). Health Facts® contains anonymized data of encounters for over 41 million people and includes demographics, diagnoses, prescriptions, procedures, laboratory testing, hospital information, service location, and billing data. At the time of analysis this datawarehouse contained encrypted and time-stamped information on distinct inpatient admissions and discharges, emergency department encounters, and outpatient encounters. Each patient encounter within the datawarehouse is linked by unique patient and encounter identifiers to permit the assessment of treatments over time including diagnostics and procedures, and medications prescribed and dispensed. Information contained in the datawarehouse used for the analyses consisted of patient demographics, hospital or clinic



characteristics, prescribed and dispensed medications (orders, dispensing events, billing information, National Drug Code number, quantity, and date of administration), and medical events, procedures, and diagnoses (International Classification of Diseases, 9th Edition [ICD-9] codes).

### **Study population**

Type 2 diabetics often receive antidiabetic drug prescriptions from a general practitioner outside of a hospital setting. This introduces the possibility of capturing prevalent users in hospital-based data [42]. To address potential prevalent user bias, a study design [43] was employed that first assembled a base cohort population of patients who have a similar level of T2DM disease severity, and from that base cohort, a study cohort of patients who intensified or progressed their treatment regime by switching to, or adding-on another oral antihyperglycemic agent (OHA) or insulin to establish a population that is more likely to contain incident drug users (**Figure 1**).

#### *Base cohort*

A base cohort was assembled consisting of all patients who commenced treatment for T2DM with a first ever antidiabetic drug prescription of metformin or sulphonylurea monotherapy between January 1, 2000 and December 31, 2012. Patients initiating treatment with these drugs were selected to establish a patient population with a comparable level of T2DM severity, to the extent possible, from which to sample from for the study cohort. The date of each patient's first metformin or sulphonylurea monotherapy prescription defined entry into the base cohort. Patients were then excluded if they had any of the following characteristics at entry to the

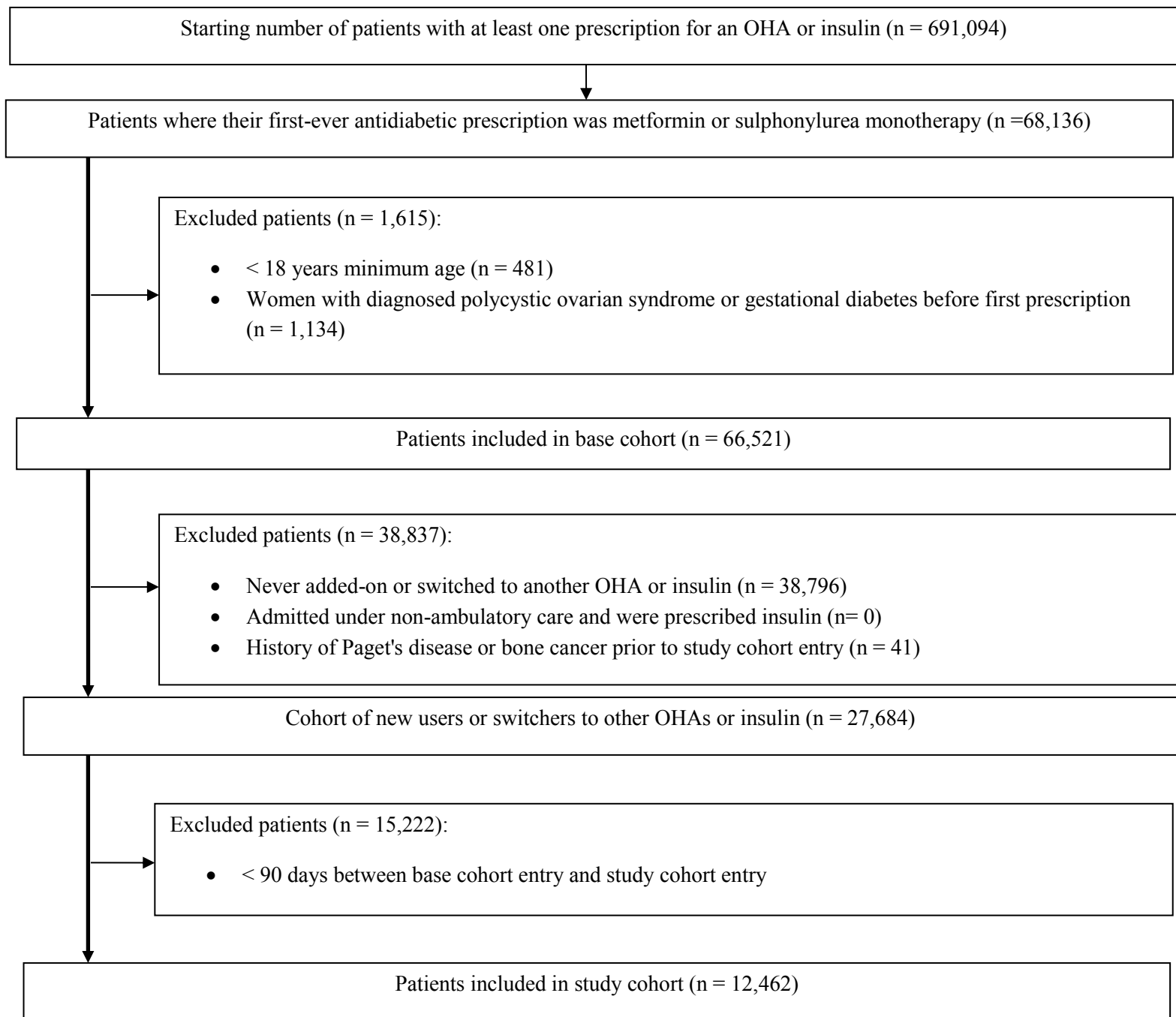


**Figure 1.** Establishment of base and study cohorts and flow of participants in the bone fracture study design.

base cohort: age less than 18 years and women with a history of diagnosed PCOS or a diagnosis of gestational diabetes before entry into the base cohort, as these conditions are other possible indications for metformin.

### *Study cohort*

Within the base cohort, a study cohort was established consisting of all patients who added-on or switched to an OHA drug class not previously identified in their drug history, or insulin, on or after March 30, 2000 (the year where rosiglitazone and pioglitazone first appeared in the dataset and the year immediately following the approval of rosiglitazone and pioglitazone for the US market) until December 31, 2012. The date of this new prescription defined entry to the study cohort. Patient encounters where the first new antidiabetic prescription was for insulin and where that patient was not in an ambulatory state (i.e. being treated in an intensive care unit) were censored to account for situations where insulin may be administered in-hospital to non-ambulatory patients instead of their normal course of antidiabetic therapy (e.g. an OHA). However, these patients were permitted to re-enter the cohort at the time of their next antidiabetic prescription where they were in an ambulatory state. Patients were excluded if they had a history of bone cancer or Paget's disease prior to study cohort entry [22], or if had less than 90 days between base cohort entry and study cohort entry to take into account a timeframe within which other antidiabetic drug prescriptions would reasonably be expected to appear in their medical records.

## **Follow-up**

Patients meeting the study inclusion criteria were followed from the date of study cohort entry until a diagnosis of any closed fracture (ICD-9 codes 800.x-829.x), death from any cause, their last encounter in the dataset, or end of the study period (December 31, 2012), whichever occurred first. Open fractures were excluded to minimize the capture of traumatic fractures. Because fracture risk may be site-specific, fractures were further classified into the following non-mutually exclusive categories for secondary analyses: any peripheral fracture (ICD-9 codes 810.x and 812.x-828.x; upper or lower limb fracture including hand, wrist, foot, or ankle) and any major osteoporotic fracture as defined by the University of Sheffield Centre for Metabolic Bone Diseases Fracture Risk Assessment Tool (FRAX) that was developed in conjunction with the World Health Organization (ICD-9 codes 805.x, 806.x, 812.x, 813.x, 820.x, and 821.x; hip, radius/ulna, vertebrae, or humerus).

## **Selection of cases and controls**

To investigate associations between TZD pharmacotherapy and bone fractures we carried out nested case-control analyses. As described by Azoulay et al. [45], this approach was used because of the time varying nature of drug use, the size of the cohort, and the long duration of follow-up in the dataset [46]. Compared with a full cohort approach, using a nested case-control analysis is computationally more efficient [47]. We used risk set sampling for the matching of controls to cases as this method produces ORs that are unbiased estimators of HRs [46-48].

All incident cases of closed fracture were identified during follow-up. For each case, the first hospital admission with a diagnosis of a closed fracture was used to define the index date.

Up to 10 controls were randomly selected from the case's risk set after matching on age ( $\pm 1$

year), sex, race, year of cohort entry ( $\pm 1$  year), and duration of follow-up ( $\pm 1$  year). Matched controls were assigned the index date of their respective cases.

### **Drug exposure and use of thiazolidinediones**

All OHAs and insulin approved by the US Food and Drug Administration (US FDA) for use during the study period (including those under restricted access, i.e. rosiglitazone) were identified in the dataset. For cases and controls we obtained prescription information for drugs prescribed at any time before the index date using time and date-stamped pharmacy orders, dispensing events, and National Drug Code numbers within the dataset. Antidiabetic drug exposure was defined as receiving at least one prescription preceding the index date.

Use of TZDs was classified into one of the four mutually exclusive categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and rosiglitazone use (mainly switchers from one drug to the other), and 4) never use of any TZD. Never users of any TZD were used as the reference group. Patients were considered unexposed to TZDs until the time of their first TZD prescription.

### **Statistical analysis**

Descriptive statistics were used to summarise the baseline characteristics of matched cases and controls at cohort entry. Conditional logistic regression was used to estimate ORs and corresponding 95% CIs for associations between TZD use and risk of fracture.

In addition to age, sex, race, year of cohort entry, and duration of follow-up (on which the logistic regression models were conditioned) models were adjusted for several potential confounders if their inclusion changed the estimate of risk by 10% or more. Potential

confounders measured at entry to the study cohort included: payer class (as a surrogate for socioeconomic status), census region, region type (urban/rural), treatment center size (number of hospital beds), and treatment center type (teaching/non-teaching, acute care/non-acute care). Known risk factors for fractures [44] measured at any time before study cohort entry included: previous fracture (open or closed), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and osteoporosis. Models were also adjusted for excessive alcohol use (based on alcohol related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), obesity (treatment for obesity or body mass index greater than 30 kg/m<sup>2</sup>), and smoking (ever/never) measured at any time prior to, or after study cohort entry. Finally, models were adjusted for total number of hospital admissions and total number of unique non-diabetic drugs prescribed, both measured in the 90 days prior to, and after cohort entry, and entered as four level ordered categorical variables, as general measures of comorbidity [49].

The primary analysis evaluated whether exclusive ever use of pioglitazone, exclusive ever use rosiglitazone, or use of pioglitazone and rosiglitazone, when compared with never use of any TZD (the reference group), were associated with an increased risk of any closed fracture. Due to the hospital-based nature of the data, analyses investigating potential dose-response relationships could not be reliably conducted as it could not be determined if patients received other prescriptions outside of the Cerner network (e.g. by a general practitioner).

### *Secondary Analyses*

To determine if fracture risk varied by site, the primary analyses were repeated to determine associations between TZD use and peripheral fracture and osteoporotic fracture. To

assess associations between fracture risk and sex, all primary and secondary analyses were also repeated by stratifying by sex.

### *Sensitivity Analyses*

To assess the robustness of the findings of this study, three sensitivity analyses were conducted. In the first, we contrasted the use of pioglitazone with the use of rosiglitazone by repeating our primary analysis with the latter as the reference category to further assess whether an association between pioglitazone and closed bone fractures is drug-specific compared to a TZD class effect. In the second, the primary and secondary analyses were repeated with a lag period of less than one year between study cohort entry and the index date to investigate possible early treatment effects. Finally, the primary and secondary analyses were repeated with a lag period of at least one year between study cohort entry and the index date to account for uncertainty in the length of a possible latency period. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Results are presented where the number of cases are five or more to account for where the effect estimate is highly uncertain because of small sample size.

## **RESULTS**

Of the 68,136 patients with a first prescription that was metformin or sulphonylurea monotherapy, 12,462 met the study inclusion criteria (**Figure 1.**). The mean age at entry to the study cohort was 69.0 years, 47.6% were men, and the median duration of follow-up across participating facilities in the Cerner network ranged from 0.2 to 2.6 years with a maximum of 11.9 years. Overall, the study cohort generated 21,109 person years of follow-up. During this

time 749 patients were newly diagnosed as having any closed fracture (cases), generating a crude incidence rate of 35.5 per 1,000 person years (95% CI: 32.9-38.0).

The baseline characteristics of the 749 cases of any closed fracture and 6,894 matched controls are presented in **Table 1**. Compared with controls, cases were less likely to be located in the Midwest and to have had a previous fracture, but were slightly more likely to have a history of ever smoking, and more likely to have a history of obesity, treatment for alcohol related disorders, and COPD. Overall, the number of different antidiabetic drugs prescribed to cases was slightly higher than for controls (i.e. a greater number of cases were prescribed combination therapy) and the number of cases with a prescription for a TZD drug was also higher than for controls with 8.1% and 4.1% of cases receiving pioglitazone or rosiglitazone (respectively), compared with 2.9% and 1.5% of controls (respectively). Cases also received a higher percentage of insulin prescriptions than controls (96.7% versus 93.7%, respectively). Cases and matched controls were similar for other characteristics including number of hospital admissions and number of unique non-diabetic drugs.

The results of the primary analysis are presented in **Table 2**. Compared with never use of any TZD drug, exclusive ever use of either pioglitazone (OR: 2.66, 95% CI: 1.93-3.66) or rosiglitazone (OR: 3.23, 95% CI: 2.08-5.02) were associated with an increased risk of any closed fracture, as was ever use of both pioglitazone and rosiglitazone (OR: 3.65, 95% CI: 1.02-13.08). In sensitivity analyses, when pioglitazone use was directly compared to rosiglitazone use (i.e. rosiglitazone was included in the reference group), pioglitazone use was associated with a similar level of risk of any closed fracture (OR: 1.00, 95% CI: 0.06-15.99). When the effects of adding a lag period between study cohort entry and index date were explored, less than one year (**Table 3**)



**Table 1.** Baseline characteristics of cases and matched controls for any closed fracture. Values are numbers (percentages) unless stated otherwise.

| <b>Characteristic</b>                           | <b>Cases (n = 749)</b> | <b>Controls (n = 6,894)</b> |
|-------------------------------------------------|------------------------|-----------------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>74.4 (12.0)</b>     | <b>75.7 (11.3)</b>          |
| <b>18-25</b>                                    | 5 (0.7)                | 16 (0.2)                    |
| <b>26-35</b>                                    | 8 (1.1)                | 109 (1.6)                   |
| <b>36-45</b>                                    | 36 (4.8)               | 316 (4.6)                   |
| <b>46-55</b>                                    | 82 (11.0)              | 847 (12.3)                  |
| <b>56-65</b>                                    | 155 (20.7)             | 1285 (18.6)                 |
| <b>66-75</b>                                    | 199 (26.6)             | 1675 (24.3)                 |
| <b>76-85</b>                                    | 191 (25.5)             | 1871 (27.1)                 |
| <b>&gt;85</b>                                   | 73 (9.8)               | 775 (11.2)                  |
| <b>Men*</b>                                     | 346 (46.2)             | 3302 (47.9)                 |
| <b>2000</b>                                     | 4 (0.5)                | 12 (0.2)                    |
| <b>2001</b>                                     | 29 (3.9)               | 208 (3.0)                   |
| <b>2002</b>                                     | 43 (5.7)               | 345 (5.0)                   |
| <b>2003</b>                                     | 48 (6.4)               | 403 (5.9)                   |
| <b>2004</b>                                     | 56 (7.5)               | 496 (7.2)                   |
| <b>2005</b>                                     | 60 (8.0)               | 530 (7.7)                   |
| <b>2006</b>                                     | 47 (6.3)               | 428 (6.2)                   |
| <b>2007</b>                                     | 69 (9.2)               | 690 (10.0)                  |
| <b>2008</b>                                     | 76 (10.2)              | 719 (10.4)                  |
| <b>2009</b>                                     | 100 (13.4)             | 967 (14.0)                  |
| <b>2010</b>                                     | 89 (11.9)              | 878 (12.7)                  |
| <b>2011</b>                                     | 77 (10.3)              | 716 (10.4)                  |
| <b>2012</b>                                     | 51 (6.8)               | 502 (7.3)                   |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.6 (1.8)</b>       | <b>1.6 (1.8)</b>            |
| <b>Race*</b>                                    |                        |                             |
| <b>Caucasian</b>                                | 588 (78.5)             | 5459 (79.2)                 |
| <b>African-American</b>                         | 128 (17.1)             | 1191 (17.3)                 |
| <b>Other</b>                                    | 33 (4.4)               | 244 (3.5)                   |
| <b>Payer class</b>                              |                        |                             |
| <b>Medicare</b>                                 | 232 (31.0)             | 2137 (31.0)                 |
| <b>Other</b>                                    | 152 (20.3)             | 1328 (19.3)                 |
| <b>Unknown</b>                                  | 365 (48.7)             | 3429 (49.7)                 |
| <b>Census region</b>                            |                        |                             |
| <b>Northeast</b>                                | 333 (44.5)             | 2961 (43.0)                 |
| <b>Midwest</b>                                  | 110 (14.7)             | 1310 (19.0)                 |
| <b>West</b>                                     | 44 (5.9)               | 365 (5.3)                   |
| <b>South</b>                                    | 262 (35.0)             | 2258 (32.8)                 |

Table 1. *Continued.*

| Characteristic                                             | Cases (n = 749) | Controls (n = 6,894) |
|------------------------------------------------------------|-----------------|----------------------|
| <b>Region type</b>                                         |                 |                      |
| Urban                                                      | 748 (99.9)      | 6882 (99.8)          |
| Rural                                                      | 1 (0.1)         | 12 (0.2)             |
| <b>Treatment center type</b>                               |                 |                      |
| Acute care                                                 | 727 (97.1)      | 6747 (97.9)          |
| Non-acute care                                             | 20 (2.7)        | 144 (2.1)            |
| Missing                                                    | 2 (0.3)         | 3 (0.0)              |
| <b>Treatment center teaching status</b>                    |                 |                      |
| Teaching                                                   | 480 (64.1)      | 4309 (62.5)          |
| Non-teaching                                               | 269 (35.9)      | 2585 (37.5)          |
| <b>Treatment center beds</b>                               |                 |                      |
| 1-199                                                      | 62 (8.3)        | 537 (7.8)            |
| 100-199                                                    | 81 (10.8)       | 856 (12.4)           |
| 200-299                                                    | 238 (31.8)      | 2060 (29.9)          |
| 300-499                                                    | 127 (17.0)      | 1288 (18.7)          |
| ≥ 500                                                      | 241 (32.2)      | 2153 (31.2)          |
| Ever smoker†                                               | 106 (14.2)      | 959 (13.9)           |
| Ever diagnosis or treatment for obesity‡                   | 350 (46.7)      | 3179 (46.1)          |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 40 (5.3)        | 313 (4.5)            |
| Previous fracture                                          | 32 (4.3)        | 365 (5.3)            |
| Chronic obstructive pulmonary disease                      | 132 (17.6)      | 1125 (16.3)          |
| Rheumatoid arthritis                                       | 11 (1.5)        | 102 (1.5)            |
| Osteoporosis                                               | 29 (3.4)        | 236 (3.4)            |
| Mean number hospital admissions (SD)                       | 3.0 (3.2)       | 2.9 (2.9)            |
| <b>Number of hospital admissions</b>                       |                 |                      |
| 1                                                          | 301 (40.2)      | 2685 (39.0)          |
| 2                                                          | 157 (21.0)      | 1532 (22.2)          |
| 3                                                          | 101 (13.5)      | 852 (12.4)           |
| ≥ 4                                                        | 190 (25.4)      | 1825 (26.5)          |
| Mean number unique non-diabetic drugs (SD)                 | 4.1 (1.7)       | 4.1 (1.7)            |
| <b>Number of unique non-antidiabetic drugs</b>             |                 |                      |
| 0                                                          | 22 (2.9)        | 166 (2.4)            |
| 1                                                          | 24 (3.2)        | 287 (4.2)            |
| 2                                                          | 64 (8.5)        | 665 (9.7)            |
| 3                                                          | 153 (20.4)      | 1428 (20.7)          |
| ≥ 4                                                        | 486 (64.9)      | 4348 (63.1)          |

**Table 1. Continued.**

| <b>Characteristic</b>           | <b>Cases (n = 749)</b> | <b>Controls (n = 6,894)</b> |
|---------------------------------|------------------------|-----------------------------|
| <b>Antidiabetic drug use¶</b>   |                        |                             |
| <b>Metformin</b>                | 404 (53.9)             | 3,603 (52.3)                |
| <b>Sulphonylureas</b>           | 540 (72.1)             | 5,066 (73.5)                |
| <b>Pioglitazone</b>             | 61 (8.1)               | 203 (2.9)                   |
| <b>Rosiglitazone</b>            | 35 (4.7)               | 100 (1.5)                   |
| <b>DPP-4 inhibitors</b>         | 38 (5.1)               | 412 (6.0)                   |
| <b>α-glucosidase inhibitors</b> | 1 (0.1)                | 36 (0.5)                    |
| <b>Meglitinides</b>             | 29 (3.9)               | 279 (4.1)                   |
| <b>Insulins</b>                 | 724 (96.7)             | 6,458 (93.7)                |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

**Table 2.** Thiazolidinedione use and risk of any closed fracture among cases and matched controls\*

| <b>Thiazolidinedione use</b>                           | <b>Cases<br/>(n = 749)<br/>n (%)</b> | <b>Controls<br/>(n = 6,894)<br/>n (%)</b> | <b>Crude<br/>OR<br/>(95% CI)</b> | <b>Minimal<br/>Adjusted<br/>OR<br/>(95% CI)†</b> | <b>Maximum<br/>Adjusted OR<br/>(95% CI)</b> |
|--------------------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------|--------------------------------------------------|---------------------------------------------|
| <b>Never use of any thiazolidinedione (reference)</b>  | 658<br>(87.9)                        | 6,599<br>(95.7)                           | 1.00<br>(reference)              | 1.00<br>(reference)                              | 1.00<br>(reference)                         |
| <b>Exclusive ever use of pioglitazone</b>              | 56<br>(7.5)                          | 195<br>(2.8)                              | 2.69<br>(1.96-3.69)              | 2.66<br>(1.93-3.66)                              | ‡                                           |
| <b>Exclusive ever use of rosiglitazone</b>             | 30<br>(4.0)                          | 92<br>(1.3)                               | 2.97<br>(1.93-4.58)              | 3.23<br>(2.08-5.02)                              | ‡                                           |
| <b>Ever use of both pioglitazone and rosiglitazone</b> | 5<br>(0.7)                           | 8<br>(0.1)                                | 3.38<br>(1.01-11.34)             | 3.65<br>(1.02-13.08)                             | ‡                                           |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 3.** Thiazolidinedione use and risk of any closed fracture among cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 205<br>(93.6)  | 2,083<br>(98.1)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 10<br>(4.6)    | 23<br>(1.1)       | 4.32<br>(2.04-9.15)     | 3.96<br>(1.86-8.44)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

and one year or more (**Table 4**) of lag time were associated with an increased risk of any closed fracture for exclusive ever use of pioglitazone (< 1 year OR: 3.96, 95% CI: 1.86-8.44;  $\geq$  1 year OR: 2.69, 95% CI: 1.88-3.86). Both exclusive ever use of rosiglitazone (OR: 3.08, 95% CI: 1.90-5.00) and ever use of pioglitazone and rosiglitazone (OR: 7.82, 95% CI: 1.75-34.9) were associated with an increased risk of any closed fracture when the lag period was one year or more, however, there were an insufficient number of cases to adequately assess these associations when the lag period was less than one year.

### *Site-specific analyses*

The results of the site-specific secondary analyses are presented in **Tables 5-10**. Overall, the analyses for peripheral fractures yielded findings that were consistent with those of the primary analysis. The findings for osteoporotic fractures were less consistent with the primary analysis with only pioglitazone significantly associated with an increased risk of osteoporotic fracture.

### Peripheral fractures

There were a total of 543 peripheral fracture cases and 4,980 matched controls. Mean age at entry to the study cohort for peripheral fracture cases was slightly higher than for cases with any closed fracture (74.7 years versus 74.4 years, respectively). However, peripheral fracture cases were less likely to be male than cases of any closed fracture (42.7% male versus 46.2% male, respectively). Peripheral fracture cases were less likely to be located in the Southern US, to have ever smoked, and less likely to have a history of obesity, alcohol abuse, COPD, or rheumatoid arthritis compared to cases with any closed fracture. Peripheral fracture cases were also more

**Table 4.** Thiazolidinedione use and risk of any closed fracture among cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use                           | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI) <sup>†</sup> | Maximum<br>Adjusted OR<br>(95% CI) |
|-------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                      |                |                   |                         |                                                 |                                    |
| Never use of any thiazolidinedione (reference)  | 451<br>(85.6)  | 4,499<br>(95.0)   | 1.00<br>(reference)     | 1.00<br>(reference)                             | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone              | 45<br>(8.5)    | 153<br>(3.2)      | 2.71<br>(1.90-3.87)     | 2.69<br>(1.88-3.86)                             | ‡                                  |
| Exclusive ever use of rosiglitazone             | 26<br>(4.9)    | 78<br>(1.6)       | 3.00<br>(1.85-4.85)     | 3.08<br>(1.90-5.00)                             | ‡                                  |
| Ever use of both pioglitazone and rosiglitazone | 5<br>(0.9)     | 4<br>(0.1)        | 6.29<br>(1.51-26.21)    | 7.82<br>(1.75-34.9)                             | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

<sup>†</sup>Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

<sup>‡</sup>Maximum adjusted model the same as minimal adjusted model.

likely to be Caucasian and have a history of previous fracture and osteoporosis. Other baseline characteristic trends were similar to those for cases and matched controls for any closed fracture.

Both peripheral fracture cases and their matched controls had a similar number of mean hospital admissions and mean number of unique non-diabetic drugs (refer to **Table S1** in supplementary materials). Cases were slightly less likely than their matched controls to have a history of osteoporosis, and were less likely to be insured through Medicare, located in the Southern US, and have a history of smoking, obesity, alcoholism, rheumatoid arthritis, and COPD. Cases were more likely than controls to have been treated in an acute care or teaching facility, and to have a history of previous fracture. Peripheral fracture cases were also prescribed a greater number of TZD drugs than controls (pioglitazone: 7.6% of cases versus 2.8% of controls; rosiglitazone: 5.0% of cases versus 1.4% of controls).

Compared with never use of any TZD drug, exclusive ever use of either pioglitazone (OR: 2.58, 95% CI: 1.77-3.78) or rosiglitazone (OR: 3.33, 95% CI: 2.02-5.50) were associated with an increased risk of peripheral fracture (**Table 5**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases). In sensitivity analyses, when pioglitazone use was directly compared to rosiglitazone use, pioglitazone use was associated with a lower risk of peripheral fracture compared to rosiglitazone, but this association was not statistically significant (OR: 0.61, 95% CI: 0.16-2.35). When the effects of adding a lag period between study cohort entry and index date were explored (**Tables 6 and 7**; there were no cases for analysis for ever use of both pioglitazone and rosiglitazone), exclusive ever use of pioglitazone was associated with an increased risk of peripheral fracture with both a lag period of less than one year (OR: 4.58, 95% CI: 1.84-11.40) and a lag period of one year or more (OR: 2.30, 95% CI: 1.51-3.49). Exclusive ever use of rosiglitazone was associated with an increased



**Table 5.** Thiazolidinedione use and risk of peripheral fracture among cases and matched controls\*

| <b>Thiazolidinedione use**</b>                        | <b>Cases<br/>(n = 543)<br/>n (%)</b> | <b>Controls<br/>(n = 4,980)<br/>n (%)</b> | <b>Crude<br/>OR<br/>(95% CI)</b> | <b>Minimal<br/>Adjusted OR<br/>(95% CI)†</b> | <b>Maximum<br/>Adjusted OR<br/>(95% CI)</b> |
|-------------------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------|----------------------------------------------|---------------------------------------------|
| <b>Never use of any thiazolidinedione (reference)</b> | 478<br>(88.0)                        | 4,774<br>(95.9)                           | 1.00<br>(reference)              | 1.00<br>(reference)                          | 1.00<br>(reference)                         |
| <b>Exclusive ever use of pioglitazone</b>             | 38<br>(7.0)                          | 136<br>(2.7)                              | 2.58<br>(1.77-3.76)              | 2.58<br>(1.77-3.78)                          | ‡                                           |
| <b>Exclusive ever use of rosiglitazone</b>            | 24<br>(4.4)                          | 68<br>(1.4)                               | 3.22<br>(1.96-5.28)              | 3.33<br>(2.02-5.50)                          | ‡                                           |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 6.** Thiazolidinedione use and risk of peripheral fracture among cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted<br>OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|----------------------------------------|------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                         |                                        |                                    |
| Never use of any thiazolidinedione (reference) | 147<br>(93.0)  | 1,505<br>(98.0)   | 1.00<br>(reference)     | 1.00<br>(reference)                    | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 7<br>(4.4)     | 17<br>(1.1)       | 4.16<br>(1.68-10.29)    | 4.58<br>(1.84-11.40)                   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 7.** Thiazolidinedione use and risk of peripheral fracture among cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 333<br>(86.7)  | 3,241<br>(94.5)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 31<br>(8.1)    | 128<br>(3.7)      | 2.21<br>(1.46-3.34)     | 2.30<br>(1.51-3.49)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 20<br>(5.2)    | 60<br>(1.7)       | 2.92<br>(1.71-5.02)     | 3.08<br>(1.79-5.31)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

risk of peripheral fractures when the lag period was one year or more (OR: 3.08, 95% CI: 1.79-5.31), but the number of cases was insufficient for analysis for a lag period of less than one year (results not shown).

### Osteoporotic fractures

There were a total of 485 cases of osteoporotic fracture and 4,580 matched controls. Mean age at entry to the study cohort was higher than for any closed fracture (76.5 years versus 74.4 years, respectively), however, the percentage of osteoporotic fracture cases that were male was the same as for cases with any closed fracture (46.2%). Compared to cases with any closed fracture, cases of osteoporotic fracture were slightly more likely to have a history of osteoporosis, and were more likely to be Caucasian, have health coverage through Medicare and have a history of smoking and COPD. Cases were also more likely to have suffered a previous fracture (5.4% of osteoporotic fracture cases compared to 4.3% of any closed fracture cases), but less likely to have a history of obesity and rheumatoid arthritis. Other baseline characteristic trends were similar to those for any closed fracture.

Osteoporotic fracture cases and their matched controls had the same mean number of distinct non-diabetic drugs prescribed and a similar number of mean total hospital admissions (refer to **Table S2** in supplementary materials). Cases were less likely to have health coverage through Medicare and a history of rheumatoid arthritis compared to controls but were more likely to be located in the Northeast, to have been treated at a teaching facility, and to have a history of smoking, COPD, and alcohol abuse. Osteoporotic fracture cases were prescribed a higher number of TZD drugs compared to their matched controls (pioglitazone: 5.8% of cases versus 3.0% of controls; rosiglitazone: 2.5% of cases versus 1.3% of controls).

Compared with never use of any TZD drug, exclusive ever use of pioglitazone (OR: 1.95, 95% CI: 1.27-2.99), but not rosiglitazone (OR: 1.78, 95% CI: 0.91-3.49), was associated with an increased risk of osteoporotic fracture (**Table 8**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), though the OR was elevated for rosiglitazone. In sensitivity analyses, when pioglitazone use was directly compared to rosiglitazone use, pioglitazone use was associated with a slightly higher, but not statistically significant, risk of osteoporotic fracture (OR: 1.20, 95% CI: 0.16-9.29). When the effects of adding a lag period between study cohort entry and index date were explored (**Tables 9 and 10**), exclusive ever use of pioglitazone remained significant when there was a lag period of one year or more (OR: 2.15, 95% CI: 1.32-3.48), but not when there was a lag period less than one year (OR: 2.15, 95% CI: 0.81-5.74), though the OR remained elevated and the same in both analyses. A low number of cases for rosiglitazone when the lag period was set to less than one year meant that results could not reliably be ascertained for this analysis (results not shown) and results when the lag period was a year or more were not statistically significant (OR: 1.52, 95% CI: 0.69-3.32).

### *Sex-specific analyses*

The results of the sex-specific analyses and their associated sensitivity analyses and presented in **Tables 11-23**. Baseline characteristics are presented in the supplementary materials at the end of this chapter.

**Table 8.** Thiazolidinedione use and risk of osteoporotic fracture among cases and matched controls\*¶

| Thiazolidinedione use**                        | Cases<br>(n = 485)<br>n (%) | Controls<br>(n = 4,580)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| Never use of any thiazolidinedione (reference) | 446<br>(92.0)               | 4,391<br>(95.9)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 27<br>(5.6)                 | 135<br>(2.9)                     | 1.88<br>(1.22-2.88)               | 1.95<br>(1.27-2.99)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 11<br>(2.3)                 | 57<br>(1.2)                      | 1.79 <sup>NS</sup><br>(0.92-3.49) | 1.78 <sup>NS</sup><br>(0.91-3.49)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture is includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX].

<sup>NS</sup>Not statistically significant.

**Table 9.** Thiazolidinedione use and risk of osteoporotic fracture among cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*¶

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                                   |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 150<br>(94.9)  | 1,490<br>(97.6)   | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 5<br>(3.2)     | 24<br>(1.6)       | 2.04 <sup>NS</sup><br>(0.77-5.38) | 2.15 <sup>NS</sup><br>(0.81-5.74)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX].

<sup>NS</sup>Not statistically significant.

**Table 10.** Thiazolidinedione use and risk of osteoporotic fracture among cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*¶

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                                   |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 295<br>(90.4)  | 2,889<br>(95.1)   | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 22<br>(6.7)    | 99<br>(3.3)       | 2.06<br>(1.27-3.33)               | 2.15<br>(1.32-3.48)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 8<br>(2.5)     | 47<br>(1.5)       | 1.53 <sup>NS</sup><br>(0.71-3.31) | 1.52 <sup>NS</sup><br>(0.69-3.32)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture is includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX].

<sup>NS</sup>Not statistically significant.



### Any closed fracture - males and females

For any closed fracture, there were a total of 290 cases and 2,649 matched controls for males, and a total of 459 cases and 4,245 matched controls for females. Mean age of cases for males was 73.0 years compared to 75.3 years for female cases. Male cases were slightly less likely to have a history of smoking and obesity, less likely to have health coverage under Medicare or to have been prescribed pioglitazone, and were much less likely to have a history of alcohol abuse than their matched controls (3.1% of cases versus 6.5% of controls; refer to **Table S3** in the supplemental materials of this chapter). Male cases were more likely to be located in the Western or Northwestern US, treated at an acute care facility, or have a history of COPD than controls. Female cases of any closed fracture were less likely to have health coverage under Medicare, to have been treated in a rural area or acute care facility, or to have history of smoking or alcohol abuse (refer to **Table S4** in the supplemental materials of this chapter) than their matched controls. Cases were also less likely to have a history of previous fracture (4.8% of cases versus 6.4% of controls). Female cases with any closed fracture were more likely to be located in the Western or Southern US, to have been treated in a teaching facility, and have a history of obesity and rheumatoid arthritis. Female cases were also much more likely to have been prescribed a TZD than their matched controls (pioglitazone: 10.2% versus 2.3%; rosiglitazone: 5.2% versus 1.3%).

When male cases of any closed fracture are compared with female cases, males were more likely to be Caucasian and located in the Midwest than females. They were less likely to have health care coverage under Medicare, to have a history of smoking, and have a lower number of hospital admissions than female cases. Male cases were also much less likely than female cases to have a history of obesity (35.5% versus 49.5%), previous fracture (3.1% versus

4.8%), COPD (15.5% versus 17.0%), rheumatoid arthritis (0% versus 2.8%), or osteoporosis (0.3% versus 5.7%), or to have been prescribed pioglitazone (4.8% versus 10.2%) or rosiglitazone (3.8% versus 5.2%).

In the sex-specific analyses for any closed fracture, the association with exclusive ever use of pioglitazone was only consistent with the primary analysis for females. Sex-specific associations between exclusive ever use of rosiglitazone and any closed fracture were consistent with the primary analysis however, the OR was higher for females and lower for males. Compared with never use of any TZD drug, exclusive ever use of rosiglitazone (OR: 2.54, 95% CI: 1.23-5.22) but not pioglitazone (OR: 1.47, 95% CI: 0.79-2.72) was associated with an increased risk of any closed fracture in males (**Table 11**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), though the OR was elevated for pioglitazone. In females, compared with never use of any TZD drug, both exclusive use of pioglitazone (OR: 4.40, 95% CI: 2.97-6.52) and exclusive use of rosiglitazone (OR: 4.06, 95% CI: 2.30-7.18) were associated with an increased risk of closed fracture (**Table 12**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases).

When users of pioglitazone were directly compared with users of rosiglitazone, use of pioglitazone by males was associated with a lower, but not statistically significant risk of any closed fracture (OR: 0.67, 95% CI: 0.11-3.99). The trend in females was similar (OR: 0.73, 95% CI 0.19-2.84). In sensitivity analyses exploring the effects of a lag period between study cohort entry and index date (**Table 13**), the association between exclusive ever use of rosiglitazone and any closed fracture in males remained significant when there was a lag period of one year or more (OR: 3.27, 95% CI: 1.46-7.32). Results for ever use of both pioglitazone and rosiglitazone with a lag period of a year or more are not presented due to a low number of cases. Results when

**Table 11.** Thiazolidinedione use and risk of any closed fracture among male cases and matched controls\*

| Thiazolidinedione use**                               | Cases<br>(n = 290)<br>n (%) | Controls<br>(n = 2,649)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|-------------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>Never use of any thiazolidinedione (reference)</b> | 266<br>(91.7)               | 2,530<br>(95.5)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| <b>Exclusive ever use of pioglitazone</b>             | 13<br>(4.5)                 | 80<br>(3.0)                      | 1.44 <sup>NS</sup><br>(0.78-2.65) | 1.47 <sup>NS</sup><br>(0.79-2.72)   | ‡                                  |
| <b>Exclusive ever use of rosiglitazone</b>            | 10<br>(3.4)                 | 38<br>(1.4)                      | 2.37<br>(1.16-4.87)               | 2.54<br>(1.23-5.22)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

<sup>NS</sup>Not statistically significant.

**Table 12.** Thiazolidinedione use and risk of any closed fracture among female cases and matched controls\*

| <b>Thiazolidinedione use**</b>                        | <b>Cases<br/>(n = 459)<br/>n (%)</b> | <b>Controls<br/>(n = 4,245)<br/>n (%)</b> | <b>Crude<br/>OR<br/>(95% CI)</b> | <b>Minimal<br/>Adjusted OR<br/>(95% CI)†</b> | <b>Maximum<br/>Adjusted OR<br/>(95% CI)</b> |
|-------------------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------|----------------------------------------------|---------------------------------------------|
| <b>Never use of any thiazolidinedione (reference)</b> | 392<br>(85.4)                        | 4,098<br>(96.5)                           | 1.00<br>(reference)              | 1.00<br>(reference)                          | 1.00<br>(reference)                         |
| <b>Exclusive ever use of pioglitazone</b>             | 43<br>(9.4)                          | 94<br>(2.2)                               | 4.38<br>(2.97-6.45)              | 4.40<br>(2.97-6.52)                          | ‡                                           |
| <b>Exclusive ever use of rosiglitazone</b>            | 20<br>(4.4)                          | 49<br>(1.2)                               | 3.83<br>(2.20-6.66)              | 4.06<br>(2.30-7.18)                          | ‡                                           |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 13.** Thiazolidinedione use and risk of any closed fracture among male cases and matched controls based on a lag period of a year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                                   |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 191<br>(90.5)  | 1,762<br>(94.5)   | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 10<br>(4.7)    | 75<br>(4.0)       | 1.15 <sup>NS</sup><br>(0.58-2.31) | 1.16 <sup>NS</sup><br>(0.58-2.33)   | ‡                                  |
| Exclusive ever use of rosiglitazone            | 9<br>(4.3)     | 27<br>(1.4)       | 2.71<br>(1.22-6.04)               | 3.27<br>(1.46-7.32)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

<sup>NS</sup> Not statistically significant.

the lag period was set to less than one year are also not presented for males due to a low number of cases.

In females, both exclusive ever use of pioglitazone (OR: 3.77, 95% CI: 2.45-5.80) and exclusive ever use of rosiglitazone (OR: 3.79, 95% CI: 2.05-7.00) remained significantly associated with an increased risk of any closed fracture, though the ORs were lower when the lag period was set to a year or more (**Table 14**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases). When the lag period was less than a year (**Table 15**), exclusive ever use of pioglitazone increased in significance (OR: 5.96, 95% CI: 2.23-15.93), however, there were an insufficient number of cases to reliably ascertain associations with exclusive ever use of rosiglitazone, or ever use of pioglitazone and rosiglitazone (results not shown).

#### Peripheral fractures - males and females

When further stratified by fracture site, the same trend existed between the non-sex-stratified analyses for peripheral fracture and the sex-specific analyses. Namely, the association between exclusive ever use of pioglitazone and peripheral fracture was only consistent for females. Sex-specific associations between exclusive ever use of rosiglitazone and peripheral fracture were consistent with the non-sex-stratified analyses, but the OR was higher for females and lower for males.

For peripheral fractures, there were a total of 201 cases and 1,807 matched controls for males, and a total of 342 cases and 3,173 matched controls for females. Mean age of cases for males was 73.2 years compared to 75.6 years for female cases. Other baseline characteristics

**Table 14.** Thiazolidinedione use and risk of any closed fracture among female cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 260<br>(82.3)  | 2,734<br>(95.3)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 35<br>(11.1)   | 93<br>(3.2)       | 3.65<br>(2.39-5.57)     | 3.77<br>(2.45-5.80)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 17<br>(5.4)    | 40<br>(1.4)       | 3.87<br>(2.11-7.12)     | 3.79<br>(2.05-7.00)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 15.** Thiazolidinedione use and risk of any closed fracture among female cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 130<br>(92.9)  | 1,329<br>(98.3)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 7<br>(5.0)     | 12<br>(0.9)       | 6.36<br>(2.40-16.83)    | 5.96<br>(2.23-15.93)                | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, and smoking status.

‡Maximum adjusted model the same as minimal adjusted model.



were similar to those of male and female cases and controls in the any closed fracture analyses (results not shown).

Compared with never use of any TZD drug, exclusive ever use of rosiglitazone (OR: 2.97, 95% CI: 1.20-7.33) but not pioglitazone (OR: 1.58, 95% CI: 0.78-3.22) was associated with an increased risk of peripheral fracture in males (**Table 16**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), though the OR was elevated for pioglitazone. In females, compared with never use of any TZD drug, both exclusive ever use of pioglitazone (OR: 3.35, 95% CI: 2.12-5.30) or rosiglitazone (OR: 3.68, 95% CI: 2.01-6.75) were associated with an increased risk of peripheral fracture (**Table 17**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases).

When pioglitazone use was directly compared to rosiglitazone use, pioglitazone was not associated with an increased risk of peripheral fracture in males ( $P < 0.001$ ). In females, pioglitazone use was associated with a higher, but not statistically significant increased risk of peripheral fracture compared to rosiglitazone (OR: 1.91, 95% CI: 0.32-11.55). In the sensitivity analyses exploring the effects of a lag period between study cohort entry and index date (**Table 18**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), neither exclusive ever use of pioglitazone or rosiglitazone were associated with an increased risk of peripheral fractures in males when there was a lag period of one year or more (pioglitazone OR: 1.52, 95% CI: 0.69-3.34; rosiglitazone OR: 2.12, 95% CI: 0.82-5.45). Results when the lag period was set to less than one year are not presented for males due to a low number of cases.

**Table 16.** Thiazolidinedione use and risk of peripheral fracture among male cases and matched controls\*

| Thiazolidinedione use**                        | Cases<br>(n = 201)<br>n (%) | Controls<br>(n = 1,807)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| Never use of any thiazolidinedione (reference) | 183<br>(91.0)               | 1,730<br>(95.7)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 10<br>(5.0)                 | 53<br>(2.9)                      | 1.67 <sup>NS</sup><br>(0.82-3.38) | 1.58 <sup>NS</sup><br>(0.78-3.22)   | ‡                                  |
| Exclusive ever use of rosiglitazone            | 7<br>(3.5)                  | 23<br>(1.3)                      | 2.62<br>(1.08-6.39)               | 2.97<br>(1.20-7.33)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

<sup>NS</sup>Not statistically significant.

**Table 17.** Thiazolidinedione use and risk of peripheral fracture among female cases and matched controls\*

| <b>Thiazolidinedione use**</b>                        | <b>Cases<br/>(n = 342)<br/>n (%)</b> | <b>Controls<br/>(n = 3,173)<br/>n (%)</b> | <b>Crude<br/>OR<br/>(95% CI)</b> | <b>Minimal<br/>Adjusted OR<br/>(95% CI)†</b> | <b>Maximum<br/>Adjusted OR<br/>(95% CI)</b> |
|-------------------------------------------------------|--------------------------------------|-------------------------------------------|----------------------------------|----------------------------------------------|---------------------------------------------|
| <b>Never use of any thiazolidinedione (reference)</b> | 295<br>(86.3)                        | 3,044<br>(95.9)                           | 1.00<br>(reference)              | 1.00<br>(reference)                          | 1.00<br>(reference)                         |
| <b>Exclusive ever use of pioglitazone</b>             | 17<br>(5.0)                          | 82<br>(2.6)                               | 3.28<br>(2.08-5.17)              | 3.35<br>(2.12-5.30)                          | ‡                                           |
| <b>Exclusive ever use of rosiglitazone</b>            | 28<br>(8.2)                          | 46<br>(1.4)                               | 3.53<br>(1.93-6.43)              | 3.68<br>(2.01-6.75)                          | ‡                                           |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 18.** Thiazolidinedione use and risk of peripheral fracture among male cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>(n = 146)<br>n (%) | Controls<br>(n = 1,264)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                             |                                  |                                   |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 131<br>(89.7)               | 1,194<br>(94.5)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 8<br>(5.5)                  | 44<br>(3.5)                      | 1.56 <sup>NS</sup><br>(0.71-3.41) | 1.52 <sup>NS</sup><br>(0.69-3.34)   | ‡                                  |
| Exclusive ever use of rosiglitazone            | 6<br>(4.1)                  | 26<br>(2.1)                      | 1.92 <sup>NS</sup><br>(0.76-4.87) | 2.12 <sup>NS</sup><br>(0.82-5.45)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

<sup>NS</sup>Not statistically significant.

In females, both exclusive ever use of pioglitazone (OR: 2.86, 95% CI: 1.73-4.71) and exclusive ever use of rosiglitazone (OR: 4.00, 95% CI: 2.03-7.90) remained significantly associated with an increased risk of peripheral fracture when the lag period was set to one year or more, though the OR for pioglitazone was lower and the OR for rosiglitazone was higher than in the main sex-specific peripheral fractures analyses (**Table 19**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases). When the lag period was less than one year (**Table 20**), exclusive ever use of pioglitazone was similar in significance (OR: 3.22, 95% CI: 1.15-9.02), however, there were an insufficient number of cases to reliably ascertain associations with exclusive ever use of rosiglitazone, or ever use of pioglitazone and rosiglitazone (results not shown).

#### Osteoporotic fractures - males and females

The association between exclusive ever use of pioglitazone and osteoporotic fracture in females was consistent with the results of the non-sex-stratified analysis for osteoporotic fracture, but the OR was higher for females. However, when pioglitazone was included in the reference group for females there was an association with an increased risk of osteoporotic fracture which is contrary to the non-sex-stratified results and inconsistent with the results for rosiglitazone in females. The results for males were not consistent with the non-sex-stratified analyses for pioglitazone. Associations with rosiglitazone use were consistent however; the low number of cases for rosiglitazone did not permit for reliable comparisons.

For osteoporotic fractures, there were a total of 124 cases and 1,114 matched controls for males, and a total of 302 cases and 2,904 matched controls for females. Mean age of cases for males was 75.5 years compared to 77.0 years for female cases. Other baseline characteristics

**Table 19.** Thiazolidinedione use and risk of peripheral fracture among female cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 199<br>(83.6)  | 2,052<br>(94.8)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 23<br>(9.7)    | 77<br>(3.6)       | 2.79<br>(1.70-4.58)     | 2.86<br>(1.73-4.71)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 14<br>(5.9)    | 34<br>(1.6)       | 3.83<br>(1.95-7.54)     | 4.00<br>(2.03-7.90)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

**Table 20.** Thiazolidinedione use and risk of peripheral fracture among female cases and matched controls based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>&lt; 1 year lag period</b>                  |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 95<br>(92.2)   | 976<br>(97.6)     | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 5<br>(4.9)     | 16<br>(1.6)       | 3.18<br>(1.15-8.79)     | 3.22<br>(1.15-9.02)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

were similar to those of male and female cases and controls in the any closed fracture analyses (results not shown).

Compared with never use of any TZD drug, exclusive ever use of pioglitazone (OR: 1.56, 95% CI: 0.71-3.44) was not associated with an increased risk of osteoporotic fracture in males (**Table 21**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), though the OR was elevated. The association between rosiglitazone use and osteoporotic fracture in males could not be assessed due to a low number of cases (results not shown). In females, compared with never use of any TZD drug, exclusive ever use of pioglitazone (OR: 2.71, 95% CI: 1.60-4.60), but not rosiglitazone (OR: 2.14, 95% CI: 0.93-4.93), was significantly associated with an increased risk of osteoporotic fracture (**Table 22**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases), though the OR for rosiglitazone was elevated.

In sensitivity analyses, when pioglitazone use was directly compared to rosiglitazone use there were an inadequate number of rosiglitazone cases to determine associations for males. In females, pioglitazone use was not associated with a statistically significant risk of osteoporotic fracture, though the OR was greatly elevated (crude OR: 6.90, 95% CI: 0.44-108.22). When the effects of a lag period between study cohort entry and the index date were explored, only exclusive ever use of pioglitazone could be assessed for males, and only when there was a lag period of one year or more due to a low number of cases (other results not shown). The association was not statistically significant (OR: 1.34, 95% CI: 0.54-3.23), though the OR remained elevated. In females, exclusive ever use of pioglitazone remained significantly associated with an increased risk of osteoporotic fracture (OR: 2.56, 95% CI: 1.44-4.55), and exclusive ever use of rosiglitazone remained insignificant (OR: 2.27, 95% CI: 0.87-5.93), though



**Table 21.** Thiazolidinedione use and risk of osteoporotic fracture among male cases and matched controls\*¶

| Thiazolidinedione use**                        | Cases<br>(n = 183)<br>n (%) | Controls<br>(n = 1,676)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| Never use of any thiazolidinedione (reference) | 172<br>(94.0)               | 1,601<br>(95.5)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 8<br>(4.4)                  | 44<br>(2.6)                      | 1.56 <sup>NS</sup><br>(0.72-3.40) | 1.56 <sup>NS</sup><br>(0.71-3.44)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for exclusive ever use of rosiglitazone or ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX].

<sup>NS</sup>Not statistically significant.

**Table 22.** Thiazolidinedione use and risk of osteoporotic fracture among female cases and matched controls\*¶

| Thiazolidinedione use**                        | Cases<br>(n = 302)<br>n (%) | Controls<br>(n = 2,904)<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|-----------------------------|----------------------------------|-----------------------------------|-------------------------------------|------------------------------------|
| Never use of any thiazolidinedione (reference) | 274<br>(90.7)               | 2,796<br>(96.3)                  | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 19<br>(6.3)                 | 73<br>(2.5)                      | 2.55<br>(1.51-4.30)               | 2.71<br>(1.60-4.60)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 8<br>(2.6)                  | 34<br>(1.2)                      | 2.26 <sup>NS</sup><br>(1.00-5.12) | 2.14 <sup>NS</sup><br>(0.93-4.93)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture is includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX].

<sup>NS</sup>Not statistically significant.

the OR was still elevated when the lag period was set to a year or more (**Table 23**; results not presented for ever use of both pioglitazone and rosiglitazone due to a low number of cases).

There were an insufficient number of cases to assess associations for females when the lag period was less than a year (results not shown).

**Table 23.** Thiazolidinedione use and risk of osteoporotic fracture among female cases and matched controls based on a lag period of one year or more between study cohort entry and index date\*¶

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI)           | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-----------------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                                   |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 179<br>(88.6)  | 1,833<br>(95.3)   | 1.00<br>(reference)               | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 16<br>(7.9)    | 65<br>(3.4)       | 2.39<br>(1.35-4.24)               | 2.56<br>(1.44-4.55)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 6<br>(3.0)     | 24<br>(1.2)       | 2.31 <sup>NS</sup><br>(0.90-5.91) | 2.27 <sup>NS</sup><br>(0.87-5.93)   | ‡                                  |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous fracture, COPD, rheumatoid arthritis, osteoporosis, excessive alcohol use, obesity, smoking status.

‡Maximum adjusted model the same as minimal adjusted model.

¶A major osteoporotic fracture includes fractures of the hip, radius/ulna, vertebrae, or humerus [as defined by FRAX]

<sup>NS</sup>Not statistically significant.

## **DISCUSSION**

In this hospital-based study we investigated the association between use of TZD drugs and risk of bone fracture. The findings of this study, based on a cohort of more than 12,000 patients with T2DM, suggest that use of TZD drugs is associated with an increased risk of fracture compared with never use of TZD drugs. These results remained consistent in several secondary and sensitivity analyses, including when fractures were stratified by site, though associations decreased in men and increased in women in sex-specific secondary analyses.

### **Comparison with previous studies**

To date, several observational studies have assessed associations between the use of TZD drugs and incidence of bone fractures. Overall, most of these studies have reported significant associations with fractures across various fracture sites [6, 22-25, 27, 29, 30, 32, 34-35, 37, 38-41, 50-52]. However, results when comparing individual TZD drugs and when stratifying by sex have varied across studies.

In a nested case-control analysis of patients with a diagnosis of incident fracture in the UK General Practice Research Database (now called the Clinical Practice Research Datalink), Meier et al. [25] found a similarly increased risk of fracture (predominantly hip and wrist) with rosiglitazone (OR: 2.38, 95% CI: 1.39-4.09) and pioglitazone (OR: 2.59, 95% CI: 0.96-7.01) when compared to controls. These associations were independent of patient age or sex but increased with TZD dose. Similar results were observed in a study by Douglas et al. [23] where patients who experienced a fracture at a range of sites (including hip, spine, arm, foot, wrist, and hand) had an increased risk of fracture during periods of TZD exposure compared to unexposed periods (risk ratio [RR]: 1.43, 95% CI: 1.25-1.62). Risk of fracture was similar in both men (RR:

1.44, 95% CI: 1.18-1.77) and women (RR: 1.42, 95% CI: 1.20-1.69) and increased with duration of TZD exposure (RR: 2.00, 95% CI: 1.48-2.70). However, when stratified by TZD drug, rosiglitazone (RR: 1.49, 95% CI: 1.28-1.74) but not pioglitazone was associated with an increased risk fracture of fracture at any site (RR: 1.26, 95% CI: 0.95-1.68), though a test for interaction showed no evidence that the effect varied by TZD type ( $P = 0.47$ ). In a retrospective cohort study investigating adverse cardiovascular effects and all-cause mortality associated with antidiabetic drugs, Tzoulaki et al. [27] found that rosiglitazone combination therapy was associated with an increased risk of non-hip fractures when compared to metformin therapy alone (HR: 1.53, 95% CI: 1.25-1.88), whereas the risk associated with pioglitazone was not statistically significant (HR: 1.28, 95% CI: 0.93-1.77). Alternatively, Dormuth et al. [29] found an increased risk of peripheral fractures with any TZD use (HR: 1.28, 95% CI: 1.10-1.48) and with pioglitazone use in both women (HR: 1.76, 95% CI: 1.32-2.38) and men (HR: 1.61, 95% CI: 1.18-2.20), but not rosiglitazone use (HR: 1.00, 95% CI: 0.75-1.34), and Motola et al. [35] found an increased risk of multiple site fractures, particularly upper and lower limb and pelvic fractures (OR: 2.00, 95% CI: 1.70-2.35).

The results of our primary analysis are consistent with several studies that have found an increased risk of fractures across all sites for both pioglitazone and rosiglitazone [22, 25, 38], though our associations are higher than these studies (pioglitazone OR: 2.66, 95% CI: 1.93-3.66; rosiglitazone OR: 3.23, 95% CI: 2.08-5.02), with the exception of the aforementioned Meier et al. [25] study. This may in part be a function of the older age group of our cohort (approximately 75 years of age compared to an approximate average age of 60 years across other studies) and the skeletal fragility, in combination with a greater propensity to fall, that results in an increased

susceptibility to fractures in an aging population [53] even when we attempted to control for traumatic fractures through exclusion (also refer to the *Strengths and limitations* section below).

Though we could not assess dose-related associations in our analyses, when a lag period of a year or more between study cohort entry and the index date was included in sensitivity analyses as a proxy for increasing exposure, the associations between both pioglitazone and rosiglitazone and increased risk of any closed fracture remained. We also found that pioglitazone (OR: 3.96, 95% CI: 1.86-8.44), but not rosiglitazone, was associated with an increased risk of any closed fracture when the lag period was less than one year. Differences between pioglitazone and rosiglitazone may be a result of the lower number of rosiglitazone cases compared to pioglitazone cases in the main analysis (30 versus 56, respectively), however, because other studies have found an increasing risk of fracture in TZD-exposed periods versus unexposed periods [23, 37] and with duration of treatment [e.g. 23, 50], and our results also shown the inverse for pioglitazone, this could suggest that there may also be an earlier treatment effect for pioglitazone. Such an effect is unclear in the literature and one study [31] found that fracture risk only appeared after one year of treatment in women treated with TZDs.

When fractures were categorized by site in secondary analyses, results were generally [24, 29-30, 35, 39, 41, 52] but not always [41] consistent with the literature. For peripheral fractures, as previously mentioned, Dormuth et al. [29] also found an increased risk of fracture with any TZD use. In a three year cross-sectional study investigating distal upper and lower limb fractures in a cohort of Type 2 diabetics aged 18 to 64 years, Jones et al. [24] also found that mean fracture proportions were significantly higher for TZD users (5.1%) versus nonusers (4.5%;  $P = 0.03$ ), that there were no significant differences among patients using pioglitazone versus rosiglitazone, and that fracture proportions increased with age. For osteoporotic fractures,

which include fractures of the hip and spine, we found that only pioglitazone use was significantly associated with an increased risk of osteoporotic fracture (pioglitazone OR: 1.95, 95% CI: 1.27-2.99; rosiglitazone OR: 1.78, 95% CI: 0.91-3.49) and this association increased when the analysis was repeated with a lag period of a year or more between study cohort entry and the index date (OR: 2.15, 95% CI: 1.32-3.48). Similar results were found in a study by Colhoun et al. [39] examining cumulative TZD exposure in patients with T2DM in Scotland where hip fracture risk (only) increased with cumulative exposure to TZDs (OR per year of exposure: 1.18, 95% CI: 1.09-1.28), and in a recent study [52] examining the association between use of TZDs and hip fracture in persons aged 65 years and older in Taiwan (OR: 1.64, 95% CI: 1.01-2.67). However, unlike our results where only pioglitazone use was significantly associated with an increased risk of osteoporotic fracture, when TZD use was stratified by TZD drug in the Colhoun et al. [39] study, hip fracture risk did not differ between rosiglitazone and pioglitazone. Though it should be noted that our sensitivity analysis comparing the use of pioglitazone directly with use of rosiglitazone could not exclude a class effect. These differences may also be a result of analyses focusing on hip fractures alone versus major osteoporotic fractures that also include fractures of the radius/ulna, vertebrae, and humerus.

When stratified by sex, we found differing trends between men and women. In men, only rosiglitazone was significantly associated with an increased risk of any closed fracture and peripheral fracture. In women, pioglitazone was associated with an increased risk of fracture across fracture sites and rosiglitazone was associated with an increased risk of any closed fracture and peripheral fracture, but not osteoporotic fracture. Other observational studies have also generated conflicting results for the effects of TZD drugs in men and women as some have found fractures primarily in women, others have found comparable risk between men and

women, and few have found an increased risk in men alone. For example, Dormuth et al. [29] found an increased risk of peripheral fractures with pioglitazone (but not rosiglitazone) use in both women (HR: 1.76, 95% CI: 1.32-2.38) and men (HR: 1.61, 95% CI: 1.18-2.20) when compared to users of sulphonylureas, whereas our study found an increased risk associated with rosiglitazone use in women (OR: 3.68, 95% CI: 2.01-6.75) and men (OR: 2.97, 95% CI: 1.20-7.33) but only found an increased risk with pioglitazone in women (OR: 3.35, 95% CI: 2.12-5.30) compared to users of other antidiabetic drugs.

For vertebral fractures, Kanazawa et al. [34] found that TZD use was significantly associated an increased risk in women (OR: 3.38, 95% CI: 1.07-10.71), but not men (OR: 1.09, 95% CI: 0.48-2.46) and we saw the same trend in our study for osteoporotic fractures with pioglitazone (women OR: 2.71, 95% CI: 1.60-4.60; men OR: 1.56, 95% CI: 0.71-3.44), but not rosiglitazone use. However, Mancini et al. [41] found that rosiglitazone plus metformin treatment was significantly associated with an increased risk of vertebral fractures (OR 6.50, 95% CI 1.30-38.10) in men and our study could not reliably assess this association due to a low number of rosiglitazone cases in men.

The conflicting results for associations between fracture risk and sex in the studies conducted to date may be a result of various factors. These factors may include differences in study design such as the use of different reference groups between studies leading to differing comparisons based on varying levels of T2DM severity (e.g. metformin versus sulphonylureas versus never users of TZDs), a lack of control of factors that may bias the results, such as potentially capturing prevalent users of TZDs (across most studies to date), and comparisons based on different sub-categorizations of fractures (e.g. hip fractures versus hip and vertebral fractures versus major osteoporotic fractures). Differences in results may also be a function of



other sex-specific or biological factors. For example, in a case-control study investigating the risk of incident fracture in men and women with T2DM (across all sites), Aubert et al. [22] found that age may play a role in the differing results between men and women. In their study of 69,047 patients treated with a TZD (48% of whom were treated with rosiglitazone), TZD use was associated with a higher risk of fracture in women aged below 50 years (HR: 1.47, 95% CI: 1.20-1.79) and women (HR: 1.50, 95% CI: 1.40-1.61) and men (HR: 1.25, 95% CI: 1.14-1.37) aged 50 years or greater, but not in men aged below 50 years (HR: 1.20, 95% CI, 0.97-1.49) when compared to controls [22]. When stratified by TZD drug the HRs associated with pioglitazone and rosiglitazone were nearly identical. Taken together, the conflicting results to date signify that more research is needed to clarify associations between TZD pharmacotherapy and sex, including other factors that may be responsible for differing levels of risk.

### **Biological mechanisms**

As described by Davidson et al. ([21] - refer to **Chapter 2** of this thesis), the underlying biological mechanism responsible for TZD-associated bone fractures remains unclear and the empirical evidence remains conflicting. Some *in vitro* studies have suggested that TZDs may inhibit bone resorption and prevent bone loss [e.g. 54], whereas other studies have demonstrated opposite effects. At the receptor level, PPAR $\gamma$  is expressed in skeletal tissue and evidence from some *in vitro* and *in vivo* studies suggests that activation of PPAR $\gamma$  actually inhibits bone formation by shifting cells towards fat formation [55]. There is also evidence that PPAR $\gamma$  activation may increase bone resorption [56] and indirectly affect the skeletal system by modulating circulating levels of hormones that influence bone metabolism [57-58].

In humans, several randomized controlled trials have explored measures of bone strength and related biomarkers. For example, alterations in the circulating levels of bone metabolism biomarkers (C-terminal telopeptide, procollagen type 1 N-propeptide, and bone alkaline phosphatase) in a subset of the ADOPT population suggest that changes in bone resorption may have been partly responsible for the increased fracture risk observed in women in this trial [59]. Other trials have also found decreases in bone mineral density and bone mineral content in addition to changes in biochemical markers of bone turnover indicating potential negative effects on bone metabolism [21].

Observational studies have also reported that TZD treatment increases bone loss and decreases bone strength in women [6, 10-11], but because most studies have focused on patients with an average age of approximately 60 years (when averaged over the observational studies conducted to date), and in particular postmenopausal women, it is still unclear how the risk of fracture associated with TZDs extends to men from a mechanistic perspective. Observational studies reporting increased bone loss and decreased bone strength in women have not found the same effects in men [10-11], whereas other studies have shown that men are also at risk [12]. For example, Yaturu et al. [12] found that older men (mean age of 70 years) undergoing rosiglitazone therapy experienced significant bone loss at the hip and lumbar spine compared to men not on TZD therapy, whereas Mancini et al. [41] found no correlation between rosiglitazone-metformin combination therapy and reduced BMD in men (median age of 69 years) in a cross-sectional study.

Together, the aforementioned biological mechanisms may be responsible for the bone loss and decreased bone strength that can increase fracture risk in patients undergoing TZD pharmacotherapy. For example, endocrine changes such as increases or decreases in circulating

hormones could explain, at least in part, why differing results for fracture risk have been reported in men and women in some studies. However, more research is required to determine the mechanism(s) behind these differing results, whether these changes are drug-specific (e.g. rosiglitazone and pioglitazone have been demonstrated to have different mechanisms of action with pioglitazone also demonstrating a weak affinity for PPAR $\alpha$  [21]), and if there is a combined drug and sex-specific effect that may explain differences in fracture risk between men and women.

### **Strengths and limitations**

This population-based study has several strengths. Firstly, this study had a cohort of 12,462 patients with T2DM who were followed for up to 11.9 years. Thus the size and long term follow-up of patients enabled the identification of a large number of bone fracture cases with varying duration of diabetes. Secondly, because the Cerner Health Facts® database contains pre-recorded information on prescriptions, and these prescriptions are filled in-hospital, the possibility of recall bias was eliminated. Thirdly, the study design was constructed so that patients entering the base and study cohorts were more likely to be new users of antidiabetic drugs, therefore, this addressed biases related to the inclusion of prevalent users, and increased the likelihood that patients included in the study cohort were at a similar level of diabetes severity [43], to the extent possible. Fourthly, by excluding open fractures the capture of traumatic fractures that would not be expected to result from TZD pharmacotherapy was minimized. Fifthly, the inclusion of a lag period in the sensitivity analyses provided an approximation of latency and findings were consistent in several sensitivity analyses in which the duration of the lag period was varied. Finally, the use of population based cohorts from more

than 480 contributing hospitals throughout the US strengthens the generalisability of our findings.

Our study also has several limitations. Firstly, we acknowledge that some of our ORs were higher than the literature which is likely a consequence of the greater proportion of cases that received TZD drugs compared to controls (refer to **Chapter 6** of this thesis for a general discussion related to this observation in the dataset). Our ORs were especially high in the sex-stratified analyses which may also indicate that other sex-specific factors further contributed to the greater ORs in women. In general, the number of cases undergoing rosiglitazone therapy was less than those undergoing pioglitazone therapy. This is most likely a function of the change in prescribing practices that resulted from the warnings of adverse cardiovascular events associated with rosiglitazone pharmacotherapy beginning in 2007, and a shift towards pioglitazone prescriptions by many physicians after these warnings [21]. This shift may have included preferentially switching men, but not women, from rosiglitazone to pioglitazone therapy due to their higher overall risk for cardiovascular disease. It may have also resulted in more men than women being switched completely from TZDs to other non-TZD antidiabetic drugs as we observed that the percentage of TZD drugs prescribed to men in our cohort was half of that prescribed to women. Conversely, it is also possible that a high incidence of fractures in women in this cohort, who are postmenopausal and of a more advanced age than in many previous studies, may have influenced the results for fractures in the entire study cohort and that this became apparent when the analyses were stratified by sex. At baseline, female cases were more likely than controls to have a history of obesity, alcoholism, and rheumatoid arthritis but these factors were adjusted for in the analyses. However, given that women represented 74% of fractures in the US in 2005 [53], it is possible that our results may reflect a greater number of

fractures in women by chance, or that other factors that were not controlled for (e.g. diabetic neuropathy or retinopathy) may have contributed to a greater number of fragility falls in women.

A second limitation is that drug information in the database represents prescriptions written only by hospital physicians. As such, it is unknown whether additional prescriptions were provided to patients from other health care providers, such as general practitioners, outside of the Cerner network. Because many diabetic patients are primarily under the care of general practitioners and would be assumed to receive prescriptions for antihyperglycaemic drugs from these practitioners, this does introduce exposure misclassification into the study and also meant that it was not possible to assess the dose-specific effects of TZDs. However, our study was designed to capture incident users, to the extent possible, and thus minimizes this bias, though it does not preclude TZD patients adding on or substituting other medications after study cohort entry, such as insulin, that indicate intensification or a change in treatment.

Thirdly, when working with administrative hospital data there is always the possibility that coding errors or omissions may have occurred, and that ICD-9 codes may not accurately or completely reflect the patient's diagnosis. This also includes the possibility that fracture outcomes may have been misclassified. Given the hospital-based setting of the database, fractures would be reasonably expected to be confirmed through radiography, however, this could still lead to an underestimation of the number of fracture cases (e.g. a hairline fracture not appearing on film). This is unlikely given that our overall incidence rate of any closed fracture (35.5 per 1,000 person years, 95% CI: 38.0-32.9) was similar to that of other studies in older diabetic adults. For example, in a study of Medicare beneficiaries aged 65 years and older in Pennsylvania the rate for a composite of fractures was 28.7 per 1,000 person-years in patients [40]. Finally, given the observational nature of the study, and the use of hospital-based versus

general practice data, it is possible that there may have been residual confounding by disease severity as we had no information on the duration of treated diabetes prior to a patient's first recorded encounter in the dataset. However, the design of this study attempted to control for this through the criteria for entry to the base cohort and by matching cases and controls on duration of follow-up during the study period, which has been shown to be a good proxy for disease severity [60].

## **CONCLUSIONS AND IMPLICATIONS**

In this hospital-based study, we found that use of TZD drugs was associated with an increased risk of bone fracture compared with never users of TZD drugs in patients followed for up to 11.9 years (median 1.1 years). In sensitivity analyses rosiglitazone remained significantly associated with an increased risk of fractures when a lag period of a year or more was incorporated into the analyses, but only pioglitazone demonstrated a significant association with an increased risk of fractures when the lag period was less than a year. This implies that there could be a different mechanism by which pioglitazone induces bone fractures in Type 2 diabetics compared to rosiglitazone, and that further research is necessary to explore and confirm the duration-specific effects of TZD pharmacotherapy.

When fracture site was further investigated in secondary analyses, pioglitazone was associated with an increased risk of fracture across all fracture site categories. This association remained when a lag period of a year or more was incorporated into the analyses, but only for peripheral fractures when the lag period was less than a year. Rosiglitazone was significantly associated with an increased risk of peripheral, but not osteoporotic fracture, and not when the lag period was less than a year. Because there is some overlap between the peripheral fracture

category and the osteoporotic fracture category (i.e. ulna/radius and humerus), associations between fracture risk and rosiglitazone use may be more site-specific when compared to pioglitazone use. Further research into this area could provide additional insights into whether a site-specific effect does in fact exist or if the results obtained in this study are a reflection of a greater incidence of fractures at peripheral sites, especially in the upper limbs, compared to other osteoporotic sites such as the hip or vertebrae.

When sex was investigated in secondary analyses, use of pioglitazone or rosiglitazone was associated with an increased risk of any closed fracture and peripheral fracture in women, but only pioglitazone use was associated with an increased risk of osteoporotic fracture. Similar to in the previous analyses, associations between pioglitazone use, any closed fracture, and peripheral fracture were also significant when the lag period was less than one year. In men, only rosiglitazone use was significantly associated with an increased risk of any closed fracture or peripheral fracture, but not osteoporotic fracture, and these associations only remained significant when the lag period was set to a year or more. These trends may indicate different drug-specific and sex-specific mechanisms of action for pioglitazone and rosiglitazone whereas both TZDs affect women and adverse effects appear sooner with pioglitazone use, but where only rosiglitazone use affects men and only after a longer period of use. These remain other potential areas for further investigation.

Though prescribing rates for TZD drugs have decreased in recent years in reaction to reports of adverse reactions (also refer to **Chapter 6** of this thesis for prescribing trends within this population), including bone fractures, and because new Type 2 diabetic drugs continue to be developed and marketed, TZDs continue to be used as a second or third-line treatment for T2DM. In addition, TZD drugs are increasingly being repurposed and used off-label for the

treatment of other diseases and conditions such as some cancers, neurodegenerative disorders, and PCOS. As such, it is important that continued monitoring occur as the user profile of TZDs evolves over time and prescribing practices shift to other non-diabetic populations. In this study we demonstrated significant associations between TZD pharmacotherapy and bone fractures in patients with T2DM. Our findings support the results of previous studies investigating the effects of TZDs on bone fractures and reiterate the need for careful consideration of the overall risks and benefits of TZD therapy by the medical and regulatory communities, especially when used in patients with existing risk factors for bone fractures.

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### **Author's roles**

M.A. Davidson formulated the hypothesis and design for this study and performed the SAS coding, statistical analyses, and literature review required for the manuscript under the guidance of D. Krewski and with advice from C. Gravel, D. Mattison, and D. McNair. C. Gravel provided assistance in validating the accuracy of the SAS code. M.A. Davidson drafted all text, figures, and tables with editorial input from the co-authors. All contributors were involved in the evaluation and interpretation of the study findings.

### **Authors' disclosures of potential conflicts of interest**

M.A. Davidson, C. Gravel, D. Mattison, and D. Krewski have no actual or potential competing financial interest. D. Krewski is the Natural Sciences and Engineering Research



Council of Canada Chair in Risk Science at the University of Ottawa. He also serves as Chief Risk Scientist and CEO for Risk Sciences International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa to provide consulting services in risk science to both public and private sector clients. To date, RSI has not conducted work on antihyperglycaemics, the subject of the present paper. D. Mattison was supported by RSI. D. McNair is the President of Cerner Math Inc. and has ownership interest in Cerner Corporation.

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## **SUPPLEMENTARY TABLES**

The purpose of the following supplementary tables is to present the baseline characteristics for each of the secondary analyses conducted by fracture site, and the baseline characteristics of the secondary analyses for any closed fracture for males and females, respectively.

**Table S1.** Baseline characteristics of all peripheral bone fracture cases and matched controls. Values are numbers (percentages) unless stated otherwise.

| Characteristic                                  | Cases (n = 543)    | Controls (n = 4,980) |
|-------------------------------------------------|--------------------|----------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>74.7 (12.0)</b> | <b>76.1 (11.1)</b>   |
| 18-25                                           | 1 (0.2)            | 15 (0.3)             |
| 26-35                                           | 8 (1.5)            | 74 (1.5)             |
| 36-45                                           | 21 (3.9)           | 224 (4.5)            |
| 46-55                                           | 72 (13.3)          | 593 (11.9)           |
| 56-65                                           | 105 (19.3)         | 946 (19.0)           |
| 66-75                                           | 129 (23.8)         | 1217 (24.4)          |
| 76-85                                           | 141 (26.0)         | 1360 (27.3)          |
| >85                                             | 66 (12.2)          | 551 (11.1)           |
| <b>Men*</b>                                     | <b>232 (42.7)</b>  | <b>2368 (47.6)</b>   |
| <b>Year of study cohort entry*</b>              |                    |                      |
| 2000                                            | 2 (0.4)            | 6 (0.1)              |
| 2001                                            | 23 (4.2)           | 165 (3.3)            |
| 2002                                            | 33 (6.1)           | 255 (5.1)            |
| 2003                                            | 31 (5.7)           | 251 (5.0)            |
| 2004                                            | 44 (8.1)           | 387 (7.8)            |
| 2005                                            | 48 (8.8)           | 435 (8.7)            |
| 2006                                            | 34 (6.3)           | 308 (6.2)            |
| 2007                                            | 54 (9.9)           | 540 (10.8)           |
| 2008                                            | 58 (10.7)          | 544 (10.9)           |
| 2009                                            | 62 (11.4)          | 592 (11.9)           |
| 2010                                            | 68 (12.5)          | 668 (13.4)           |
| 2011                                            | 53 (9.8)           | 506 (10.2)           |
| 2012                                            | 33 (6.1)           | 323 (6.5)            |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.5 (1.8)</b>   | <b>1.5 (1.8)</b>     |
| <b>Race*</b>                                    |                    |                      |
| Caucasian                                       | 437 (80.5)         | 4023 (80.8)          |
| African-American                                | 84 (15.5)          | 785 (15.8)           |
| Other                                           | 22 (4.1)           | 172 (3.5)            |
| <b>Payer class</b>                              |                    |                      |
| Medicare                                        | 164 (30.2)         | 1638 (32.9)          |
| Other                                           | 115 (21.2)         | 973 (19.5)           |
| Unknown                                         | 264 (48.6)         | 2369 (47.6)          |
| <b>Census region</b>                            |                    |                      |
| Northeast                                       | 235 (43.3)         | 2159 (43.4)          |
| Midwest                                         | 104 (19.2)         | 744 (14.9)           |
| West                                            | 33 (6.1)           | 261 (5.2)            |
| South                                           | 171 (31.5)         | 1816 (36.5)          |



Table S1. *Continued.*

| Characteristic                                             | Cases (n = 543)  | Controls (n = 4,980) |
|------------------------------------------------------------|------------------|----------------------|
| <b>Region type</b>                                         |                  |                      |
| Urban                                                      | 543 (100.0)      | 4967 (99.7)          |
| Rural                                                      | 0 (0.0)          | 13 (0.3)             |
| <b>Treatment center type</b>                               |                  |                      |
| Acute care                                                 | 536 (98.7)       | 4824 (96.9)          |
| Non-acute care                                             | 7 (1.3)          | 152 (3.1)            |
| Missing                                                    | 0 (0.0)          | 4 (0.1)              |
| <b>Treatment center teaching status</b>                    |                  |                      |
| Teaching                                                   | 324 (59.7)       | 2858 (57.4)          |
| Non-teaching                                               | 7 (1.3)          | 2122 (42.6)          |
| <b>Treatment center beds</b>                               |                  |                      |
| 1-199                                                      | 39 (7.2)         | 456 (9.2)            |
| 100-199                                                    | 61 (11.2)        | 646 (13.0)           |
| 200-299                                                    | 180 (33.2)       | 1676 (33.7)          |
| 300-499                                                    | 116 (21.4)       | 846 (17.0)           |
| ≥ 500                                                      | 147 (27.1)       | 1356 (27.2)          |
| Ever smoker†                                               | 72 (13.3)        | 762 (15.3)           |
| Ever diagnosis or treatment for obesity‡                   | 236 (43.5)       | 2300 (46.2)          |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 17 (3.1)         | 237 (4.8)            |
| Previous fracture                                          | 34 (6.3)         | 260 (5.2)            |
| Chronic obstructive pulmonary disease                      | 84 (15.5)        | 863 (17.3)           |
| Rheumatoid arthritis                                       | 6 (1.1)          | 82 (1.7)             |
| Osteoporosis                                               | 21 (3.9)         | 173 (3.5)            |
| Mean number hospital admissions (SD)                       | <b>3.1 (3.0)</b> | <b>3.0 (3.0)</b>     |
| <b>Number of hospital admissions</b>                       |                  |                      |
| 1                                                          | 202 (37.2)       | 1898 (38.1)          |
| 2                                                          | 116 (21.4)       | 1108 (22.3)          |
| 3                                                          | 71 (13.1)        | 646 (13.0)           |
| ≥ 4                                                        | 154 (28.4)       | 1328 (26.7)          |
| Mean number unique non-diabetic drugs (SD)                 | <b>4.0 (1.8)</b> | <b>4.1 (1.7)</b>     |
| <b>Number of unique non-antidiabetic drugs</b>             |                  |                      |
| 0                                                          | 21 (3.9)         | 115 (2.3)            |
| 1                                                          | 28 (5.2)         | 207 (4.2)            |
| 2                                                          | 57 (10.5)        | 459 (9.2)            |
| 3                                                          | 108 (19.9)       | 1011 (20.3)          |
| ≥ 4                                                        | 329 (60.6)       | 3188 (64.0)          |

**Table S1. Continued.**

| <b>Characteristic</b>           | <b>Cases (n = 543)</b> | <b>Controls (n = 4,980)</b> |
|---------------------------------|------------------------|-----------------------------|
| <b>Antidiabetic drug use¶</b>   |                        |                             |
| <b>Metformin</b>                | 296 (54.5)             | 2,537 (50.9)                |
| <b>Sulphonylureas</b>           | 393 (72.4)             | 3,656 (73.4)                |
| <b>Pioglitazone</b>             | 41 (7.6)               | 138 (2.8)                   |
| <b>Rosiglitazone</b>            | 27 (5.0)               | 70 (1.4)                    |
| <b>DPP-4 inhibitors</b>         | 26 (4.8)               | 288 (5.8)                   |
| <b>α-glucosidase inhibitors</b> | 1 (0.2)                | 32 (0.6)                    |
| <b>Meglitinides</b>             | 18 (3.3)               | 214 (4.3)                   |
| <b>Insulins</b>                 | 526 (96.9)             | 4,650 (93.4)                |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

**Table S2.** Baseline characteristics of all osteoporotic bone fracture cases and matched controls. Values are numbers (percentages) unless stated otherwise.

| <b>Characteristic</b>                           | <b>Cases (n = 485)</b> | <b>Controls (n = 4,580)</b> |
|-------------------------------------------------|------------------------|-----------------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>76.5 (10.8)</b>     | <b>77.5 (10.2)</b>          |
| 18-25                                           | 0 (0.0)                | 14 (0.3)                    |
| 26-35                                           | 5 (1.0)                | 69 (1.5)                    |
| 36-45                                           | 13 (2.7)               | 217 (4.7)                   |
| 46-55                                           | 67 (13.8)              | 545 (11.9)                  |
| 56-65                                           | 93 (19.2)              | 858 (18.7)                  |
| 66-75                                           | 111 (22.9)             | 1141 (24.9)                 |
| 76-85                                           | 150 (30.9)             | 1218 (26.6)                 |
| >85                                             | 46 (9.5)               | 518 (11.3)                  |
| <b>Men*</b>                                     | <b>224 (46.2)</b>      | <b>2165 (47.3)</b>          |
| <b>Year of study cohort entry*</b>              |                        |                             |
| 2000                                            | 4 (0.8)                | 19 (0.4)                    |
| 2001                                            | 18 (3.7)               | 155 (3.4)                   |
| 2002                                            | 25 (5.2)               | 208 (4.5)                   |
| 2003                                            | 28 (5.8)               | 243 (5.3)                   |
| 2004                                            | 36 (7.4)               | 334 (7.3)                   |
| 2005                                            | 35 (7.2)               | 323 (7.1)                   |
| 2006                                            | 30 (6.2)               | 280 (6.1)                   |
| 2007                                            | 42 (8.7)               | 414 (9.0)                   |
| 2008                                            | 61 (12.6)              | 582 (12.7)                  |
| 2009                                            | 61 (12.6)              | 601 (13.1)                  |
| 2010                                            | 61 (12.6)              | 605 (13.2)                  |
| 2011                                            | 51 (10.5)              | 486 (10.6)                  |
| 2012                                            | 33 (6.8)               | 330 (7.2)                   |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.6 (1.9)</b>       | <b>1.5 (1.8)</b>            |
| <b>Race*</b>                                    |                        |                             |
| Caucasian                                       | 407 (83.9)             | 3714 (81.1)                 |
| African-American                                | 67 (13.8)              | 709 (15.5)                  |
| Other                                           | 11 (2.3)               | 157 (3.4)                   |
| <b>Payer class</b>                              |                        |                             |
| Medicare                                        | 157 (32.4)             | 1528 (33.4)                 |
| Other                                           | 98 (20.2)              | 886 (19.3)                  |
| Unknown                                         | 230 (47.4)             | 2166 (47.3)                 |
| <b>Census region</b>                            |                        |                             |
| Northeast                                       | 217 (44.7)             | 1933 (42.2)                 |
| Midwest                                         | 65 (13.4)              | 693 (15.1)                  |
| West                                            | 28 (5.8)               | 254 (5.6)                   |
| South                                           | 175 (36.1)             | 1700 (37.1)                 |

Table S2. *Continued.*

| Characteristic                                             | Cases (n = 485)  | Controls (n = 4,580) |
|------------------------------------------------------------|------------------|----------------------|
| <b>Region type</b>                                         |                  |                      |
| Urban                                                      | 483 (99.6)       | 4569 (99.8)          |
| Rural                                                      | 2 (0.4)          | 11 (0.2)             |
| <b>Treatment center type</b>                               |                  |                      |
| Acute care                                                 | 467 (96.3)       | 4435 (96.8)          |
| Non-acute care                                             | 16 (3.3)         | 143 (3.1)            |
| Missing                                                    | 2 (0.4)          | 2 (0.0)              |
| <b>Treatment center teaching status</b>                    |                  |                      |
| Teaching                                                   | 274 (56.5)       | 2561 (55.9)          |
| Non-teaching                                               | 211 (43.5)       | 2019 (44.1)          |
| <b>Treatment center beds</b>                               |                  |                      |
| 1-199                                                      | 49 (10.1)        | 413 (9.0)            |
| 100-199                                                    | 69 (14.2)        | 599 (13.1)           |
| 200-299                                                    | 174 (35.9)       | 1585 (34.6)          |
| 300-499                                                    | 66 (13.6)        | 816 (17.8)           |
| ≥ 500                                                      | 127 (26.2)       | 1167 (25.5)          |
| Ever smoker†                                               | 78 (16.1)        | 696 (15.2)           |
| Ever diagnosis or treatment for obesity‡                   | 218 (45.0)       | 2074 (45.3)          |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 26 (5.4)         | 206 (4.5)            |
| Previous fracture                                          | 26 (5.4)         | 244 (5.3)            |
| Chronic obstructive pulmonary disease                      | 88 (18.1)        | 806 (17.6)           |
| Rheumatoid arthritis                                       | 6 (1.2)          | 73 (1.6)             |
| Osteoporosis                                               | 18 (3.7)         | 166 (3.6)            |
| Mean number hospital admissions (SD)                       | <b>3.1 (3.0)</b> | <b>3.0 (3.0)</b>     |
| <b>Number of hospital admissions</b>                       |                  |                      |
| 1                                                          | 167 (34.4)       | 1750 (38.2)          |
| 2                                                          | 116 (23.9)       | 997 (21.8)           |
| 3                                                          | 62 (12.8)        | 600 (13.1)           |
| ≥ 4                                                        | 140 (28.9)       | 1233 (26.9)          |
| Mean number unique non-diabetic drugs (SD)                 | <b>4.1 (1.7)</b> | <b>4.1 (1.7)</b>     |
| <b>Number of unique non-antidiabetic drugs</b>             |                  |                      |
| 0                                                          | 13 (2.7)         | 116 (2.5)            |
| 1                                                          | 25 (5.2)         | 189 (4.1)            |
| 2                                                          | 39 (8.0)         | 438 (9.6)            |
| 3                                                          | 101 (2.8)        | 914 (20.0)           |
| ≥ 4                                                        | 307 (63.3)       | 2923 (63.8)          |

**Table S2. Continued.**

| <b>Characteristic</b>           | <b>Cases (n = 485)</b> | <b>Controls (n = 4,580)</b> |
|---------------------------------|------------------------|-----------------------------|
| <b>Antidiabetic drug use¶</b>   |                        |                             |
| <b>Metformin</b>                | 253 (52.2)             | 2,237 (48.8)                |
| <b>Sulphonylureas</b>           | 358 (73.8)             | 3,407 (74.4)                |
| <b>Pioglitazone</b>             | 28 (5.8)               | 137 (3.0)                   |
| <b>Rosiglitazone</b>            | 12 (2.5)               | 59 (1.3)                    |
| <b>DPP-4 inhibitors</b>         | 22 (4.5)               | 264 (5.8)                   |
| <b>α-glucosidase inhibitors</b> | 1 (0.2)                | 25 (0.6)                    |
| <b>Meglitinides</b>             | 21 (4.3)               | 183 (4.0)                   |
| <b>Insulins</b>                 | 471 (97.1)             | 4,313 (94.2)                |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

**Table S3.** Baseline characteristics for male matched cases and controls for any closed fracture. Values are numbers (percentages) unless stated otherwise.

| Characteristic                                  | Cases (n = 290)    | Controls (n = 2,649) |
|-------------------------------------------------|--------------------|----------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>73.0 (11.8)</b> | <b>74.1 (11.2)</b>   |
| 18-25                                           | 0 (0.0)            | 1 (0.0)              |
| 26-35                                           | 1 (0.3)            | 14 (0.5)             |
| 36-45                                           | 4 (1.4)            | 103 (3.9)            |
| 46-55                                           | 45 (15.5)          | 328 (12.4)           |
| 56-65                                           | 64 (22.1)          | 559 (21.1)           |
| 66-75                                           | 75 (25.9)          | 714 (27.0)           |
| 76-85                                           | 84 (29.0)          | 749 (28.3)           |
| >85                                             | 17 (5.9)           | 181 (6.8)            |
| <b>Year of study cohort entry*</b>              |                    |                      |
| 2000                                            | 3 (1.0)            | 11 (0.4)             |
| 2001                                            | 12 (4.1)           | 89 (3.4)             |
| 2002                                            | 18 (6.2)           | 151 (5.7)            |
| 2003                                            | 18 (6.2)           | 141 (5.3)            |
| 2004                                            | 17 (5.9)           | 144 (5.4)            |
| 2005                                            | 24 (8.3)           | 212 (8.0)            |
| 2006                                            | 15 (5.2)           | 123 (4.6)            |
| 2007                                            | 26 (9.0)           | 260 (9.8)            |
| 2008                                            | 36 (12.4)          | 344 (13.0)           |
| 2009                                            | 37 (12.8)          | 355 (13.4)           |
| 2010                                            | 37 (12.8)          | 358 (13.5)           |
| 2011                                            | 31 (10.7)          | 301 (11.4)           |
| 2012                                            | 16 (5.5)           | 160 (6.0)            |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.6 (1.9)</b>   | <b>1.6 (2.0)</b>     |
| <b>Race*</b>                                    |                    |                      |
| Caucasian                                       | 254 (87.6)         | 2,296 (86.7)         |
| African-American                                | 31 (10.7)          | 297 (11.2)           |
| Other                                           | 5 (1.7)            | 56 (2.1)             |
| <b>Payer class</b>                              |                    |                      |
| Medicare                                        | 85 (29.3)          | 805 (30.4)           |
| Other                                           | 56 (19.3)          | 392 (14.8)           |
| Unknown                                         | 149 (51.4)         | 1,452 (54.8)         |
| <b>Census region</b>                            |                    |                      |
| Northeast                                       | 123 (42.4)         | 1,136 (42.9)         |
| Midwest                                         | 54 (18.6)          | 435 (16.4)           |
| West                                            | 16 (5.5)           | 123 (4.6)            |
| South                                           | 97 (33.5)          | 955 (36.1)           |

Table S3. *Continued.*

| Characteristic                                             | Cases (n = 290) | Controls (n = 2,649) |
|------------------------------------------------------------|-----------------|----------------------|
| <b>Region type</b>                                         |                 |                      |
| Urban                                                      | 289 (99.7)      | 2,642 (99.7)         |
| Rural                                                      | 1 (0.3)         | 7 (0.3)              |
| <b>Treatment center type</b>                               |                 |                      |
| Acute care                                                 | 279 (96.2)      | 2,526 (95.4)         |
| Non-acute care                                             | 11 (3.8)        | 121 (4.6)            |
| Missing                                                    | 0 (0.0)         | 2 (0.1)              |
| <b>Treatment center teaching status</b>                    |                 |                      |
| Teaching                                                   | 163 (56.2)      | 1,478 (55.8)         |
| Non-teaching                                               | 127 (43.8)      | 1,171 (44.2)         |
| <b>Treatment center beds</b>                               |                 |                      |
| 1-199                                                      | 24 (8.3)        | 301 (11.4)           |
| 100-199                                                    | 45 (15.5)       | 357 (13.5)           |
| 200-299                                                    | 89 (30.7)       | 750 (28.3)           |
| 300-499                                                    | 51 (17.6)       | 506 (19.1)           |
| ≥ 500                                                      | 81 (27.9)       | 735 (27.8)           |
| Ever smoker†                                               | 35 (12.1)       | 331 (12.5)           |
| Ever diagnosis or treatment for obesity‡                   | 103 (35.5)      | 949 (35.8)           |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 9 (3.1)         | 172 (6.5)            |
| Previous fracture                                          | 9 (3.1)         | 87 (3.3)             |
| Chronic obstructive pulmonary disease                      | 45 (15.5)       | 381 (14.4)           |
| Rheumatoid arthritis                                       | 0 (0.0)         | 16 (0.6)             |
| Osteoporosis                                               | 1 (0.3)         | 11 (0.4)             |
| Mean number hospital admissions (SD)                       | 2.8 (2.7)       | 2.8 (2.9)            |
| <b>Number of hospital admissions</b>                       |                 |                      |
| 1                                                          | 121 (41.7)      | 1,080 (40.8)         |
| 2                                                          | 65 (22.4)       | 602 (22.7)           |
| 3                                                          | 38 (13.1)       | 317 (12.0)           |
| ≥ 4                                                        | 66 (22.8)       | 650 (24.5)           |
| Mean number unique non-diabetic drugs (SD)                 | 4.2 (1.5)       | 4.2 (1.6)            |
| <b>Number of unique non-antidiabetic drugs</b>             |                 |                      |
| 0                                                          | 1 (0.3)         | 43 (1.6)             |
| 1                                                          | 9 (3.1)         | 75 (2.8)             |
| 2                                                          | 27 (9.3)        | 234 (8.8)            |
| 3                                                          | 61 (21.0)       | 532 (20.1)           |
| ≥ 4                                                        | 192 (66.2)      | 1,765 (66.6)         |

**Table S3. Continued.**

| Characteristic                  | Cases (n = 290) | Controls (n = 2,649) |
|---------------------------------|-----------------|----------------------|
| <b>Antidiabetic drug use¶</b>   |                 |                      |
| <b>Metformin</b>                | 151 (52.1)      | 1,319 (49.8)         |
| <b>Sulphonylureas</b>           | 215 (74.1)      | 2,061 (77.8)         |
| <b>Pioglitazone</b>             | 14 (4.8)        | 81 (3.1)             |
| <b>Rosiglitazone</b>            | 11 (3.8)        | 39 (1.5)             |
| <b>DPP-4 inhibitors</b>         | 14 (4.8)        | 173 (6.5)            |
| <b>α-glucosidase inhibitors</b> | 1 (0.3)         | 25 (0.9)             |
| <b>Meglitinides</b>             | 14 (4.8)        | 105 (4.0)            |
| <b>Insulins</b>                 | 283 (97.6)      | 2,475 (93.4)         |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.



**Table S4.** Baseline characteristics for female matched cases and controls for any closed fracture. Values are numbers (percentages) unless stated otherwise.

| <b>Characteristic</b>                           | <b>Cases (n = 459)</b> | <b>Controls (n = 4,245)</b> |
|-------------------------------------------------|------------------------|-----------------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>75.3 (12.1)</b>     | <b>76.7 (11.3)</b>          |
| <b>18-25</b>                                    | 1 (0.2)                | 20 (0.5)                    |
| <b>26-35</b>                                    | 7 (1.5)                | 70 (1.7)                    |
| <b>36-45</b>                                    | 25 (5.5)               | 201 (4.7)                   |
| <b>46-55</b>                                    | 57 (12.4)              | 521 (12.3)                  |
| <b>56-65</b>                                    | 64 (13.9)              | 769 (18.1)                  |
| <b>66-75</b>                                    | 123 (26.8)             | 1,014 (23.9)                |
| <b>76-85</b>                                    | 125 (27.2)             | 1,084 (25.5)                |
| <b>&gt;85</b>                                   | 57 (12.4)              | 566 (13.3)                  |
| <b>Year of study cohort entry*</b>              |                        |                             |
| <b>2000</b>                                     | 1 (0.2)                | 1 (0.0)                     |
| <b>2001</b>                                     | 17 (3.7)               | 119 (2.8)                   |
| <b>2002</b>                                     | 25 (5.5)               | 194 (4.6)                   |
| <b>2003</b>                                     | 30 (6.5)               | 262 (6.2)                   |
| <b>2004</b>                                     | 39 (8.5)               | 352 (8.3)                   |
| <b>2005</b>                                     | 36 (7.8)               | 318 (7.5)                   |
| <b>2006</b>                                     | 32 (7.0)               | 305 (7.2)                   |
| <b>2007</b>                                     | 43 (9.4)               | 430 (10.1)                  |
| <b>2008</b>                                     | 40 (8.7)               | 375 (8.8)                   |
| <b>2009</b>                                     | 63 (13.7)              | 612 (14.4)                  |
| <b>2010</b>                                     | 52 (11.3)              | 520 (12.3)                  |
| <b>2011</b>                                     | 46 (10.0)              | 415 (9.8)                   |
| <b>2012</b>                                     | 35 (7.6)               | 342 (8.1)                   |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.6 (1.8)</b>       | <b>1.6 (1.9)</b>            |
| <b>Race*</b>                                    |                        |                             |
| <b>Caucasian</b>                                | 367 (80.0)             | 3,337 (78.6)                |
| <b>African-American</b>                         | 70 (15.3)              | 764 (18.0)                  |
| <b>Other</b>                                    | 22 (4.8)               | 144 (3.4)                   |
| <b>Payer class</b>                              |                        |                             |
| <b>Medicare</b>                                 | 143 (31.2)             | 1,345 (31.7)                |
| <b>Other</b>                                    | 86 (18.7)              | 873 (20.6)                  |
| <b>Unknown</b>                                  | 230 (50.1)             | 2,027 (47.8)                |
| <b>Census region</b>                            |                        |                             |
| <b>Northeast</b>                                | 192 (41.8)             | 1,793 (42.2)                |
| <b>Midwest</b>                                  | 65 (14.2)              | 646 (15.2)                  |
| <b>West</b>                                     | 25 (5.5)               | 216 (5.1)                   |
| <b>South</b>                                    | 177 (38.6)             | 1,590 (37.5)                |

Table S4. *Continued.*

| Characteristic                                             | Cases (n = 459)  | Controls (n = 4,245) |
|------------------------------------------------------------|------------------|----------------------|
| <b>Region type</b>                                         |                  |                      |
| Urban                                                      | 453 (98.7)       | 4,236 (99.8)         |
| Rural                                                      | 6 (1.3)          | 9 (0.2)              |
| <b>Treatment center type</b>                               |                  |                      |
| Acute care                                                 | 442 (96.3)       | 4,113 (96.9)         |
| Non-acute care                                             | 16 (3.5)         | 127 (3.0)            |
| Missing                                                    | 1 (0.2)          | 5 (0.1)              |
| <b>Treatment center teaching status</b>                    |                  |                      |
| Teaching                                                   | 268 (58.4)       | 2,385 (56.2)         |
| Non-teaching                                               | 191 (41.6)       | 1,860 (43.8)         |
| <b>Treatment center beds</b>                               |                  |                      |
| 1-199                                                      | 49 (10.7)        | 399 (9.4)            |
| 100-199                                                    | 64 (13.9)        | 515 (12.1)           |
| 200-299                                                    | 149 (32.5)       | 1,525 (35.9)         |
| 300-499                                                    | 70 (15.3)        | 675 (15.9)           |
| ≥ 500                                                      | 127 (27.7)       | 1,131 (26.6)         |
| Ever smoker†                                               | 66 (14.3)        | 641 (15.1)           |
| Ever diagnosis or treatment for obesity‡                   | 227 (49.5)       | 2,066 (48.7)         |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 14 (3.1)         | 114 (2.7)            |
| Previous fracture                                          | 22 (4.8)         | 270 (6.4)            |
| Chronic obstructive pulmonary disease                      | 78 (17.0)        | 723 (17.0)           |
| Rheumatoid arthritis                                       | 13 (2.8)         | 86 (2.0)             |
| Osteoporosis                                               | 26 (5.7)         | 242 (5.7)            |
| Mean number hospital admissions (SD)                       | <b>3.1 (3.0)</b> | <b>3.0 (3.1)</b>     |
| <b>Number of hospital admissions</b>                       |                  |                      |
| 1                                                          | 158 (34.4)       | 1,598 (37.6)         |
| 2                                                          | 101 (22.0)       | 930 (21.9)           |
| 3                                                          | 77 (16.8)        | 574 (13.5)           |
| ≥ 4                                                        | 123 (26.8)       | 1,143 (26.9)         |
| Mean number unique non-diabetic drugs (SD)                 | <b>4.2 (1.6)</b> | <b>4.2 (1.7)</b>     |
| <b>Number of unique non-antidiabetic drugs</b>             |                  |                      |
| 0                                                          | 9 (2.0)          | 83 (2.0)             |
| 1                                                          | 13 (2.8)         | 171 (4.0)            |
| 2                                                          | 42 (9.2)         | 399 (9.4)            |
| 3                                                          | 89 (19.4)        | 856 (20.2)           |
| ≥ 4                                                        | 306 (66.7)       | 2,736 (64.5)         |

**Table S4. Continued.**

| <b>Characteristic</b>           | <b>Cases (n = 459)</b> | <b>Controls (n = 4,245)</b> |
|---------------------------------|------------------------|-----------------------------|
| <b>Antidiabetic drug use¶</b>   |                        |                             |
| <b>Metformin</b>                | 253 (55.1)             | 2,258 (53.2)                |
| <b>Sulphonylureas</b>           | 325 (70.8)             | 3,025 (71.3)                |
| <b>Pioglitazone</b>             | 47 (10.2)              | 98 (2.3)                    |
| <b>Rosiglitazone</b>            | 24 (5.2)               | 53 (1.3)                    |
| <b>DPP-4 inhibitors</b>         | 24 (5.2)               | 247 (5.8)                   |
| <b>α-glucosidase inhibitors</b> | 0 (0.0)                | 16 (0.4)                    |
| <b>Meglitinides</b>             | 15 (3.3)               | 185 (4.4)                   |
| <b>Insulins</b>                 | 441 (96.1)             | 3,989 (94.0)                |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

## **CHAPTER 5: DATA ARTICLE 3 - Risk of bladder cancer in patients undergoing thiazolidinedione therapy – a nested case-control analysis of hospital-based data**

Davidson MA, Gravel C, McNair D, Mattison DR, Krewski, D. Risk of bladder cancer in patients undergoing thiazolidinedione therapy – a nested case-control analysis of hospital-based data. Unpublished manuscript;2018.

### **PREFACE**

This manuscript presents the results of a pharmacoepidemiological study investigating potential associations between thiazolidinedione drug use and an increased risk of cancer. Specifically, a nested case-control study was designed and conducted to investigate associations between pioglitazone, rosiglitazone, and pioglitazone and rosiglitazone use and risk of bladder cancer in a population of Type 2 diabetics. The study accounts for the potential confounding effects of a variety of demographic factors, health care facility characteristics, concomitant therapies, and comorbidities. The statement of contributions of collaborators and co-authors, including the student's individual contribution, can be found in the acknowledgements at the end of this manuscript.

## **Risk of bladder cancer in patients undergoing thiazolidinedione therapy – a nested case-control analysis of hospital-based data**

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of Ottawa Canada.

Keywords: Thiazolidinedione, pioglitazone, rosiglitazone, bladder cancer.

The data used in this study were provided to the University of Ottawa by Cerner Corporation under a Material Transfer Agreement allowing for the data to be used for research purposes. Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this manuscript.

## ABSTRACT

**Objective:** To determine if use of thiazolidinedione (TZD) drugs is associated with an increased risk of bladder cancer in Type 2 diabetics.

**Design:** A nested case-control analysis within a large retrospective cohort.

**Setting:** Hospitals in the United States contributing to the Cerner HealthFacts® datawarehouse.

**Participants:** A base cohort of patients who initiated treatment with metformin or sulphonylurea monotherapy who then switched to or added-on another antidiabetic drug between January 1, 2000 and December 31, 2012 to form a study cohort of 6,378 patients.

**Main outcome measures:** Incident cases of bladder cancer were matched to up to 10 controls on sex, age, race, year of study cohort entry, and duration of follow-up. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated comparing use of TZDs with use of other antidiabetic drugs, with drug use lagged by one year for latency purposes.

**Results:** During 19,337 person years of follow-up (median follow-up ranging from 1.6 to 3.9 years; maximum 10.9 years), 33 patients were newly diagnosed as having bladder cancer (incidence rate 1.7 per 1,000 person years). Compared with use of other antidiabetic drugs, pioglitazone (OR: 4.75, 95% CI: 1.29-17.58; 5 cases) and rosiglitazone (OR: 5.20, 95% CI: 1.32-20.59; 5 cases) were associated with an increased risk of bladder cancer. A low number of cases that were TZD users resulted in analyses that were underpowered and that also did not permit sensitivity analyses to investigate the effects of varying the lag period between study cohort entry and the index date.

**Conclusions:** In this hospital-based cohort, use of either pioglitazone or rosiglitazone were associated with an increased risk of incident bladder cancer. However, given the low number of bladder cancer cases in the study cohort and in the TZD treatment groups, these associations should be interpreted with caution.

## INTRODUCTION

Thiazolidinedione (TZD) class drugs are peroxisome proliferator-activated receptor (PPAR) agonists used in the treatment of Type 2 diabetes mellitus (T2DM). First marketed in the late 1990s, this class of insulin sensitizing drugs has elicited controversy for over a decade due to potential associations with several adverse health effects, most recently bladder cancer. Originally reported in rats in the 2-year animal carcinogenicity study included in the licensing application for the TZD drug pioglitazone [1], little attention was paid to potential associations between TZD therapy and bladder cancer in humans until a statistically non-significant increase in bladder tumours (14 versus six;  $P = 0.069$ ) was reported in pioglitazone-treated patients compared to placebo-treated patients in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) [2]. Though adjudication of the trial results concluded that the observed number of cases was too small to consider bladder cancer a safety issue [3], the United States Food and Drug Administration (US FDA) announced in 2010 that it was reviewing data from an ongoing 10-year study designed to evaluate whether pioglitazone was associated with an increased risk of bladder cancer [4]. In this longitudinal cohort study using the Kaiser Permanente Northern California database [5], patients who used pioglitazone for greater than 24 months showed a 40% increased risk of bladder cancer. A signal was also observed in the US FDA passive Adverse Event Reporting System (FAERS) database [6], and a French prospective cohort study [7] also suggested that pioglitazone use was associated with a small, but statistically significant increased risk of bladder cancer that was dose and duration-dependant. These findings prompted the suspension of pioglitazone from the French market [8] and the release of a safety announcement by the US FDA [9] cautioning that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer.



Since the time of these announcements, several observational studies investigating links between TZDs, and more specifically pioglitazone, and bladder cancer have been conducted with mixed and at times conflicting results. For example, in a nested case-control analysis of patients in the United Kingdom General Practice Research Database (GPRD; now the Clinical Practice Research Datalink [CPRD]) who were newly treated with diabetes drugs, Azoulay et al. [10] found an 83% increased risk of bladder cancer for patients who had ever taken pioglitazone versus never users. Similar results were not observed for the TZD drug rosiglitazone in the Azoulay et al. [10] study, nor have they been demonstrated for rosiglitazone in randomized controlled trials [11] or in most [12-14], but not all [15-18] observational studies. However, fewer than half of all observational studies conducted to date have included rosiglitazone in their analyses [19 - also refer to **Chapter 2** of this thesis]. Regardless, associations have been primarily linked to pioglitazone usage [5, 7, 10, 12-16]. But not all studies have generated such associations, even those analyzing the same databases. For example, using the same GPRD database as the Azoulay et al. [10] study, Wei et al. [20] reported a non-statistically significant risk using a propensity score-matched design. An updated case-control analysis [21] of the 10-year US FDA pioglitazone bladder cancer study [5] also did not confirm the increased risk originally observed, nor have other studies using different patient populations [22-32].

The continued lack of concurrence of the aforementioned findings demonstrates that more research is needed to further clarify associations between TZD use and bladder cancer risk, for pioglitazone, but also for rosiglitazone. This is especially needed given the differences in study outcomes observed which may be due to methodological differences and limitations such as a lack of consideration of disease latency in several studies [13, 16, 24, 29-30] and the inclusion of prevalent users in most studies. To this end, we conducted a nested case-control

study to determine if pioglitazone or rosiglitazone are associated with an increased risk of bladder cancer in Type 2 diabetics in a hospital-based setting.

## **METHODS**

This study was approved by the Health Sciences and Science Research Ethics Board at the University of Ottawa, Ottawa, ON, Canada.

### **Data source**

This study was carried out using the Cerner Health Facts® datawarehouse (Kansas City, MO, US), a longitudinal database of electronic health record data from over 480 contributing hospitals throughout the US. Health Facts® contains anonymized data of encounters for over 41 million people and includes demographics, diagnoses, prescriptions, procedures, laboratory testing, hospital information, service location, and billing data. At the time of analysis this datawarehouse contained encrypted and time-stamped information on distinct inpatient admissions and discharges, emergency department encounters, and outpatient encounters. Each patient encounter within the datawarehouse is linked by unique patient and encounter identifiers to permit the assessment of treatments over time including diagnostics and procedures, and medications prescribed and dispensed. Information contained in the datawarehouse used for the analyses consisted of patient demographics, hospital or clinic characteristics, prescribed and dispensed medications (orders, dispensing events, billing information, National Drug Code number, quantity, and date of administration), and medical events, procedures, and diagnoses (International Classification of Diseases, 9th Edition [ICD-9] codes).

## Study population

Type 2 diabetics often receive antidiabetic drug prescriptions from a general practitioner outside of a hospital setting or outpatient setting. This introduces the possibility of capturing prevalent users in hospital-based administrative data [33]. To address potential prevalent user bias in this study, a design [34] was employed that first assembled a base cohort population of patients who had a similar level of T2DM disease severity, and from that base cohort, a study cohort of patients who intensified or progressed their treatment regime by switching to, or adding-on another oral antihyperglycemic agent (OHA) or insulin to establish a study population that is more likely to contain incident diabetic drug users (**Figure 1**).

### *Base cohort*

A base cohort was assembled consisting of all patients who commenced treatment for T2DM with a first ever antidiabetic drug prescription of metformin or sulphonylurea monotherapy between January 1, 2000 and December 31, 2012. Patients initiating treatment with these drugs were selected to establish a patient population with a comparable level of T2DM severity, to the extent possible, from which to sample from for the study cohort. The date of each patient's first metformin or sulphonylurea monotherapy prescription defined entry into the base cohort. Patients were then excluded if they had any of the following characteristics at entry to the base cohort: age less than 18 years and women with a history of diagnosed polycystic ovarian syndrome or a diagnosis of gestational diabetes before entry into the base cohort, as these conditions are other possible indications for metformin.

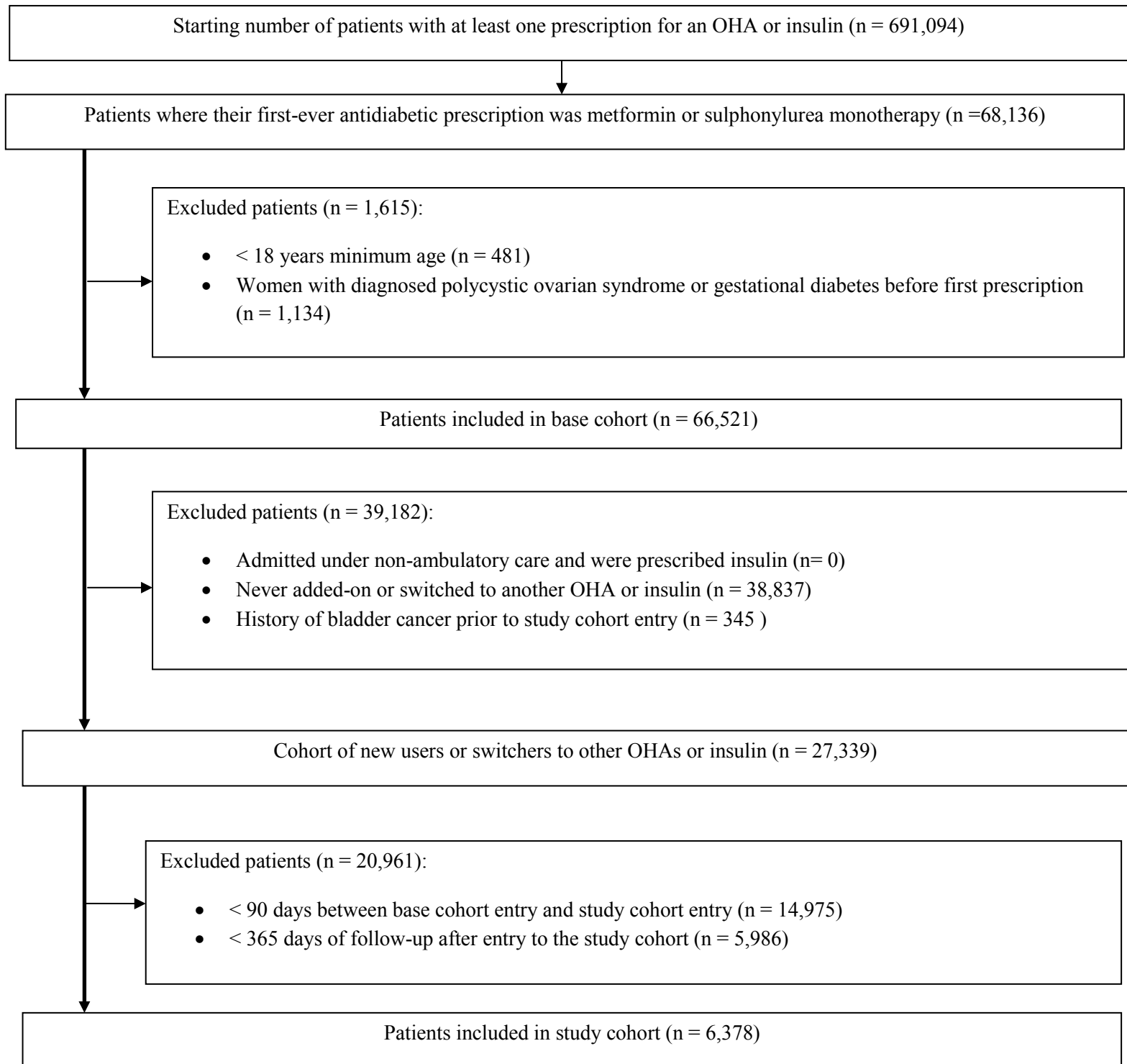


**Figure 1.** Establishment of base and study cohorts and flow of participants in the prevalent user bladder cancer study design.

### *Study cohort*

Within the base cohort, a study cohort was established consisting of all patients who added-on or switched to an OHA drug class not previously identified in their drug history, or insulin, on or after March 30, 2001 (the year after rosiglitazone and pioglitazone first appeared in the dataset) until December 31, 2012. The date of this new prescription defined entry to the study cohort. Patient encounters where the first new antidiabetic prescription was for insulin and where that patient was not in an ambulatory state (i.e. being treated in an intensive care unit) were censored to account for situations where insulin may be administered in-hospital to non-ambulatory patients instead of their normal course of antidiabetic therapy (e.g. an OHA). However, these patients were permitted to re-enter the cohort at the time of their next antidiabetic prescription where they were in an ambulatory state. Patients were also excluded if they had a history of bladder cancer prior to study cohort entry or if they had less than 90 days between base cohort entry and study cohort entry to take into account a timeframe within which other antidiabetic drug prescriptions would reasonably be expected to appear in their medical records. Finally, we excluded patients with less than 365 days of follow-up after entry to the study cohort to ensure a minimum potential duration of drug use [34].

### **Follow-up**

For all patients meeting the study inclusion criteria, the start of follow-up was set to 365 days after entry to the study cohort (i.e. the start of person time at risk). Patients were followed until a diagnosis of incident bladder cancer, death from any cause, their last encounter in the dataset, or end of the study period (December 31, 2012), whichever occurred first.

## **Selection of cases and controls**

To investigate associations between TZD pharmacotherapy and risk of bladder cancer, we carried out nested case-control analyses. As described by Azoulay et al. [10], this approach was used because of the time varying nature of drug use, the size of the cohort, and the long duration of follow-up in the dataset [35]. Compared with a full cohort approach, using a nested case-control analysis is computationally more efficient [36-37]. We used risk set sampling for the matching of controls to cases as this method produces odds ratios (ORs) that are unbiased estimators of hazard ratios (HRs) [35, 37-38].

All incident cases of bladder cancer were identified during follow-up. For each case, the first hospital admission with a diagnosis of bladder cancer (ICD-9 diagnostic codes 188.x) was used to define the index date. Up to 10 controls were randomly selected from the case's risk set after matching on age ( $\pm 1$  year), sex, race, year of cohort entry ( $\pm 1$  year), and duration of follow-up ( $\pm 1$  year). Matched controls were assigned the index date of their respective cases.

## **Drug exposure and use of thiazolidinediones**

All OHAs and insulin approved by the US FDA for use during the study period (including those under restricted access, i.e. rosiglitazone) were identified in the dataset. For cases and controls we obtained prescription information for drugs prescribed at any time before the index date using time and date-stamped pharmacy orders, dispensing events, and National Drug Code numbers within the dataset. Antidiabetic drug exposure was defined as receiving at least one prescription preceding the index date.

Use of TZDs was classified into one of the four mutually exclusive categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and

rosiglitazone use (mainly switchers from one drug to the other), and 4) never use of any TZD.

Never users of any TZD were used as the reference group. Patients were considered unexposed to TZDs until the time of their first TZD prescription.

## **Statistical analysis**

Descriptive statistics were used to summarise the baseline characteristics of matched cases and controls at cohort entry. Conditional logistic regression was used to estimate ORs and corresponding 95% CIs for associations between TZD use and risk of bladder cancer.

In addition to age, sex, race, year of cohort entry, and duration of follow-up (on which the logistic regression models were conditioned) models were adjusted for several potential confounders if their inclusion changed the estimate of risk by 10% or more. Potential confounders measured at entry to the study cohort included: payer class (as a surrogate for socioeconomic status), census region, region type (urban/rural), treatment center size (number of hospital beds), and treatment center type (teaching/non-teaching, acute care/non-acute care). We also adjusted for previous urinary conditions (cystitis, calculus of the kidney, ureter, lower urinary tract, and urinary tract infection) and previous cancer (other than non-melanoma skin cancer) measured at any time prior to study cohort entry, and excessive alcohol use (based on alcohol related disorders such as alcoholism, alcoholic cirrhosis of the liver, alcoholic hepatitis and failure, and other related disorders), obesity (treatment for obesity or body mass index greater than 30 kg/m<sup>2</sup>), and smoking (ever/never) measured at any time prior to, or after study cohort entry [14]. Finally, models were adjusted for total number of hospital admissions and total number of unique non-diabetic drugs prescribed, both measured in the 90 days prior to, and after

cohort entry, and entered as four level ordered categorical variables, as general measures of comorbidity [39].

The primary analyses evaluated whether exclusive ever use of pioglitazone, exclusive ever use of rosiglitazone, or use of pioglitazone and rosiglitazone were associated with an increased risk of bladder cancer when compared with never use of any TZD (the reference group). Due to the hospital-based nature of the data, analyses investigating potential dose-response relationships could not be reliably conducted as it could not be determined if patients received other prescriptions outside of the Cerner network (e.g. by a general practitioner).

### *Sensitivity Analyses*

To assess the robustness of the findings of this study, four sensitivity analyses were conducted. In the first, we contrasted use of pioglitazone with use of rosiglitazone by repeating our primary analysis with the latter as the reference category to further assess whether an association between pioglitazone and bladder cancer is drug-specific compared with a class effect. In the second, the primary analyses were repeated without the 365 day lag period prior to the commencement of follow-up (i.e. the start of follow-up was set to immediately after entry to the study cohort). In the third, the primary analyses were repeated with a lag period of less than one year between study cohort entry and the index date. Finally, the primary analyses were repeated with a lag period of at least two years between study cohort entry and the index date to account for uncertainty in the length of a possible latency period. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Results are presented where the number of cases are five or more to account for where the effect estimate is highly uncertain because of small sample size.



## RESULTS

Of the 68,136 patients with a first prescription that was metformin or sulphonylurea monotherapy, 6,378 met the study inclusion criteria (**Figure 1**). Mean age at cohort entry was 67.5 years and the median duration of follow-up across participating facilities in the Cerner network ranged from 1.6 to 3.9 years (not including the one year follow-up required for the purposes of latency) with a maximum of 10.9 years. Overall, the study cohort generated 19,337 person years of follow-up. During this time 33 patients were newly diagnosed with bladder cancer, generating a crude incidence rate of 1.7 per 1,000 person years (95% CI: 1.1-2.3). Prior to matching, cases were 75.8% male which is expected given the higher incidence of bladder cancer in men compared to women in the US population [40]. Cases were also more likely to have had a previous urinary condition (24.2% of cases versus 15.6% of unmatched controls), and were more likely to have been admitted to hospital (45.5% of cases had four or more hospital admissions compared to 28.1% of unmatched controls).

### *Baseline characteristics*

The baseline characteristics of the 33 cases of bladder cancer and their 297 matched controls are presented in **Table 1**. When compared with their matched controls, bladder cancer cases were more likely to have health coverage through Medicare, be located in the US Midwest, treated in a larger medical facility, and have a greater mean number of hospital admissions. However, they were less likely to have received treatment for a previous urinary condition, cancer, or alcohol abuse than controls. Bladder cancer cases were prescribed a greater number of different antidiabetic drugs than their matched controls including TZDs where cases had a higher percentage of pioglitazone (15.2% of cases versus 3.7% of controls) and rosiglitazone (15.2% of

**Table 1.** Baseline characteristics of bladder cancer cases and matched controls. Values are numbers (percentages) unless stated otherwise.

| <b>Characteristic</b>                           | <b>Cases (n = 33)</b> | <b>Controls (n = 297)</b> |
|-------------------------------------------------|-----------------------|---------------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>76.9 (9.9)</b>     | <b>78.0 (9.1)</b>         |
| <b>18-25</b>                                    | 0 (0.0)               | 1 (0.3)                   |
| <b>26-35</b>                                    | 1 (3.0)               | 3 (1.0)                   |
| <b>36-45</b>                                    | 1 (3.0)               | 10 (3.4)                  |
| <b>46-55</b>                                    | 5 (15.2)              | 45 (15.2)                 |
| <b>56-65</b>                                    | 6 (18.2)              | 82 (27.6)                 |
| <b>66-75</b>                                    | 10 (30.3)             | 74 (24.9)                 |
| <b>76-85</b>                                    | 8 (24.2)              | 67 (22.6)                 |
| <b>&gt;85</b>                                   | 2 (6.1)               | 15 (5.1)                  |
| <b>Men*</b>                                     | 16 (48.5)             | 130 (43.8)                |
| <b>2000</b>                                     | 1 (3.0)               | 3 (1.0)                   |
| <b>2001</b>                                     | 2 (6.1)               | 8 (2.7)                   |
| <b>2002</b>                                     | 2 (6.1)               | 20 (6.7)                  |
| <b>2003</b>                                     | 2 (6.1)               | 20 (6.7)                  |
| <b>2004</b>                                     | 4 (12.1)              | 40 (13.5)                 |
| <b>2005</b>                                     | 6 (18.2)              | 59 (19.9)                 |
| <b>2006</b>                                     | 3 (9.1)               | 26 (8.8)                  |
| <b>2007</b>                                     | 2 (6.1)               | 20 (6.7)                  |
| <b>2008</b>                                     | 2 (6.1)               | 20 (6.7)                  |
| <b>2009</b>                                     | 5 (15.2)              | 48 (16.2)                 |
| <b>2010</b>                                     | 2 (6.1)               | 13 (4.4)                  |
| <b>2011</b>                                     | 2 (6.1)               | 20 (6.7)                  |
| <b>2012</b>                                     | 0 (0.0)               | 0 (0.0)                   |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>4.4 (2.6)</b>      | <b>4.8 (3.1)</b>          |
| <b>Race*</b>                                    |                       |                           |
| <b>Caucasian</b>                                | 28 (84.9)             | 250 (84.2)                |
| <b>African-American</b>                         | 5 (15.2)              | 45 (15.2)                 |
| <b>Other</b>                                    | 0 (0.0)               | 2 (0.7)                   |
| <b>Payer class</b>                              |                       |                           |
| <b>Medicare</b>                                 | 5 (15.2)              | 27 (9.1)                  |
| <b>Other</b>                                    | 5 (15.2)              | 26 (8.8)                  |
| <b>Unknown</b>                                  | 23 (69.7)             | 244 (82.2)                |
| <b>Census region</b>                            |                       |                           |
| <b>Northeast</b>                                | 16 (48.5)             | 151 (50.8)                |
| <b>Midwest</b>                                  | 2 (6.1)               | 11 (3.7)                  |
| <b>West</b>                                     | 0 (0.0)               | 2 (0.7)                   |
| <b>South</b>                                    | 15 (45.5)             | 133 (44.9)                |

Table 1. *Continued.*

| Characteristic                                             | Cases (n = 33) | Controls (n = 297) |
|------------------------------------------------------------|----------------|--------------------|
| <b>Region type</b>                                         |                |                    |
| Urban                                                      | 33 (100.0)     | 297 (100.0)        |
| Rural                                                      | 0 (0.0)        | 0 (0.0)            |
| <b>Treatment center type</b>                               |                |                    |
| Acute care                                                 | 33 (100.0)     | 297 (100.0)        |
| Non-acute care                                             | 0 (0.0)        | 0 (0.0)            |
| <b>Treatment center teaching status</b>                    |                |                    |
| Teaching                                                   | 29 (87.9)      | 255 (85.9)         |
| Non-teaching                                               | 4 (12.1)       | 42 (14.1)          |
| <b>Treatment center beds</b>                               |                |                    |
| 1-199                                                      | 2 (6.1)        | 31 (10.4)          |
| 100-199                                                    | 2 (6.1)        | 3 (1.0)            |
| 200-299                                                    | 9 (27.3)       | 113 (38.1)         |
| 300-499                                                    | 0 (0.0)        | 8 (2.7)            |
| ≥ 500                                                      | 20 (60.6)      | 147 (47.8)         |
| Ever smoker†                                               | 0 (0.0)        | 0 (0.0)            |
| Ever diagnosis or treatment for obesity‡                   | 8 (24.2)       | 71 (23.9)          |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 1 (3.0)        | 12 (4.0)           |
| Previous urinary conditions                                | 3 (9.1)        | 33 (11.1)          |
| Previous cancer (other than non-melanoma skin cancer)      | 0 (0.0)        | 12 (4.0)           |
| Mean number hospital admissions (SD)                       | 3.1 (3.6)      | 2.9 (3.0)          |
| <b>Number of hospital admissions</b>                       |                |                    |
| 1                                                          | 13 (39.4)      | 117 (39.4)         |
| 2                                                          | 7 (21.2)       | 61 (20.5)          |
| 3                                                          | 5 (15.2)       | 50 (16.8)          |
| ≥ 4                                                        | 8 (24.2)       | 69 (23.2)          |
| Mean number unique non-diabetic drugs (SD)                 | 4.0 (2.0)      | 4.0 (1.6)          |
| <b>Number of unique non-antidiabetic drugs</b>             |                |                    |
| 0                                                          | 2 (6.1)        | 6 (2.0)            |
| 1                                                          | 3 (9.1)        | 15 (5.1)           |
| 2                                                          | 0 (0.0)        | 13 (4.4)           |
| 3                                                          | 7 (21.2)       | 79 (26.6)          |
| ≥ 4                                                        | 21 (63.6)      | 184 (62.0)         |

**Table 1. Continued.**

| Characteristic                  | Cases (n = 33) | Controls (n = 297) |
|---------------------------------|----------------|--------------------|
| <b>Antidiabetic drug use¶</b>   |                |                    |
| <b>Metformin</b>                | 14 (42.4)      | 143 (48.1)         |
| <b>Sulphonylureas</b>           | 27 (81.8)      | 235 (79.1)         |
| <b>Pioglitazone</b>             | 5 (15.2)       | 11 (3.7)           |
| <b>Rosiglitazone</b>            | 5 (15.2)       | 11 (3.7)           |
| <b>DPP-4 inhibitors</b>         | 2 (6.1)        | 15 (5.1)           |
| <b>α-glucosidase inhibitors</b> | 0 (0.0)        | 1 (0.3)            |
| <b>Meglitinides</b>             | 0 (0.0)        | 9 (3.0)            |
| <b>Insulins</b>                 | 33 (100.0)     | 266 (89.6)         |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

cases versus 3.7% of controls) prescriptions, and insulin prescriptions (100% of cases versus 89.6% of controls). The cases and matched controls were similar on the other characteristics.

### *Primary and secondary analyses*

The results of the primary analysis are presented in **Table 2**. Compared with never use of any TZD drug, exclusive ever use of either pioglitazone (OR: 4.41, 95% CI: 1.23-15.79) or rosiglitazone (OR: 4.72, 95% CI: 1.22-18.33) were associated with a statistically significant increased risk of bladder cancer. There were no cases of patients who had been treated with both pioglitazone and rosiglitazone.

In the sensitivity analyses, an insufficient number of TZD-treated cases did not permit a head to head assessment of pioglitazone use versus rosiglitazone use, nor did it permit the assessment of the effects of removing the 365 day follow-up lag period after study cohort entry, adding a lag period of less than one year between study cohort entry and the index date, or adding a lag period of two or more years between study cohort entry and the index date (results not shown). The 10 TZD-exposed cases were diagnosed with bladder cancer one year or more after study cohort entry with one pioglitazone case and one rosiglitazone case diagnosed between one and two years. When the lag period was removed the cohort contained the same five cases exposed to pioglitazone and five cases exposed to rosiglitazone and 30 cases that had never been exposed to TZDs. When the lag period was restricted to less than one year it contained no TZD-exposed cases and only seven cases in the reference group. Finally, when the lag period was increased to two years or more the cohort contained four pioglitazone cases and four rosiglitazone cases and only seven cases in the reference group.

**Table 2.** Thiazolidinedione use and risk of bladder cancer among cases and matched controls\*

| Thiazolidinedione use**                        | Cases<br>(n = 33)<br>n (%) | Controls<br>(n = 297)<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI)‡ |
|------------------------------------------------|----------------------------|--------------------------------|-------------------------|-------------------------------------|-------------------------------------|
| Never use of any thiazolidinedione (reference) | 23<br>(69.7)               | 278<br>(93.6)                  | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                 |
| Exclusive ever use of pioglitazone             | 5<br>(15.2)                | 10<br>(3.4)                    | 4.39<br>(1.33-14.45)    | 4.53<br>(1.35-15.22)                | 4.41<br>(1.23-15.79)                |
| Exclusive ever use of rosiglitazone            | 5<br>(15.2)                | 9<br>(3.0)                     | 4.34<br>(1.27-14.81)    | 4.43<br>(1.21-16.19)                | 4.72<br>(1.22-18.33)                |

\*Matched on age, year of study cohort entry, sex, race, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for previous urinary conditions, previous non-melanoma cancer, excessive alcohol use, obesity, and smoking status.

‡Further adjusted for payer class and total number of hospital admissions.

## DISCUSSION

In this hospital-based cohort study with up to 10.9 years of follow-up, pioglitazone was associated with a 341% increased risk and rosiglitazone was associated with a 372% increased risk of incident bladder cancer. A class effect and the effects of varying the lag period could not be assessed due to a low number of bladder cancer cases.

### Comparison with previous studies

It is difficult to compare the results of our study with previous observational studies given our high ORs resulting from a low number of cases that produced underpowered analyses, and a greater proportion of cases that received TZD drugs compared to controls (refer to **Chapter 6** of this thesis for a general discussion related to this observation in the dataset). However, our results do suggest that there could be a trend towards an association between both pioglitazone and rosiglitazone and an increased risk of bladder cancer, though this suggestion is merely hypothetical at this stage and would require further investigation with a larger cohort to confirm.

To date, most studies have found associations between pioglitazone therapy and bladder cancer. For example, the first observational study investigating associations between TZD use and bladder cancer [5] found that ever-use of pioglitazone was associated with an increased risk of bladder cancer, but only when patients used pioglitazone for greater than 2 years (HR: 1.4, 95% CI: 1.03-2.00) [5]. However, updated analyses of this cohort [21] found that ever use of pioglitazone was not associated with an increased bladder cancer risk using a cohort study design (HR: 1.06, 95% CI: 0.89-1.26), or using a case-control design (OR: 1.18, 95% CI: 0.78-1.80). In addition, contrary to the initial findings, duration of treatment was not associated with an increased risk, though the authors noted that the study had limited statistical power for

subgroup analyses related to time since initiation, dose, and duration, even within a large cohort of 193,099 patients [21].

The second large-scale observational study, a French prospective cohort study [7] found that pioglitazone use was associated with a statistically significant risk of bladder cancer (HR: 1.22, 95% CI: 1.05-1.43) that was dose ( $\geq 28\ 000$  mg: 1.75, 1.22-2.50) and duration-dependant ( $\geq 24$  months: 1.36, 1.04-1.79). However, the study's inability to adjust for major confounders such as smoking, diabetes duration, or comorbidities may have introduced selection bias. Nevertheless, the results of this study prompted a re-evaluation of the safety of pioglitazone by the European Medicines Agency [41] that revealed the results of an unpublished meta-analysis conducted by the manufacturer using its clinical trial database that included 36 trials (24 lasting  $< 1$  year, six lasting 1-2 years, and six lasting  $> 2$  years [the PROactive study was analyzed separately]) and 22,000 patients. Results were not statistically significant when cases in the first year of exposure were excluded (HR: 3.48, 95% CI: 0.72-16.76,  $P = 0.12$ ), but were significant (HR: 2.64, 1.11-6.31,  $P = 0.03$ ) when all studies and the first year of exposure were included with 19 cases of bladder cancer observed in the pioglitazone group (0.19%) versus seven in the comparator group (0.07%) [41]. Similarly, a meta-analysis of one clinical trial (PROactive) and four observational studies [42] also found that pioglitazone therapy was associated with a statistically significant increased risk of bladder cancer when all studies were pooled (relative risk [RR]: 1.17, 95% CI: 1.03-1.32,  $P = 0.013$ ), but not when duration of therapy was less than one year or cumulative dose was less than 28,000 mg. Results were significant in patients with between 12 and 24 months of pioglitazone use (RR: 1.34, 95% CI: 1.08-1.66,  $P = 0.008$ ), a cumulative treatment duration greater than 24 months (RR: 1.38, 95% CI: 1.12-1.70,  $P = 0.003$ ), and a cumulative dose greater than 28,000 mg (RR: 1.58, 95% CI: 1.12-2.06,  $P = 0.001$ ).



Another meta-analysis by Colmers et al. [43] investigating associations between both rosiglitazone and pioglitazone and incidence of bladder cancer also found that pioglitazone (but not rosiglitazone) was associated with a significant risk (pooled RR: 1.22, 95 % CI: 1.07-1.39) when three cohort studies were pooled and further confirmed these results when additional data from the Azoulay et al. [10] study using the GPRD was included, though the study failed to address the effects of sex, duration of therapy, or cumulative dose [43].

Though the events in the PROactive trial occurred within one year of starting pioglitazone treatment [2], it has been hypothesized that these may have been prevalent cases, or occurred in patients that already had a greater susceptibility to developing bladder cancer [44]. Some recent observational studies have taken into account these potential issues, for example, by using a one-year lag period after the first prescription of a TZD to provide a minimum potentiation of drug use [14], and have continued to observe potential adverse effects that increase with longer use. Though we attempted to investigate changes in duration of use in our sensitivity analyses we had an insufficient number of cases to assess associations.

As previously mentioned, the general consensus in the epidemiology community is that most likely only pioglitazone is associated with bladder cancer as increased risks were not seen in rosiglitazone trials such as ADOPT [45] or RECORD [46] and some observational studies have demonstrated a lack of association. However, to date only eight of 19 observational studies have investigated rosiglitazone alone in their analyses [19] and not all of these studies have found a lack of association. For example, using a general practice research database from the UK (the Health Improvement Network database) Mamtani et al. [15] found that when compared to patients taking a sulphonylurea drug, risk of bladder cancer was increased among long-term TZD-treated patients ( $\geq 5$  years of use HR: 3.25, 95% CI: 1.08-9.71) and that risk also increased

with increasing time since initiating either pioglitazone ( $P < 0.001$ ) or rosiglitazone ( $P = 0.006$ ) therapy. In addition, comparison of pioglitazone to rosiglitazone use did not demonstrate a difference in cancer risk ( $P = 0.49$ ) indicating a potential TZD class effect. Hsiao et al. [16] also found that both rosiglitazone and pioglitazone use were associated with an increased risk of bladder cancer and that associations were stronger with a longer term of exposure (pioglitazone  $<1$  year OR: 1.45, 95% CI: 1.12–1.87; 1-2 years OR: 1.74, 95 % CI: 1.05-2.90; and  $\geq 2$  years OR: 2.93, 95 % CI: 1.59-5.38; rosiglitazone  $<1$  year OR 0.98, 95 % CI: 0.82-1.17; 1-2 years OR: 1.78, 95 % CI: 1.31-2.39;  $\geq 2$  years OR: 2.00 95 % CI: 1.37-2.92). This nested case-control study using Taiwan's National Health Insurance Research Database had a large number of TZD-exposed bladder cancer cases (3,412) compared to previous observational studies largely owing to the fact that 99.9% of Taiwan's population is enrolled in the database [47] and all prescriptions are recorded within it, thus ensuring that only incident users are captured. A recent study by Han et al. [17] also reported results that are extremely similar to the results of our analyses but only for rosiglitazone. In a nested case-control study using data from the Korean National Health Insurance Service National Sample, exclusive ever use of rosiglitazone was associated with an increased risk of bladder cancer (OR: 3.07, 95% CI: 1.48-6.37) compared to non-TZD users that was first apparent after less than 3 months of use (OR: 3.30, 95% CI: 1.02-10.70) and that peaked at 3 to 12 months of use (OR: 4.48, 95% CI: 1.51-13.31). Patients that were first exposed to rosiglitazone within 1 year (OR: 11.74, 95% CI: 2.46-56.12) and those who used it consistently for 1 year (OR: 4.48, 95% CI: 1.51-13.31), had higher risks of bladder cancer compared with non-TZD users. Unlike in our study, no increased risks were observed for pioglitazone therapy. In a US Medicare population, Mackenzie et al. [18] found that diabetics in a prevalent user cohort who used rosiglitazone for 1 to 12 months had a 19% increased risk of

bladder cancer and that users for 13 to 24 months had a 28% increased risk compared with diabetics who had never used rosiglitazone. Users of pioglitazone for 2 years or more also demonstrated a 10% increased risk of bladder cancer [18]. However, it should be noted that when these analyses were repeated in an incident user cohort associations between rosiglitazone or pioglitazone use and bladder cancer were no longer significant.

### **Biological mechanisms**

As described by Davidson et al. [19], the mechanism by which TZDs might elevate the risk of bladder cancer is unclear and remains the subject of much debate, especially given the increased number of bladder cancer cases observed in numerous (and mostly pioglitazone) studies for a disease that normally has a long latency period. TZD drugs are ligands of PPAR $\gamma$  which is widely distributed in various tissue and cell types and where activation or repression leads to diverse biological effects [48]. Initial animal model studies in rats suggested that the observed occurrences of bladder cancer associated with PPAR $\gamma$  agonist therapy may be specific to crystal formation in the bladder [49]. However, because the urinary composition of humans differs from that of rats, and urinary microsolids formed in the human bladder are usually only present for brief periods of time [50], and because increases in microsolids were not observed in clinical trials [51: muraglitazar], this hypothesis is unlikely. It has also been proposed that interactions between TZDs in the urine and the high number of PPAR receptors in the human bladder urothelium may exert mitogenic effects [49] as expression of PPAR $\gamma$  has been demonstrated to be significantly higher with increasing grade and stage of bladder cancer [52]. However, the PPAR $\gamma$  agonists described in the US FDA review of 2-year rodent carcinogenicity studies were not associated with urinary bladder tumourigenesis [53], *in vitro* studies using

human urothelial cell lines have shown that PPAR $\gamma$  agonists inhibit cell proliferation and potentiation of differentiation [52-56], PPAR agonists are highly lipophilic with only a small percentage of the drugs excreted in urine [49], and some studies, though not the present study, have failed to find associations between rosiglitazone and bladder cancer.

As the aforementioned hypotheses have been largely discounted, others have proposed that some cases of bladder cancer, especially those observed after only brief exposure to pioglitazone, may be a result of the increased cancer risk associated with T2DM itself rather than TZD exposure [57], or lifestyle factors that are known risks for bladder cancer such as occupational exposure to chemicals or smoking. However, pioglitazone has been shown to both inhibit DNA damage in urothelial cells and induce histopathological changes in the urinary tract in mice exposed to cigarette smoke [58] suggesting a non-genotoxic mechanism of action. More recently, it been hypothesized that the adverse effects associated with pioglitazone could in fact be the result of differences in active metabolites [57] since only pioglitazone has dual PPAR $\alpha/\gamma$  activity [59]. However, this avenue remains to be fully explored. Additional studies are needed to elucidate the biological mechanism behind the potential associations between TZDs and bladder cancer.

### **Strengths and limitations**

This study has several strengths. Firstly, we assembled a population-based cohort of patients newly treated with antidiabetic drugs and followed them for up to 10.9 years, thus enabling a long follow-up time to permit the identification of incident cases of bladder cancer. Secondly, because the Cerner Health Facts® database contains pre-recorded information on prescriptions, and these prescriptions are filled in-hospital, the possibility of recall bias was

eliminated. Thirdly, the increased likelihood of capturing new antidiabetic drug users based on their first switch from metformin or sulphonylurea monotherapy minimized biases related to prevalent users, to the extent possible in a hospital-based cohort [60]. Finally, we considered a lag period to account for a minimum latency between use of TZDs and the development of bladder cancer.

Our study also has several limitations, most notably a lack of sufficient TZD-treated cases to power our analyses. This is most likely a result of our attempt to control prevalent user bias which better captures incident users, but also leads to a lower sample size by excluding patients from the study cohort that would be included in a traditional nested case-control study that includes prevalent users. Bladder cancer is a rare disease with a long latency period when compared to more common or chronic diseases such as heart failure or bone fractures. Therefore, our total follow-up period of 19,337 person years was likely not long enough to detect a meaningful number of cases for a rare event. A second limitation is that drug information in the database represents prescriptions written only by hospital physicians. As such, it is unknown whether additional prescriptions were provided to patients from other health care providers, such as general practitioners, outside of the Cerner network. Because many diabetic patients are primarily under the care of general practitioners and would be assumed to received prescriptions for antihyperglycaemic drugs from these practitioners, this does introduce exposure misclassification into the study and is a disadvantage of working with hospital-based data compared to general practice data. For example, a first prescription of metformin or sulphonylurea monotherapy observed in the dataset may not have been a patients first actual antidiabetic drug prescription and they also may have been treated for T2DM for many years before first appearing in the dataset. This may have contributed towards confounding by disease

severity. The design of this study attempted to control for this through the criteria for entry to the base cohort and by matching cases and controls on duration of follow-up, which has been shown to be a good proxy for disease severity [61]. The high ORs observed for both pioglitazone and rosiglitazone, especially rosiglitazone which has not been associated with an increased risk of bladder cancer in most observational studies conducted to date, suggest that disease severity may have also confounded the associations between TZDs and bladder cancer. However, the observed ORs are more likely a function of the greater proportion of cases that received TZD drugs compared to controls (refer to **Chapter 6** of this thesis for a general discussion related to this observation in the dataset).

Another limitation is the lack of information on certain risk factors for bladder cancer that is typical of administrative hospital databases. These include occupational exposures and family history of bladder cancer. However, it is unlikely that these variables were differentially distributed between ever users of TZDs and ever users of other hypoglycaemic agents, and other risk factors such as race, payer class as a surrogate for socioeconomic status, treatment for obesity, alcohol-related disorders, and smoking status were available and included in the models. Thus we do not believe that the absence of these variables affected the internal validity of the study, although residual confounding may still be present. Finally, when working with administrative hospital data there is always the possibility that coding errors or omissions may have occurred, and that ICD-9 codes may not accurately or completely reflect a patient's diagnosis. Although cancers of the urinary tract would be expected to be well-documented given that diagnosis and treatment is received in-hospital, misclassification is possible.

## **CONCLUSIONS**

In summary, the results of this study indicate that both pioglitazone and rosiglitazone may be associated with an increased risk of bladder cancer. Given the small number of cases, including a small number of pioglitazone and rosiglitazone exposed cases, further investigation should be undertaken to clarify associations between TZDs and bladder cancer, including potential class effects, in a larger patient population of incident users.

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### **Author's roles**

M.A. Davidson formulated the hypothesis and design for this study and performed the SAS coding, statistical analyses, and literature review required for the manuscript under the guidance of D. Krewski and with advice from C. Gravel, D. Mattison, and D. McNair. C. Gravel provided assistance in validating the accuracy of the SAS code. M.A. Davidson drafted all text, figures, and tables with editorial input from the co-authors. All contributors were involved in the evaluation and interpretation of the study findings.

### **Authors' disclosures of potential conflicts of interest**

M.A. Davidson, C. Gravel, D. Mattison, and D. Krewski have no actual or potential competing financial interest. D. Krewski is the Natural Sciences and Engineering Research Council of Canada Chair in Risk Science at the University of Ottawa. He also serves as Chief

Risk Scientist and CEO for Risk Sciences International (RSI), a Canadian company established in 2006 in partnership with the University of Ottawa to provide consulting services in risk science to both public and private sector clients. To date, RSI has not conducted work on antihyperglycaemics, the subject of the present paper. D. Mattison was supported by RSI. D. McNair is the President of Cerner Math Inc. and has ownership interest in Cerner Corporation.

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## CHAPTER 6: General Discussion

The introduction of new therapeutic options for the treatment of Type 2 diabetes mellitus (T2DM) over the last two decades, including thiazolidinedione (TZD) drugs, has provided patients with more options to manage their blood sugar levels, while at the same time attempting to address some of the serious comorbidities associated with T2DM such as micro and macrovascular complications [1]. However, as demonstrated in this thesis and in other epidemiological studies, there is often a trade-off between maintaining glycaemic control and unintended treatment effects. To quote the English philosopher Francis Bacon, sometimes "the remedy is worse than the disease". While randomized controlled trials (RCTs) and observational studies have provided valuable knowledge related to the safety and efficacy of TZD drugs used in the treatment of T2DM, most of these studies have been conducted in carefully controlled populations or using data from populations that are being managed day-to-day by their general physicians. These are very different conditions when compared to a hospital-based setting where a patient may be in crisis, and where the complexities of maintaining glycaemic targets may obfuscate associations between a specific pharmacotherapy and an adverse event.

The motivations underlying the research embodied in this thesis were to examine and clarify associations between TZD pharmacotherapy and adverse events using a cohort of hospital-based patient encounters from the Cerner Health Facts® database to inform clinical decision-making in North America, and elsewhere, regarding the continued use of TZDs in the treatment of T2DM and other conditions. The specific objectives of this doctoral research were fourfold: 1) to conduct an in-depth review of the epidemiology of TZD pharmacotherapy, including pharmacokinetics and modes of action, the results of previous studies investigating health risks and benefits associated with TZD treatment, and what the future may hold for this

class of drugs; 2) to determine whether diabetic patients treated with TZDs are at increased risk of adverse cardiovascular outcomes, namely myocardial infarction (MI) and congestive heart failure (CHF); 3) to assess whether TZD pharmacotherapy is associated with an increased risk of bone fractures and whether risk differs depending on fracture site and patient sex; and, 4) to investigate associations between TZD use and risk of bladder cancer. The following sections briefly summarize these studies and their key findings. A discussion of their implications for population health is then provided within the context of a framework for the next generation of risk science that incorporates sound principles for health risk management [2]. The strengths and limitations of using Cerner Health Facts® data to conduct diabetic pharmacoepidemiology are noted, including practical examples of the general challenges of working with hospital based-data in T2DM studies. Sensitivity analyses to demonstrate potential biases are presented, prior to drawing general conclusions and proposing future areas of research.

## **SUMMARY OF RESEARCH AND KEY FINDINGS**

In addition to reviewing the literature published to date related to the safety of TZD drugs, this dissertation examined associations between TZD pharmacotherapy and adverse cardiovascular, osteological, and carcinogenic effects in Type 2 diabetics using a large administrative hospital database of electronic medical records (EMRs). The following sections briefly summarize each body of research and the key findings of each study.

### ***Thiazolidinedione drugs in the treatment of type 2 diabetes mellitus: past, present and future***

The aims of this review paper, which was published in *Critical Reviews in Toxicology* [3], were to provide a detailed overview of the mechanisms of action of TZDs, review their

history, effectiveness, and safety as pharmacotherapies for T2DM, and provide perspectives on their current and future therapeutic roles for T2DM and a variety of other non-diabetic conditions. TZDs are ligands of peroxisome proliferator-activated receptors (PPARs) that exert hypoglycaemic effects by activating pathways responsible for glycaemic control and lipid homeostasis. These drugs have been proven effective in improving insulin sensitivity, hyperglycaemia, and lipid metabolism and some studies have even associated TZD pharmacotherapy with cardioprotective effects. Though they are useful for and well tolerated by some patients, TZDs have been associated with several adverse events in other patients, as is demonstrated throughout the data chapters of this thesis. As PPAR agonists, TZDs activate a wide variety of pathways in the body in addition to those responsible for glycaemic control and lipid metabolism. These pathways include those related to inflammation, bone formation, and cell proliferation which may, at least in part, explain the associations between TZD therapy and adverse cardiovascular, osteological, and carcinogenic outcomes observed in a number of studies.

Given a string of high-profile reports of adverse events since early 2007 when rosiglitazone was first associated with an increase risk of MI (and even earlier since troglitazone was removed from the market in 2000 due to hepatotoxicity), the role of TZDs in the treatment of T2DM continues to be debated. Though prescriptions of TZDs for use in the treatment of T2DM have decreased over time, they are now being investigated as potential treatments for a wide variety of other diseases and conditions, including: acromegaly, Alzheimer's disease, Cushing's disease, anxiety, depression, bipolar disorder, erectile dysfunction, Huntington's disease, nonalcoholic steatohepatitis, Parkinson's disease, polycystic kidney disease, polycystic ovary syndrome (PCOS), psoriasis, and even stress. At the same time, new forms and isoforms



of TZDs are currently in the pre-clinical phase for use in the prevention and treatment of some cancers, especially breast cancer. It will be interesting to see how these clinical investigations progress over time, especially in patient populations with very different characteristics (e.g. young non-diabetic patients) compared to the older and oftentimes less healthy diabetics using TZDs as second or third-line treatments for T2DM.

***Myocardial infarction, congestive heart failure, and thiazolidinedione drugs: a case-control study using hospital-based data***

Attention was first drawn to the potential adverse cardiovascular effects of TZDs when an early meta-analysis of 42 short-term clinical studies reported that rosiglitazone was associated with a 43% higher risk of MI [4]. This prompted an interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial [5], where data were insufficient to determine whether rosiglitazone was associated with an increased risk of MI, but an increased risk with CHF was observed in rosiglitazone-treated patients. In reaction to the results of these studies and others, rosiglitazone access was restricted in the United States (US) in September 2010 and was completely removed from the market in Europe. Since that time, several studies have investigated associations between TZD therapy and adverse cardiovascular outcomes. However, conflicting results between these studies have limited the ability to deduce conclusions on risks of MI and CHF among diabetic patients using TZD drugs, as was illustrated when rosiglitazone restrictions were subsequently removed in the US in 2013. Therefore, as presented in **Chapter 3**, we completed a study to examine whether diabetic patients treated with TZDs are at increased risk of MI and CHF relative to diabetic patients receiving other antidiabetic treatments.

A cohort study design was employed to first assemble a population of adult diabetics who had a similar level of T2DM disease severity, as indicated by their first ever antidiabetic drug prescription being a prescription for metformin or sulphonylurea monotherapy. From that base cohort, two study cohorts of patients who intensified or progressed their treatment regime by switching to, or adding-on another oral antihyperglycaemic agent (OHA) or insulin, were established. In each of these cohorts, patients who had experienced the cardiovascular event of interest prior to study cohort entry were excluded. All incident cases of MI and CHF were identified during follow-up; for each case controls were randomly selected from the case's risk set after matching on age, sex, race, year of cohort entry, and duration of follow-up (as another proxy for diabetes severity). We then constructed conditional logistic regression models to estimate the crude and adjusted odds of MI and CHF for TZD use compared to a reference group of never users of TZDs using four mutually exclusive exposure categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and rosiglitazone use (mainly patients who switched from one drug to the other), and 4) never use of any TZD. Odds ratios (ORs) were adjusted for demographic, clinical, and care setting confounders if their inclusion changed the estimate of risk by 10% or more. Sensitivity analyses sought to examine whether observed associations would remain when adding and varying a lag period after study cohort entry, and if there was a class effect for TZD drugs.

The completed analyses indicated that both rosiglitazone and pioglitazone were associated with an increased risk of both adverse cardiovascular events in a cohort comprised of primarily older diabetic patients. Compared with use of other antidiabetic drugs, pioglitazone (OR: 3.87, 95% CI: 2.52-5.94) and rosiglitazone (OR: 3.68, 95% CI: 2.18-6.21) were associated with a comparable risk of MI. For CHF, pioglitazone (OR: 4.15, 95% CI: 3.21-5.37) was

associated with a greater risk than rosiglitazone (OR: 2.69, 95% CI: 1.91-3.80). Sensitivity analyses could not exclude a TZD class effect and suggested that there could be an increased risk of early adverse cardiovascular effects within the first year of treatment with a TZD drug.

Taking into consideration plausible biological mechanisms, study strengths, and the limitations of working with EMR data, a detailed interpretation of our findings is presented in **Chapter 3**. A discussion related to the ORs observed in this study is also presented later in this chapter, with an example that presents alternative results for the MI analyses using a traditional single cohort nested case-control design (i.e. that does not control for prevalent user bias) as a sensitivity analysis. While our findings should be interpreted with caution and are insufficient alone to contraindicate the use of TZD drugs, they add to the growing weight of evidence on cardiovascular risks associated with TZD pharmacotherapy and further support a cautious approach to prescribing TZD drugs to patients with pre-existing cardiovascular risk factors in addition to the inherent and well-recognized cardiovascular risks that accompany T2DM itself.

### ***Thiazolidinedione use and fracture risk in a cohort of Type 2 diabetics***

Associations between bone fractures and TZDs first came to light after a review of the A Diabetes Outcome Progression Trial (ADOPT) data for adverse events detected a higher rate of fractures in women participating in the trial [6]. The results of this review prompted the manufacturers of rosiglitazone and pioglitazone to release advisory letters to healthcare providers in 2007, with the manufacturer of pioglitazone also reporting that an analysis of its clinical trials database had also found an increase in fractures in women, but not in men [7]. Data from other RCTs have also corroborated an increased risk of fracture with either rosiglitazone or pioglitazone, primarily at peripheral sites. However, the results of observational studies and

meta-analyses have been less consistent with rosiglitazone and pioglitazone associated with comparable risk in some studies, and others finding that rosiglitazone or pioglitazone treatment alone may be more strongly associated with fractures. When stratified by fracture site and/or patient sex, some studies have found fractures primarily in women, especially post-menopausal women, others have found a comparable risk between the sexes, and few have investigated or found increased risks in men alone. Because of these conflicting results we conducted a study, presented in **Chapter 4**, to attempt to clarify associations between TZD pharmacotherapy and fracture risk that also investigated associations by fracture site and within the sexes.

Similar to our cardiovascular study, we employed a study design that first assembled a cohort of adult diabetics who had a similar level of T2DM disease severity. From that base cohort, a study cohort of patients who intensified or progressed their treatment regime by switching to, or adding-on another OHA or insulin was established. Patients with a diagnosis of bone cancer or Paget's disease prior to study cohort entry were excluded. For the primary analyses, all incident cases of closed bone fracture (to minimize the capture of traumatic fractures) were identified during follow-up. For each case, controls were randomly selected from the case's risk set after matching on age, sex, race, year of cohort entry, and duration of follow-up. We then constructed conditional logistic regression models to estimate the crude and adjusted odds of any closed fracture for TZD use compared to a reference group of never users of TZDs using four mutually exclusive exposure categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and rosiglitazone use, and 4) never use of any TZD. Models were adjusted for demographic, clinical, and care setting confounders if their inclusion changed the estimate of risk by 10% or more. Sensitivity analyses sought to examine whether observed associations would remain when adding and varying a lag period after study

cohort entry, and if there was a class effect for TZD drugs. To determine if fracture risk varied by site, the primary analyses were repeated to determine associations between TZD use and peripheral fracture (upper or lower limb fracture including hand, wrist, foot, or ankle) and major osteoporotic fracture (hip, radius/ulna, vertebrae, or humerus). To further assess associations between fracture risk and sex, all primary and secondary analyses were also repeated by stratifying by sex.

The analyses indicated that TZD use was associated with an increased risk of closed bone fractures among the Type 2 diabetics within the Cerner Health Facts® dataset. Compared with use of other antidiabetic drugs, exclusive ever use of pioglitazone (OR: 2.66, 95% CI: 1.93-3.66) or rosiglitazone (OR: 3.23, 95% CI: 2.08-5.02) were associated with an increased risk of any closed fracture. When stratified by fracture site, use of pioglitazone or rosiglitazone (respectively), were significantly associated with an increased risk of peripheral fracture (OR: 2.58, 1.77-3.78; OR: 3.33, 95% CI: 2.02-5.50) and use of pioglitazone (OR: 1.95, 95% CI: 1.27-2.99) but not rosiglitazone (OR: 1.78, 95% CI: 0.91-3.49) was also significantly associated with an increased risk of osteoporotic fracture, though the OR for rosiglitazone was elevated. When stratified by sex, use of either pioglitazone or rosiglitazone was associated with an increased risk of any closed fracture (OR: 4.40, 95% CI: 2.97-6.52; OR: 4.06, 95% CI: 2.30-7.18, respectively) and peripheral fracture (OR: 3.35, 95% CI: 2.12-5.30; OR: 3.68, 95% CI: 2.01-6.75) in women. Use of pioglitazone (OR: 2.71, 95% CI: 1.60-4.60), but not rosiglitazone (OR: 2.14, 95% CI: 0.93-4.93), was also significantly associated with an increased risk of osteoporotic fracture in women, though the OR for rosiglitazone remained high. In men, use of rosiglitazone (OR: 2.54, 95% CI: 1.23-5.22) but not pioglitazone (OR: 1.47, 95% CI: 0.79-2.72) was significantly associated with an increased risk of any closed fracture and peripheral fracture (rosiglitazone:

OR: 2.97, 95% CI: 1.20-7.33; pioglitazone: OR: 1.58, 95% CI: 0.78-3.22), but not osteoporotic fracture (pioglitazone: OR: 1.56, 95% CI: 0.71-3.44; rosiglitazone: low sample size). In sensitivity analyses, a TZD class effect could not be excluded which is reflected in the ORs presented above. Although some analyses did not present statistically significant results, the ORs across stratified analyses often remained comparable in magnitude to those that were statistically significant. When the effects of adding and varying a lag period between study cohort entry and index date were explored, only pioglitazone was associated with an increased risk of any closed fracture when the lag period was less than one year. However, all TZD exposures were associated with an increased risk of any closed fracture when the lag period was one year or more.

A detailed interpretation of our findings is presented in **Chapter 4** that considers potential biological mechanisms behind the increased fracture risks observed, differences between males and females, potential explanations for differences in TZD exposure, study strengths, and limitations of working with EMR data. A brief overview of TZD prescribing practices within this cohort is also presented later in this chapter, as well as an additional sensitivity analysis using the bone fractures cohort. While our findings are not definitive, they indicate that TZD pharmacotherapy may be associated with an increased risk of fractures, especially in women, and they add to the growing weight of evidence on osteological risks associated with TZD pharmacotherapy. These findings may necessitate further consideration of the use of TZDs in the treatment of other non-diabetic conditions in women, such as PCOS, where patients are often younger but may also be more susceptible to metabolic syndrome and its hormonal effects that may further impact bone health and that may be amplified with the use of

TZD drugs. Our results also provide additional evidence for potential associations with fracture risk in men, specifically with rosiglitazone therapy.

***Risk of bladder cancer in patients undergoing thiazolidinedione therapy – a nested case-control analysis of hospital-based data***

Potential associations between TZD therapy and bladder cancer in humans first received attention when a statistically non-significant increase in bladder tumours was reported in pioglitazone-treated patients compared to placebo-treated patients in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) [8]. Though adjudication of the trial results concluded that the observed number of cases was too small to consider bladder cancer a safety issue [9], a review of data from an ongoing 10-year study designed to evaluate whether pioglitazone was associated with an increased risk of bladder cancer using the Kaiser Permanente Northern California database [10] found that patients who used pioglitazone for greater than 24 months demonstrated a 40% increased risk. A signal was also observed in the US FDA passive Adverse Event Reporting System (FAERS) database [11]. A French prospective cohort study [12] also suggested that pioglitazone use was associated with a statistically significant increased dose and duration-dependant risk of bladder cancer. These findings prompted the suspension of pioglitazone from the French market and the release of a safety announcement by the US FDA in 2011 cautioning that use of pioglitazone for more than one year may be associated with an increased risk of bladder cancer. Since the time of these announcements, several observational studies investigating links between TZDs and bladder cancer have been conducted with mixed and conflicting results as not all studies have found associations. Moreover, though associations have been primarily linked to pioglitazone usage in the studies that have found associations between TZD use and bladder cancer, fewer than half of

all observational studies conducted to date have included rosiglitazone in their analyses, underscoring an important gap in the currently available evidence. Therefore, as presented in **Chapter 5**, we completed a study to examine whether diabetic patients treated with pioglitazone, rosiglitazone, or pioglitazone and rosiglitazone are at increased risk of bladder cancer relative to diabetic patients receiving other antidiabetic treatments.

In our bladder cancer study, we also employed a study design that first assembled a base cohort population of adult diabetics who had a similar level of T2DM disease severity. From that base cohort, a study cohort of patients who intensified or progressed their treatment regime by switching to, or adding-on another OHA or insulin was established. Patients were excluded if they had a history of bladder cancer prior to study cohort entry or if they had less than one year of follow-up after entry to the study cohort to ensure a minimum duration of drug use relative to a disease that normally has a long latency period. All incident cases of bladder cancer were identified during follow-up and for each case controls were randomly selected from the case's risk set after matching on age, sex, race, year of cohort entry, and duration of follow-up. We then constructed conditional logistic regression models to estimate the crude and adjusted odds of bladder cancer for TZD use compared to a reference group of never users of TZDs using four mutually exclusive TZD exposure categories: 1) exclusive ever use of pioglitazone, 2) exclusive ever use of rosiglitazone, 3) pioglitazone and rosiglitazone use, and 4) never use of any TZD. Models were adjusted for demographic, clinical, and care setting confounders if their inclusion changed the estimate of risk by 10% or more. Sensitivity analyses sought to examine whether observed associations would remain when removing the one year lag period after study cohort entry or when varying the lag period to less than one year or two years or more. Pioglitazone use



was also directly compared with rosiglitazone use to determine if there was a TZD class effect associated with any increased risk of bladder cancer that might be observed.

The completed analyses suggested that both pioglitazone (OR: 4.75, 95% CI: 1.29-17.58) and rosiglitazone (OR: 5.20, 95% CI: 1.32-20.59) may be associated with an increased risk of bladder cancer, compared with use of other antidiabetic drugs. However, a low number of cases that were TZD users (10 cases total) resulted in analyses that were underpowered and that also did not permit sensitivity analyses to investigate the effects of varying the lag period between study cohort entry and the index date.

Taking into consideration plausible mechanisms, study strengths, and the limitations of working with hospital-based EMR data, a detailed interpretation of our findings is presented in **Chapter 5**. As mentioned in that chapter, our lower number of cases is most likely in part a result of our attempt to control prevalent user bias which better captures incident users, but also leads to a lower sample size by excluding patients from the study cohort that would be included in a traditional nested case-control study. This is more apparent when studying less prevalent diseases such as bladder cancer that have a long latency period, compared to more common or chronic diseases such as heart failure or bone fractures. It should be noted that a low number of patients diagnosed with bladder cancer was apparent within the entire crude dataset itself, which also would have contributed to underpowered analyses using a traditional single cohort case-control design. Given our small sample sizes, our findings should be interpreted with caution and are insufficient to reliably characterize associations between the use of TZD drugs and an increased risk of bladder cancer. Nevertheless, our results may indicate a trend towards an association between both TZD drugs and risk of bladder cancer that should be investigated further using a larger cohort and/or a longer period of patient follow-up time.

## RELEVANCE TO POPULATION HEALTH

The extensive literature review and the studies completed as part of this dissertation both summarize and add to the body of knowledge regarding the use and safety of TZD drugs used in the treatment of T2DM. Our findings are relevant to both post-market adverse drug reaction (ADR) and T2DM research, and help inform decisions on implementing multiple evidence-based interventions that aim to reduce health inequalities and inequities within and between populations. Using the Framework for the Next Generation of Risk Science as a guide (**Chapter 1, Figure 1** [2]), also referred to as the "NextGen Framework", our study findings are discussed in the subsequent paragraphs within the broader concepts of population health.

### Characterizing Type 2 diabetes mellitus

Diabetes is a prevalent disease that currently affects nearly half a billion people worldwide [13] and that has been described as not only a health crisis, but a global societal catastrophe that is chronic, causes personal suffering, and drives individuals and families into poverty [13]. In 2015, 3.4 million Canadians [14] and 30.3 million Americans [15] were estimated to have diabetes with 90 to 95% of these diabetics suffering from T2DM [15]. This contributes to high levels of morbidity and mortality within populations worldwide from a disease, that in many cases, is preventable or curable through diet and lifestyle changes, and that places an enormous burden on health care systems.

T2DM is complex and multifaceted. Though its causes are not completely understood, there is a strong link between the development of T2DM and being overweight or obese, increasing age, ethnicity, family history, and modifiable risk factors such as poor diet and

nutrition, physical inactivity, prediabetes or impaired glucose tolerance, hypertension, smoking, and past history of gestational diabetes [13, 16]. Though many individuals will live with T2DM for years without demonstrating symptoms, during this time complications may already be developing and contributing to poor health outcomes and greater morbidity and disability [17]. Typical complications of T2DM include: hypoglycaemia, hyperglycaemic crisis, hypertension, high cholesterol, cardiovascular disease, stroke, vision-related issues, neurological issues, and renal disease [17]. Diabetes-related complications are more likely to occur in older adults, compounding other age-related conditions. In many cases, these complications can lead to physical disability and functional impairment, cognitive dysfunction, falls and fractures, amputations, depression, pressure ulcers, impaired vision and hearing, unrecognised and under-treated pain, and death [18] (also refer to **Annex 1** of this thesis for more detailed information). These are the same older diabetic adults that are more likely to be found in hospital-based datasets, including the dataset utilized for the major research emanating from this dissertation, where their often numerous diabetic complications can make it difficult to determine when adverse events are associated with a specific course of treatment versus T2DM itself. All of these factors were considered for the analyses of this thesis using the guiding principles of the objectives and risk assessment phases of the NextGen Framework.

Lifestyle changes are not always easy, possible, or effective for diabetic patients. For example, lifestyle changes are often not adequate to prevent the development of diabetes or control blood glucose levels in diabetic patients who may have a genetic predisposition towards the development of T2DM [19]. Social and environmental factors may also prevent individuals from adopting positive diet and lifestyle changes (e.g. living in a food desert or an unsafe neighbourhood that limits physical activity [20]). In these instances, oral medications or insulin

must be used to treat hyperglycaemia and maintain target blood sugar levels. This is when TZD pharmacotherapy may be prescribed to diabetic patients, especially in instances where first-line treatments such as metformin or sulphonylureas have proven ineffective or not effective enough to control hyperglycaemia alone. In short, TZDs are usually prescribed to diabetic patients that are more advanced in their disease.

### **Risk science objectives**

The problem formulation for this thesis focused on ADRs associated with the TZD class of drugs, with consideration given to the overall risk context, including the nature of T2DM itself, its prevalence, risk factors and the comorbidities mentioned above, how T2DM is treated within and between populations through both lifestyle and pharmacological management, and how decisions are made related to pharmacological treatment choices and intensification of treatment as a patient progresses in T2DM severity. For example, several pharmacotherapy options are available to treat T2DM and treatment regimes may include monotherapy, dual combination therapy, triple combination therapy, or combination injectable therapy (refer to **Annex 1** of this thesis for a detailed summary of treatment practices and guidelines). To select the most appropriate treatment for a patient, the American Diabetes Association (ADA) [21] recommends that a patient-centered approach be used to guide pharmacotherapy choices taking into consideration efficacy, cost, effects on weight, patient comorbidities, hypoglycaemia risk, and patient preferences. The ADA also recommends that treatment choice consider the side effect profile of a drug or drug combinations. The results of the studies contained within this dissertation add to the weight of evidence of serious cardiovascular, osteological, and

carcinogenic side effects associated with TZD pharmacotherapy, thus meeting the original risk science objectives set for this research.

## **Risk assessment**

As mentioned in the introductory chapter of this thesis, three broad categories of population health determinants form the foundation of the risk assessment phase of the NextGen Framework and were used to guide this research: biological and genetic, environmental and occupational, and social and behavioural. These categories are intentionally broad to better enable a wide variety of factors believed to influence the health of a population to be characterized and considered holistically when attempting to mitigate health risks [2]. Interactions between these health determinants were considered in an attempt to capture all influences on the cardiovascular, osteological, and carcinogenic outcomes examined in this thesis so that health risks were better characterized, and all analyses were conducted from a solid foundation rooted in population health.

There is perhaps no better example of a disease that demonstrates the complex interplay between population health determinants than T2DM. While it is well-documented that some individuals are biologically more susceptible to T2DM, with more than 65 genetic loci associated with T2DM discovered over the past several years; lifestyle factors such as diet play a large role in whether or not a particular gene is expressed in an individual [19]. At the same time, genetic factors can affect both the pharmacokinetics and pharmacodynamics of a drug, leading to changes in the function of a drug target and altering drug response which in and of itself can lead to ADRs [22]. Although we could not adjust for these factors, or others such as occupation that may influence the development of T2DM (e.g. overnight shift work [23]), or certain factors that

are relevant to the endpoints under investigation such as occupational exposures to chemicals (relevant to bladder cancer), we adjusted for important comorbidities wherever possible that could affect the analyses for each endpoint. These included cardiovascular risk factors and use of associated medications such as statins, conditions that may make individuals more susceptible to bone fractures such as chronic obstructive pulmonary disease (COPD) and rheumatoid arthritis that are treated with glucocorticoid therapy which itself is associated with an increased incidence of fracture [24-25], and previous urinary conditions that could indicate an increased susceptibility for, or a previously misdiagnosed case of bladder cancer [26]. Controlling for these factors, in combination with consideration of overall treatment patterns and guidelines for T2DM added to the strength of evidence presented in this thesis. Examining these factors also allowed us to make several important observations within the dataset that are also relevant to conducting pharmacoepidemiological studies in hospital-based populations of diabetics in general (further discussed in the *Strengths and limitations* section of this chapter).

## **Risk management**

The implementation of effective health risk policies and population-based interventions is essential to reducing the inequalities and inequities within patient populations that are identified through health risk science activities. This is especially true for chronic diseases such as T2DM that may develop over many years, and that may be preventable or modifiable in their early stages. The consideration and implementation of interventions form the risk management component of the NextGen Framework where health policies should be evidence-based and take into consideration the needs of the population targeted by such policies, including projected changes in population dynamics, disease characteristics, progression, and advances in treatment

patterns and guidelines, and future requirements for the target population to live healthy lives [2]. Using the NextGen Framework's model for risk management, the following interventions and health policies are proposed to minimize or prevent ADRs associated with TZD pharmacotherapy. It should be noted that the risk management strategies presented below are for the purposes of discussion only, based on the present state of knowledge of TZD medication use and safety, and were not developed in consultation with relevant stakeholders.

- **Science-based regulatory decision-making and collaboration:** Given that past decisions related to the continued availability of TZD drugs on the US market by regulatory agencies have been controversial, regulators should strive to ensure that all decisions are science-based, free from competing interests, and transparent. Greater collaboration between global regulatory agencies, including information sharing agreements related to ADRs within their jurisdictions, should be encouraged to share best practices to detect and mitigate TZD-related and other antidiabetic drug ADRs.
- **Economic incentives:** Clinician and care setting incentives based on favourable patient outcomes in diabetics (e.g. reducing patients' needs for antidiabetic medications through counselling and lifestyle changes that result in fewer hospital visits and fewer prescriptions dispensed and relying on guideline-driven prescribing practices when pharmacotherapy is required) offers potential to increase awareness of medication risks and encourage non-pharmacological alternatives in addition to adopting and following recognized standards of medical care for managing T2DM through pharmacotherapy (e.g. ADA guidelines).

- **Early ADR signal warning systems:** Clinical warning systems based on ADRs in patients undergoing antidiabetic drug therapy may prove beneficial since they may alert clinicians to prescribing risks, especially when drugs are used in new patient populations (e.g. TZDs prescribed off-label to non-diabetics) or when new antidiabetic drugs are marketed. Regulatory requirements for mandatory signal reporting by health care system data holders could also be beneficial and encourage regular active pharmacovigilance practices in the private health care and pharmaceutical sectors.
- **Community outreach, engagement, and consultation:** The most effective way to prevent ADRs related to antidiabetic drug therapy is to prevent the development of T2DM in the first place. Community-based programs that aim to increase public, patient, and care partner awareness of T2DM, its risk factors and comorbidities, and that work with existing diabetic patients to provide them with information on the benefits and risks of available antidiabetic therapies, may facilitate increased community and patient participation in shared decision-making processes specific to diabetes treatment and ultimately, its prevention.

## STRENGTHS AND LIMITATIONS

The analytic approach for this doctoral research was informed by previous studies examining adverse effects related to TZDs and included extensive examination of the entire body of literature for each endpoint, as well as other potential adverse effects associated with TZD treatment. The studies completed as part of this research have a number of strengths and limitations which have been individually acknowledged and described in the study-specific chapters of this thesis. The following discussion broadly describes the general strengths and



limitations of using Cerner Health Facts® data and hospital-based data in general to conduct pharmacoepidemiology studies in T2DM, and includes data examples to illustrate specific challenges of working with hospital-based data for Type 2 diabetics undergoing treatment with antidiabetic drugs.

The research conducted for this thesis has several strengths. Firstly, in-depth pharmacy data that captured the dispensing of drugs enabled analyses of estimates of associations between medication use and adverse health outcomes. Secondly, using study designs that controlled for prevalent users, an issue that is common when exploring hospital-based data, increased the likelihood of capturing new users of antidiabetic drugs, to the extent possible, across the studies conducted. Thirdly, detailed demographic, clinical, and care setting data for each encounter permitted multivariable models to include many *a priori* defined covariates that were hypothesized to modify or confound associations between examined exposures and outcomes. Fourthly, our analyses were largely comprised of older adults with T2DM, a group that is frequently underrepresented in RCTs and that may be most vulnerable to adverse outcomes. Fifthly, the general prescribing trends for TZDs across the entire study cohort closely reflect trends in the literature and the timings of the initial warnings of adverse cardiovascular events associated with rosiglitazone and adverse osteological events associated with pioglitazone in 2007, the restricted access of rosiglitazone in the US beginning in late 2010, and the bladder cancer warnings related to pioglitazone use in 2011 (**Figure 1**). Sixthly, examined exposures are presumed to reflect best practice guidelines, since individuals in our studies primarily sought care at urban teaching centers that are more likely to offer specialty care on-site. Finally, data were derived from large populations of hospitalized diabetic patients who received care at multiple facilities throughout the US over more than 10 years. This may render our findings

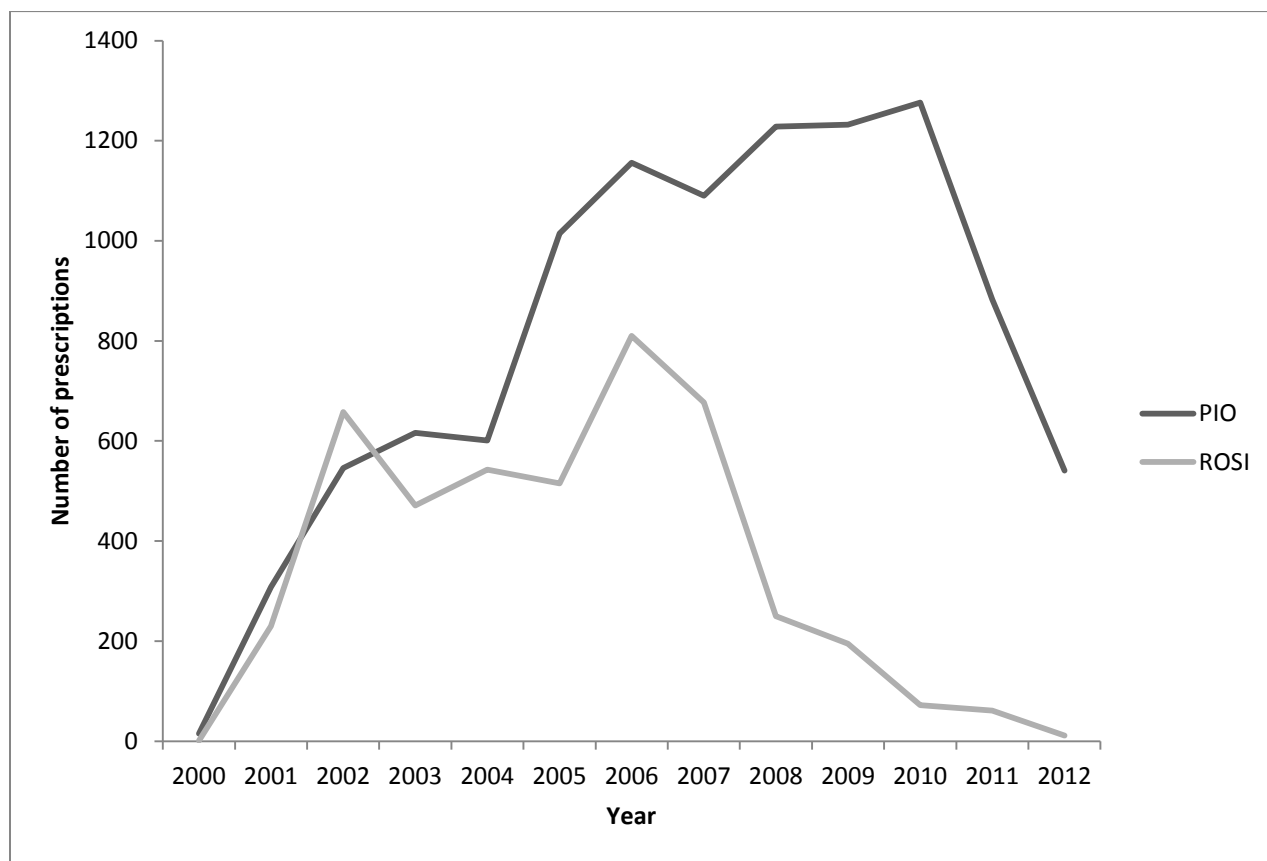


**Figure 1.** Prescribing patterns for TZD drugs within Cerner Health Facts® over the course of the study period. PIO: pioglitazone; ROSI: rosiglitazone.

more generalisable compared to smaller, single center studies, or studies of shorter duration. Additionally, since the pharmacologic management of T2DM is similar across developed countries, our findings may be applicable to diabetes care and health systems outside of the US, including Canada and Europe, recognizing that individual TZD drugs have varying levels of access within these health systems.

Despite a number of strengths, the studies contained within this thesis also have a number of limitations that also highlight the limitations of working with hospital-based data. The more significant limitations in our studies appear to be related to two potential biases that may be contributing to the surprising ORs observed. The first bias stems from the known inclusion of prevalent users in hospital-based studies that biases associations towards the null (this bias was controlled for in our study designs, to the extent possible, and in actuality demonstrates a strength while highlighting limitations in other studies that do not control for it), and the second bias relates to insulin prescribing practices in-hospital that may replace a diabetic patient's regular antidiabetic pharmacotherapy thus (in the present research) inflating associations with adverse events. Both potential biases are further discussed below.

Firstly, with respect to prevalent user bias, we can use the MI study as an example and conduct a nested case-control study using the same data and same study criteria without the double cohort design (i.e. patients enter the study cohort at the time of their first prescription for a non-insulin antidiabetic drug) as a sensitivity analysis. In this example, the sample size now increases from 418 cases of MI and 3,816 matched controls to 1,950 cases of MI and 18,805 matched controls therefore, a limitation of controlling for prevalent users in our studies is that it decreases the overall sample sizes of the patient cohorts. Baseline characteristics for the single cohort design are presented in **Table 1**. Compared to the results for MI presented in **Chapter 3**,

**Table 1.** Baseline characteristics of cases and matched controls for MI using a single cohort nested case control design. Values are numbers (percentages) unless stated otherwise.

| <b>Characteristic</b>                           | <b>Cases<br/>(n = 1,950)</b> | <b>Controls<br/>(n = 18,805)</b> |
|-------------------------------------------------|------------------------------|----------------------------------|
| <b>Mean (SD) age (years)*</b>                   | <b>70.0 (12.9)</b>           | <b>70.7 (12.6)</b>               |
| 18-25                                           | 22 (1.1)                     | 191 (1.0)                        |
| 26-35                                           | 75 (3.9)                     | 690 (3.7)                        |
| 36-45                                           | 169 (8.7)                    | 1,535 (8.2)                      |
| 46-55                                           | 334 (17.1)                   | 3,132 (16.7)                     |
| 56-65                                           | 469 (24.1)                   | 4,384 (23.3)                     |
| 66-75                                           | 445 (22.8)                   | 4,444 (23.6)                     |
| 76-85                                           | 354 (18.2)                   | 3,441 (18.3)                     |
| >85                                             | 82 (4.2)                     | 986 (5.2)                        |
| <b>Men*</b>                                     | <b>919 (47.1)</b>            | <b>9,205 (49.0)</b>              |
| <b>Year of study cohort entry*</b>              |                              |                                  |
| 2000                                            | 41 (2.1)                     | 296 (1.6)                        |
| 2001                                            | 151 (7.7)                    | 1,461 (7.8)                      |
| 2002                                            | 143 (7.3)                    | 1,332 (7.1)                      |
| 2003                                            | 135 (6.9)                    | 1,209 (6.4)                      |
| 2004                                            | 90 (4.6)                     | 827 (4.4)                        |
| 2005                                            | 109 (5.6)                    | 1,050 (5.6)                      |
| 2006                                            | 168 (8.6)                    | 1,641 (8.7)                      |
| 2007                                            | 211 (10.8)                   | 2,076 (11.0)                     |
| 2008                                            | 206 (10.6)                   | 2,022 (10.8)                     |
| 2009                                            | 206 (10.6)                   | 2,032 (10.8)                     |
| 2010                                            | 220 (11.3)                   | 2,174 (11.6)                     |
| 2011                                            | 145 (7.4)                    | 1,443 (7.7)                      |
| 2012                                            | 125 (6.4)                    | 1,242 (6.6)                      |
| <b>Mean (SD) duration of follow-up (years)*</b> | <b>1.2 (1.7)</b>             | <b>1.2 (1.8)</b>                 |
| <b>Race</b>                                     |                              |                                  |
| Caucasian                                       | 1,519 (77.9)                 | 14,809 (78.8)                    |
| African-American                                | 346 (17.7)                   | 3,219 (17.1)                     |
| Other                                           | 85 (4.4)                     | 777 (4.1)                        |
| <b>Payer class</b>                              |                              |                                  |
| Medicare                                        | 306 (15.7)                   | 3,329 (17.7)                     |
| Other                                           | 337 (17.3)                   | 3,204 (17.0)                     |
| Unknown                                         | 1,307 (67.0)                 | 12,272 (65.3)                    |
| <b>Census region</b>                            |                              |                                  |
| Northeast                                       | 808 (41.4)                   | 7,752 (41.2)                     |
| Midwest                                         | 442 (22.7)                   | 4,312 (22.9)                     |
| West                                            | 89 (4.6)                     | 982 (5.2)                        |
| South                                           | 611 (31.3)                   | 5,759 (30.6)                     |

Table 1. *Continued.*

| Characteristic                                             | Cases<br>(n = 1,950) | Controls<br>(n = 18,805) |
|------------------------------------------------------------|----------------------|--------------------------|
| <b>Region type</b>                                         |                      |                          |
| Urban                                                      | 1,947 (99.9)         | 18,763 (99.8)            |
| Rural                                                      | 3 (0.2)              | 42 (0.2)                 |
| <b>Treatment center type</b>                               |                      |                          |
| Acute care                                                 | 1,746 (89.5)         | 17,322 (92.1)            |
| Non-acute care                                             | 199 (10.2)           | 1,439 (7.7)              |
| Missing                                                    | 5 (0.3)              | 44 (0.2)                 |
| <b>Treatment center teaching status</b>                    |                      |                          |
| Teaching                                                   | 993 (50.9)           | 10,060 (53.5)            |
| Non-teaching                                               | 957 (49.1)           | 8,745 (46.5)             |
| <b>Treatment center beds</b>                               |                      |                          |
| 1-199                                                      | 361 (18.5)           | 3,077 (16.4)             |
| 100-199                                                    | 319 (16.4)           | 2,875 (15.3)             |
| 200-299                                                    | 465 (22.4)           | 4,421 (23.5)             |
| 300-499                                                    | 311 (16.0)           | 3,312 (17.6)             |
| ≥ 500                                                      | 503 (25.8)           | 5,120 (27.2)             |
| Ever smoker†                                               | 176 (9.0)            | 1,938 (10.3)             |
| Ever diagnosis or treatment for obesity‡                   | 552 (28.3)           | 5,537 (29.4)             |
| Ever diagnosis or treatment for alcohol-related disorders‡ | 49 (2.5)             | 401 (2.1)                |
| Angina                                                     | 30 (1.5)             | 208 (1.1)                |
| Atrial fibrillation                                        | 66 (3.4)             | 691 (3.7)                |
| Previous cancer                                            | 99 (5.1)             | 913 (4.9)                |
| Chronic obstructive pulmonary disease                      | 92 (4.7)             | 979 (5.2)                |
| CHF                                                        | 63 (3.2)             | 691 (3.6)                |
| Coronary artery/heart disease                              | 195 (10.0)           | 1,723 (9.2)              |
| Dyslipidemia                                               | 354 (18.2)           | 3,329 (17.7)             |
| Hypertension                                               | 487 (25.0)           | 4,695 (25.0)             |
| Peripheral vascular disease                                | 38 (2.0)             | 263 (1.4)                |
| Ischemic stroke                                            | 15 (0.8)             | 119 (0.6)                |

Table 1. *Continued.*

| Characteristic                             | Cases<br>(n = 1,950) | Controls<br>(n = 18,805) |
|--------------------------------------------|----------------------|--------------------------|
| Angiotensin-converting enzyme inhibitors   | 83 (4.3)             | 834 (4.4)                |
| Angiotensin II receptor antagonists        | 27 (1.4)             | 322 (1.7)                |
| Beta-blockers                              | 143 (7.3)            | 1,448 (7.7)              |
| Calcium channel blockers                   | 88 (4.5)             | 739 (3.9)                |
| Diuretics                                  | 111 (5.7)            | 1,100 (5.9)              |
| Digoxin                                    | 16 (0.8)             | 229 (1.2)                |
| Spironolactone                             | 14 (0.7)             | 104 (0.6)                |
| Statins                                    | 82 (4.2)             | 903 (4.8)                |
| Nonsteroidal anti-inflammatory drugs       | 232 (11.9)           | 2,239 (11.9)             |
| Mean number hospital admissions (SD)       | 2.1 (1.2)            | 2.1 (1.2)                |
| Number of hospital admissions              |                      |                          |
| 1                                          | 915 (46.9)           | 8,657 (46.0)             |
| 2                                          | 400 (20.5)           | 3,833 (20.4)             |
| 3                                          | 225 (11.5)           | 2,212 (11.8)             |
| ≥ 4                                        | 410 (21.0)           | 4,103 (21.8)             |
| Mean number unique non-diabetic drugs (SD) | 3.5 (1.6)            | 3.4 (1.6)                |
| Number of unique non-antidiabetic drugs    |                      |                          |
| 0                                          | 76 (3.9)             | 864 (4.6)                |
| 1                                          | 138 (7.1)            | 1,411 (7.5)              |
| 2                                          | 305 (15.6)           | 3,033 (16.1)             |
| 3                                          | 494 (25.3)           | 4,647 (24.7)             |
| ≥ 4                                        | 937 (48.1)           | 8,850 (47.1)             |
| Metformin                                  | 727 (37.3)           | 9,690 (51.4)             |
| Sulphonylureas                             | 1,271 (65.2)         | 10,620 (56.3)            |
| Pioglitazone                               | 265 (13.6)           | 1,221 (6.5)              |
| Rosiglitazone                              | 142 (7.3)            | 702 (3.7)                |
| DPP-4 inhibitors                           | 119 (6.1)            | 900 (4.8)                |
| α-glucosidase inhibitors                   | 8 (0.4)              | 79 (0.4)                 |
| Meglitinides                               | 65 (3.3)             | 587 (3.1)                |
| Insulins                                   | 1,797 (92.2)         | 17,451 (92.8)            |

\*Matching variable.

†Presence of any smoking-related event code in a patient's history.

‡Includes the presence of any obesity or alcohol-related event code in a patient's history.

¶Non-mutually exclusive categories; antidiabetic drugs received ever before and including cohort entry.

the single cohort design has a dampening effect on the characteristics of the study population by pulling down the mean age, duration of follow-up, mean number of hospital admissions, and mean number of unique non-diabetic drugs, in addition to reducing the proportion of men, patients insured through Medicare (as would be expected with a decrease in the age of the cohort), and cardiovascular risk factors and associated medications within the cohort. The proportion of cases and controls prescribed insulin within the cohort now becomes similar, but the proportion of cases prescribed pioglitazone or rosiglitazone decreases from approximately 3.5 times the rate of prescriptions in the matched control group, to approximately 2.0 times. This implies that some form of selection bias is occurring, which may be a result of insulin substitution in patients in the control group (further discussed below). The primary analyses (**Table 2**) demonstrate the same general trend as in the double cohort analysis in **Chapter 3**, as do the sensitivity analyses (**Tables 3-5**), but the inclusion of prevalent users has a dampening effect on the ORs. This trend is expected given that the inclusion of prevalent users tends to bias risk estimates towards the null which could be an explanation for the lack of association between TZDs and adverse events reported in other observational studies that have not controlled for this bias. However, because the ORs in our studies are still high compared to the literature this implies that another bias is also occurring and is contributing to the observed ORs. We hypothesize that this is most likely a result of insulin use.

In the normal progression of diabetes severity, when OHAs are unable to control hyperglycaemia to recommended targets insulin injections may be prescribed either alone or in combination with a drug such as metformin [21]. However, things become more complicated in situations where a patient's normal course of oral antidiabetic therapy may not be possible (i.e. a patient is physically unable to take oral medications), is not convenient or cost-effective, or if

**Table 2.** Thiazolidinedione use and risk of MI among cases and matched controls using a single cohort nested case control design\*

| Thiazolidinedione use**                        | Cases<br>(n =<br>1,950)<br>n (%) | Controls<br>(n =<br>18,805)<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------------------------|--------------------------------------|-------------------------|-------------------------------------|------------------------------------|
| Never use of any thiazolidinedione (reference) | 1,546<br>(79.3)                  | 16,892<br>(89.8)                     | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 262<br>(13.4)                    | 1,211<br>(6.4)                       | 2.27<br>(1.97-2.63)     | 2.09<br>(1.72-2.54)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 139<br>(7.1)                     | 692<br>(3.7)                         | 2.04<br>(1.69-2.48)     | 2.06<br>(1.59-2.67)                 | ‡                                  |
| Rosiglitazone versus pioglitazone              |                                  |                                      | 1.01<br>(0.72-1.41)     | 1.05<br>(0.59-1.88)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, and duration of follow-up

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, coronary artery disease, hypertension, peripheral vascular disease, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Maximum adjusted model the same as the minimal model.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.



**Table 3.** Thiazolidinedione use and risk of MI among cases and matched controls using a single cohort nested case-control design based on a lag period of less than one year between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| < 1 year lag period                            |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 837<br>(82.5)  | 8,901<br>(90.3)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 115<br>(11.3)  | 605<br>(6.1)      | 1.98<br>(1.59-2.45)     | 1.75<br>(1.30-2.35)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 63<br>(6.2)    | 346<br>(3.5)      | 1.84<br>(1.39-2.44)     | 1.65<br>(1.28-2.43)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, duration of treated diabetes before entering the study cohort, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, coronary artery disease, hypertension, peripheral vascular disease, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Maximum adjusted model the same as the minimal model.

**Table 4.** Thiazolidinedione use and risk of MI among cases and matched controls using a single cohort nested case-control design based on a lag period of one year or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>≥ 1 year lag period</b>                     |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 709<br>(75.8)  | 7,955<br>(89.5)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 147<br>(15.7)  | 589<br>(6.6)      | 2.67<br>(2.19-3.25)     | 2.57<br>(1.99-3.34)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 76<br>(8.1)    | 336<br>(3.8)      | 2.28<br>(1.75-2.96)     | 2.14<br>(1.51-3.03)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, duration of treated diabetes before entering the study cohort, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, coronary artery disease, hypertension, peripheral vascular disease, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Maximum adjusted model the same as the minimal model.

**Table 5.** Thiazolidinedione use and risk of MI among cases and matched controls using a single cohort nested case-control design based on a lag period of two years or more between study cohort entry and index date\*

| Thiazolidinedione use**                        | Cases<br>n (%) | Controls<br>n (%) | Crude<br>OR<br>(95% CI) | Minimal<br>Adjusted OR<br>(95% CI)† | Maximum<br>Adjusted OR<br>(95% CI) |
|------------------------------------------------|----------------|-------------------|-------------------------|-------------------------------------|------------------------------------|
| <b>≥ 2 year lag period</b>                     |                |                   |                         |                                     |                                    |
| Never use of any thiazolidinedione (reference) | 487<br>(75.2)  | 5,427<br>(88.9)   | 1.00<br>(reference)     | 1.00<br>(reference)                 | 1.00<br>(reference)                |
| Exclusive ever use of pioglitazone             | 99<br>(15.3)   | 414<br>(6.8)      | 2.53<br>(1.99-3.21)     | 2.52<br>(1.83-3.47)                 | ‡                                  |
| Exclusive ever use of rosiglitazone            | 59<br>(9.1)    | 259<br>(4.2)      | 2.33<br>(1.73-3.15)     | 2.34<br>(1.55-3.54)                 | ‡                                  |

\*Matched on age, year of study cohort entry, sex, duration of treated diabetes before entering the study cohort, and duration of follow-up.

\*\*There were an insufficient number of cases (< 5) to determine associations for ever use of both pioglitazone and rosiglitazone.

†Adjusted for angina, atrial fibrillation or flutter, CHF, previous cancer (other than non-melanoma skin cancer), COPD, dyslipidemia, coronary artery disease, hypertension, peripheral vascular disease, ischemic stroke, use of ACE inhibitors, angiotensin II receptor antagonists, beta-blockers, calcium-channel blockers, diuretics, digoxin, spironolactone, statins, NSAIDs, excessive alcohol use, obesity, and smoking.

‡Maximum adjusted model the same as the minimal model.

their normal course of therapy interacts with other non-diabetic medications [27]. For example, rifampicin which may be used to treat nosocomial methicillin-resistant *Staphylococcus aureus* pneumonia decreases levels of both pioglitazone and rosiglitazone in the blood and gemfibrozil, which is used to treat hyperlipidemia, has been shown to increase rosiglitazone concentrations [28]. As a result, dosages of rosiglitazone or pioglitazone may be adjusted up or down in patients undergoing rifampicin or gemfibrozil pharmacotherapy, or as discussed below, a more likely scenario is that these patients would be switched to insulin for the duration of their hospital stay as a matter of better glycaemic control and/or greater convenience in a hospital environment. This common practice may contribute to a form of selection bias that had an impact on the magnitude of the ORs observed across our studies.

It is estimated that up to 30% of all hospitalized patients in the US have diabetes and that most of these hospitalized patients are treated with insulin [29]. For many patients, use of OHAs is discontinued once they are admitted to hospital and they are switched to insulin therapy [27] as concomitant medications such as glucocorticoids prescribed in hospital may worsen glycaemic control [30]. Events such as surgery that increase stress response and impact the timing of factors such as meals may also greatly affect blood sugar levels and overall patient response to antidiabetic medications [27]. These factors complicate the investigation of associations between OHAs and ADRs in a hospital-based population.

As an example of potential insulin-related complications in hospital-based studies, we can look at our cohort of patients from the bone fractures study (**Chapter 4**) and conduct a second sensitivity analysis (**Table 6**) to examine why control patients prescribed insulin were admitted to hospital. In this study, 7.5% of bone fracture cases were prescribed pioglitazone compared to only 2.8% of their matched controls (a similar trend was also observed in the

**Table 6.** Most common diagnoses for bone fracture controls prescribed insulin after study cohort entry.

| <b>Diagnosis</b>                                                                      | <b>% of patient encounters*</b> |
|---------------------------------------------------------------------------------------|---------------------------------|
| <b>Cardiac events (e.g. congestive heart failure, atrial fibrillation or flutter)</b> | 7.0                             |
| <b>Diabetes mellitus without mention of complication</b>                              | 4.6                             |
| <b>Chronic kidney disease or acute kidney failure</b>                                 | 3.7                             |
| <b>Hypertension</b>                                                                   | 3.5                             |
| <b>Hyperlipidemia</b>                                                                 | 2.5                             |
| <b>Anemia</b>                                                                         | 1.4                             |
| <b>Esophageal reflux</b>                                                              | 1.2                             |
| <b>Urinary tract infection</b>                                                        | 1.2                             |
| <b>Pneumonia or pneumonitis</b>                                                       | 1.2                             |
| <b>Osteoarthritis</b>                                                                 | 1.1                             |
| <b>Chronic airway obstruction</b>                                                     | 1.1                             |
| <b>Diabetes mellitus with neurological, renal or other complications</b>              | 1.1                             |

\*Out of a total of 55,439 patient encounters that contained a diagnosis. Percentages do not contain duplicate diagnoses for the same patient.

cardiovascular and bladder cancer studies). This may be due to chance, or may be a marker of a true association between pioglitazone therapy and increased risk of bone fracture. However, we hypothesize that this is a second form of bias that originates from differing reasons for hospital admissions amongst controls compared to cases where controls that would normally be treated with pioglitazone may have been prescribed insulin instead. This would contribute to an increased effect resulting in high ORs. Conditions such as acute kidney failure may be more likely to result in a situation where patients are given insulin in-hospital instead of a TZD drug. Though TZDs are metabolized by the liver, they cause fluid retention which is a problem that may already be worse in patients with kidney disease [31]. Insulin is considered to be safe for use in patients with reduced kidney function, and although the risk of hypoglycaemic events is five times higher than in subjects without impairment renal function [32], the reduction in insulin dose required by patients with renal impairment may be more cost-effective and convenient in a hospital setting than prescribing a patient a TZD drug and potentially also dealing with the effects of fluid retention and edema [31]. In-hospital insulin substitution is an interesting phenomenon that would be expected to occur across hospital facilities and that presents an opportunity for future research to further define the challenges of working with hospital-based data for diabetic pharmacoepidemiology, and potential methodological solutions to such challenges.

Finally, other limitations of our studies have been discussed throughout the data chapters of this dissertation. Briefly, given the in-patient nature of our dataset, we were unable to take medication dose and prescription adherence into consideration in our analyses. However, because our cohorts were hospital-based, it is assumed that diabetic patients would be more likely to adhere to antihyperglycaemic therapy as their blood glucose levels would be monitored,

adjusted, and controlled by their clinical treatment team in-hospital. As another example, our studies of adverse outcomes examined associations between drug exposures and multiple adverse events, and therefore can only be considered exploratory. As such, adjustments for multiple comparisons were not made. Although our analyses should be replicated using other population-based datasets, especially those that link hospital-based data to general practice data to ensure that all patient prescriptions are captured, the general trends of our findings are supported by prior drug safety reports and plausible biomolecular mechanisms.

## **CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS**

In conclusion, the research completed as part of this thesis serves to address knowledge gaps pertaining to the use and safety of TZD medications used in the treatment of T2DM that are now increasingly being explored for the treatment of other disease and conditions including hormonal disorders, cognitive disorders, and cancers. Leveraging data from a cohort of diabetics contained within the Cerner Health Facts® datawarehouse, a unique hospital-based dataset that has not been used to explore adverse events associated with TZD pharmacotherapy, and advanced pharmacoepidemiology methods, our study findings demonstrate that: 1) use of TZD drugs is associated with diagnoses of MI and CHF, particularly in older patients; 2) use of TZDs is associated with an increased risk of fracture across various fracture sites, particularly in women; and that, 3) both pioglitazone and rosiglitazone use may be associated with an increased risk of bladder cancer, but that further investigation of associations between TZD use and bladder cancer is required using a larger patient population and/or patient follow-up time. This thesis also serves to demonstrate the strengths and limitations of working with hospital-based data for T2DM research and presents an interesting hypothesis related to in-hospital prescriptions

of insulin that requires further exploration. Although replication of the studies contained within this dissertation is warranted, this thesis adds to the weight of the existing evidence that continues to be provided by researchers working with other large-scale datasets and fills a gap by exploring these issues within a previously unexplored health care data system while also controlling for an important bias that inherent in hospital-based data. In summary, the evidence presented suggests that caution should be exercised when prescribing diabetic patients (and potentially non-diabetic patients) TZD drugs if they have risk factors related to or a history of cardiovascular disease, bone fractures or conditions causing fragility and falls, or bladder cancer. In the context of both population health and the principles of the NextGen Framework, these findings may be used to inform future health risk assessments and risk management strategies, especially when working with hospital-based data.

Areas of future potential research include: 1) further exploration of the adverse cardiovascular, osteological, and carcinogenic events associated with TZD pharmacotherapy demonstrated in this thesis using general practice data linked to hospital-based data to enable the capture of all prescriptions of antidiabetic medications over time; 2) re-analysis of previously analyzed published data using a design that controls for prevalent user bias and determining if similar trends to our findings are apparent in other hospital-based administrative datasets; 3) exploration of the therapeutic benefits and potential adverse effects of TZD use in non-diabetic, younger, and healthier patients with fewer comorbidities and risk factors than Type 2 diabetics; 4) assessment of changes in TZD prescribing practices over time and how prevalent TZD use is "off-label" in the treatment of non-diabetic diseases and conditions; and 5) whether our findings are relevant to health systems outside of the US. Finally, and perhaps the most interesting and exciting new area of research, would be: 6) exploring a combination of general practice and



hospital-based administrative data to better characterize in-hospital insulin use that may replace a patient's normal course of antidiabetic therapy, and determining new methodology to control or adjust for this practice when investigating associations with ADRs in hospitalized diabetic populations.

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## **ANNEX 1: Diabetes, Treatment Guidelines, and Drug Classes**

### **PREFACE**

This annex summarizes information on the incidence, demographics, distribution, risk factors, comorbidities, mortality, interactions with the health care system, and costs associated with diabetes (all types and T2DM where statistics were available), and briefly summarizes treatment standards, guidelines, interventions, and treatments (including pharmacological treatments and those found in the Cerner Health Facts<sup>®</sup> dataset) for T2DM. Because this thesis utilizes US patient data for analysis, the information presented will focus, for the most part, on statistics, guidelines, and treatments for Type 2 diabetics in the US. In addition, since the analyses conducted for this thesis used a dataset with patient encounters between January 1, 2000 and December 31, 2012, the information presented below focuses on statistics and guidelines within or just after this time period, up to and including guidelines from 2015 to reflect potential changes in treatment patterns as a result of new information (e.g. new drugs or adverse reactions) or trends that became apparent at the end of or right after the study period.

## INCIDENCE, DEMOGRAPHICS AND DISTRIBUTION

### Incidence and prevalence

In 2013, 382 million adults (**Table 1**) or 8.3% of the global adult population were estimated to have some form of diabetes, either Type 1, T2DM, or gestational, and 46% of these adults were undiagnosed [1]. This number is expected to rise to 552 million by 2035 [2].

Although the majority of cases of diabetes worldwide are in low to middle-income countries (approximately 80%), diabetes is also extremely prevalent in North America (**Table 1**). For example, in 2008-2009 it was estimated that 2.4 million Canadians, or 2.8% of the population, were living with diabetes and that nearly half a million Canadians remained undiagnosed [3]. In the US in 2012 it was estimated that 29.1 million Americans, or 9.3% of the population had diabetes, an increase of 1% since 2010 [4]. Of these 29.1 million, Americans 8.1 million were undiagnosed. In 2013, it was estimated that approximately 24.4 million US adults between the ages of 20 and 79 had diabetes, representing a national prevalence of 10.9% [2].

**Table 1.** Number of people living with diabetes by International Diabetes Federation (IDF) region and worldwide<sup>1</sup>

| IDF region                   | Number of people diagnosed <sup>2</sup> (million) |
|------------------------------|---------------------------------------------------|
| North America and Caribbean  | 37                                                |
| South and Central America    | 24                                                |
| Europe                       | 56                                                |
| Middle East and North Africa | 35                                                |
| Africa                       | 20                                                |
| South-East Asia              | 72                                                |
| Western Pacific              | 138                                               |
| <b>World Total</b>           | <b>382*</b>                                       |

<sup>1</sup> Adapted from IDF [2].

<sup>2</sup> Diagnoses of Type 1, Type 2 and gestational diabetes combined.

\*Approximately 46% of diabetics are undiagnosed.

T2DM is the most prevalent form of diabetes in both Canada and the US accounting for approximately 90 to 95% of diabetic cases versus only 5 to 10% for other types (Type 1, gestational diabetes, and others such as chemically induced) [3, 4]. In Canada it has been estimated that more than 60,000 cases of T2DM are diagnosed each year [5]. In the US, the number of adults aged 18 to 79 with newly diagnosed diabetes (all types) has more than tripled from 493,000 in 1980 to over 1.5 million in 2011 [6]. Although the number of new cases of diagnosed diabetes did not change from 2006 to 2011 [6], the incidence of diabetes (all types) in the US in 2012 was estimated at 1.7 million new diagnoses for adults aged 20 years or older, or 7.8 per 1,000 population (unadjusted) [4]. This translates to more than one million cases of T2DM diagnosed in the US in 2012 but also grossly underestimates the true number of cases considering how many diabetics are assumed to have not been diagnosed.

## **Demographics**

### *Age*

Although there is some evidence that T2DM is increasing in children and adolescents in some countries [2], globally it is still more prevalent in adults. Worldwide almost half of all adults with diabetes (all types) in 2013 were between the ages of 40 and 59 years [2]. The number of diabetics aged 60 years and older is expected to grow as life expectancy increases, and thus the number of adults worldwide aged 60 years or older continues to increase alongside of improvements in public health and advances in medical care. For example, in 2013 the International Diabetes Federation (IDF [2]) estimated that the global prevalence of diabetes (all types) in people between the ages of 60 and 79 years was 18.6%, or more than 134.6 million

people (over 120 million of which are assumed to be Type 2 diabetics). This number is projected to increase to over 252.8 million diabetics (all types) by 2035 [2].

A large proportion of the burden of impaired glucose tolerance and diabetes in the US and Canada can be attributed to the ageing of the population where 39% of the region is over 50 years of age [2]. This is expected to rise to 44% by 2035. In the US, the greatest number of diabetic (all types) adults in 2012 were aged 45 years and older (based on 2009 to 2012 National Health and Nutrition Examination Survey estimates and age groupings applied to 2012 U.S. Census data; **Table 2**). This translates into approximately 85% of all Type 2 diabetics being over the age of 44 with at least 12 million aged 45 to 64 years, 10 million aged 65 years or older, and 3.8 million aged 20 to 44 years. The mean and median age at diagnosis of diabetes (all types) among adults aged 18 to 79 remained relatively constant between 1997 and 2011 in the US and both were similar at approximately 54 years of age in 2011 [7]. Of cases diagnosed in 2011, 63% of all incident cases were diagnosed between the ages of 40 and 64 years versus 21% for those aged 65 to 79 years, and 16% for those aged 18 to 39 years [8].

### *Sex*

Globally, the IDF [2] found little difference between the number of males and females with diabetes (all types). In 2013, approximately 198 million males had diabetes versus 184 million females, though the estimated numbers for 2035 show an increased gap between approximately 303 million males projected to have diabetes versus 288 million females. The global prevalence in 2013 was found to be slightly higher in females aged 60 years or older than males in the same age grouping, 19.0% versus 18.3% [2], which can most likely be attributed to the longer lifespan of women.

**Table 2.** Distribution and demographics of diabetes.

| Region                                          |                                 | Number of people with diabetes (millions) | Percentage with diabetes (breakdown) |
|-------------------------------------------------|---------------------------------|-------------------------------------------|--------------------------------------|
| Worldwide <sup>1</sup>                          |                                 | 382                                       | 8.3*                                 |
| US Total <sup>2</sup>                           |                                 | 29.1                                      | 9.3*                                 |
| US                                              |                                 |                                           |                                      |
| Age <sup>2</sup>                                | 20+                             | 28.9                                      | 12.3*                                |
|                                                 | 20-44                           | 4.3                                       | 4.1*                                 |
|                                                 | 45-64                           | 13.4                                      | 16.2*                                |
|                                                 | 65+                             | 11.2                                      | 11.2*                                |
| Sex <sup>2</sup>                                | Male                            | 15.5                                      | 13.6*                                |
|                                                 | Female                          | 13.4                                      | 11.2*                                |
| Race <sup>3</sup>                               | Non-Hispanic Whites             | -                                         | 7.6**                                |
|                                                 | Asian Americans                 | -                                         | 9.0**                                |
|                                                 | Hispanics                       | -                                         | 12.8**                               |
|                                                 | Non-Hispanic Blacks             | -                                         | 13.2**                               |
|                                                 | American Indians/Alaska Natives | -                                         | 15.9**                               |
|                                                 |                                 | Number of people with diabetes (millions) | Percentage of diabetes cases         |
| North America and Caribbean Region <sup>1</sup> |                                 |                                           |                                      |
| Area                                            | Urban                           | 29.8                                      | 81.2***                              |
|                                                 | Rural                           | 6.9                                       | 18.8***                              |

<sup>1</sup>Type 1, Type 2 and gestational diabetes, all age groups in 2013. Source IDF [2].

<sup>2</sup>Type 1, Type 2 and gestational diabetes, diagnosed and undiagnosed, all age groups in 2012, based on 2009–2012 National Health and Nutrition Examination Survey estimates applied to 2012 U.S. Census data. Source CDC [4].

<sup>3</sup> Diagnosed cases of Type 1, Type 2 and gestational diabetes in adults aged 20 years and older 2010-2012, source CDC [4].

\*Unadjusted.

\*Adjusted for age based on the 2000 US standard population.

\*\*\*Unadjusted, adults aged 20-79 years, source IDF [2].



In the US in 2012 the number of males and females with diabetes (all types) also showed little difference (**Table 2**). From 1997 to 2011 the median age at diagnosis among adults aged 18 to 79 years showed little or no change for both, and the median age at diagnosis in 2011 was comparable between the sexes at 53.6 years for males and 55.2 years for females [9].

### *Race*

Worldwide numerous studies have shown that the prevalence of diabetes in some sub-populations is higher than in the general population. The US is no exception where it has been demonstrated that African Americans, Hispanics/Latinos, some Asians, Native Hawaiians or other Pacific Islanders, and American Indians are more likely to have diabetes, and are at a particularly high risk for T2DM and its complications [4]. For example, the Pima Indians of Arizona have been extensively studied through a long-running longitudinal study on diabetes and its complications (since 1965) that has demonstrated their high prevalence of diabetes and obesity. In 1971 the prevalence of diabetes in this population was estimated at 50% among those aged 35 years and over [10]. Age and sex-adjusted incidence rates of diabetes in Pima Indians from 1965 to 1977 were 25.3 cases per 1,000 patient-years, 22.9 cases per 1,000 patient years from 1978 to 1990, and 23.5 cases per 1,000 patient years from 1991 to 2003 [11]. This is in stark contrast to the US national incidence of diabetes in 2008 of approximately 8 cases per 1,000 person-years [12]. Explanations for differences between populations and sub-populations, such as the Pima Indians and the general US population, are complex and difficult to elucidate due to inter-relationships between genetics and the environment (including nutritional, societal, and cultural factors).

With respect to race distribution in the general US population, from 1997 to 2011 the estimated rate of diagnosed diabetes (all types) for non-Hispanic whites, non-Hispanic blacks, and Hispanics demonstrated an age-adjusted incidence that was higher among non-Hispanic blacks and Hispanics [13]. In addition, throughout this time period the incidence in non-Hispanic blacks and Hispanics increased, whereas it only increased for non-Hispanic whites from 1997 to 2007 [13]. In 2011 the age-adjusted incidence of diagnosed diabetes was 12.4 per 1,000 in non-Hispanic blacks, 11.1 per 1,000 in Hispanics, and 7.0 per 1,000 in non-Hispanic whites [13].

From 2010 to 2012 (**Table 2**) the age-adjusted percentage of people aged 20 years or older with diagnosed diabetes (all types) across five races in the US found that it was highest in American Indians and Alaskan natives followed by non-Hispanic blacks and Hispanics, and was lowest in Asians and non-Hispanic whites. Percentages also differed by region and racial subgroups [4]. For example, among American Indian and Alaska Native adults this varied by region from 6.0% among Alaska Natives to 24.1% among the previously described Pima Indians in southern Arizona. Among Asian American adults the age-adjusted rate of diagnosed diabetes was 4.4% for Chinese, 11.3% for Filipinos, 13.0% for Asian Indians, and 8.8% for other Asian groups. Among Hispanic adults it was 8.5% for Central and South Americans, 9.3% for Cubans, 13.9% for Mexican Americans, and 14.8% for Puerto Ricans.

With respect to median age at diagnosis, from 1997 to 2011 there was little to no change for adult non-Hispanic blacks, Hispanics, or non-Hispanic whites aged 18 to 79 years. In 2011 the median age at diagnosis of diabetes in the US was 49.0 years for non-Hispanic blacks, 49.4 years for Hispanics, and 55.4 years for non-Hispanic whites [14]. This analysis did not include American Indian/Alaska Native or Asian adults presumably because it was survey-based and the sample size of respondents from these races was insufficient for analysis.

### *Socioeconomic factors*

It is well-established that persons of lower SES have, in general, poorer health outcomes than those of higher status e.g. 15-17], and that in most cases people of lower SES have poorer access to health care services and preventive care [18]. Associations between SES and diabetes, metabolic syndrome, and associated conditions such as cardiovascular disease, have been explored by some studies where in most cases a strong SES gradient has been demonstrated [19]. These associations are complex as they involve the interplay of numerous factors such as sex/gender, body mass, nutrition, physical activity, race, neighbourhood/area/region, income, education, and occupational status [e.g. 20-27].

For example, in an analysis of data gathered through the third National Health and Nutrition Examination Survey (NHANES), Loucks et al. [23] found that low education level (less than 12 years) had a greater association with metabolic syndrome for women (odds ratio [OR]: 1.77, 95% confidence interval [CI]: 1.39-2.24) than men (OR: 1.27, 95% CI: 0.97-1.66) when compared to other participants with more than 12 years of education. Low income (as measured by a poverty income ratio) was also related to metabolic syndrome in women (OR: 1.81, 95% CI: 1.37-2.40) but not men (OR: 0.98, 95% CI: 0.74-1.29). Socioeconomic position (in this study it was defined as years of completed education and poverty income ratio) was found to be negatively associated with metabolic syndrome in white, black, and Mexican-American women [23].

In the Whitehall II study, metabolic syndrome was assessed in relation to employment grade (six levels of Civil Service employment based on income level) for both adult men and women who completed an oral glucose tolerance test [20]. An inverse social gradient was associated with increased prevalence of metabolic syndrome and the odds ratio for having

metabolic syndrome, comparing the lowest employment grade to the highest, was 2.2 (95% CI: 1.6-2.9) for men and 2.8 (95% CI: 1.6-4.8) for women [20].

In the NHANES I Epidemiologic Follow-up Study (NHEFS) [22], the investigation of the association between three measures of SES (income, education, and occupational status) and diabetes found that after adjusting for age and race, the hazard ratio (HR) for women with greater than 16 years of education was 0.26 (95% CI: 0.13-0.54) relative to those with less than 9 years of education. Among men both higher income and education were associated with lower diabetes incidence (HR: 0.44, 95% CI: 0.19-0.98 for men with household income greater than five times the poverty level relative to those under the poverty line), but there was no inverse association of diabetes incidence with occupational status.

With respect to national statistics in the US, from 1980 to 2011 the age-adjusted incidence of diagnosed diabetes (all types) increased across all education levels, though it was higher among people with less than a high school education than those with a higher education level [28]. The age-adjusted incidence in 2011 was 11.6 per 1,000 population among adults with less than a high school education, 7.9 per 1,000 among adults with a high school diploma or equivalent, and 6.6 per 1,000 among adults with greater than a high school education [28]. It should be noted that US national statistics were not available for other measures of SES outside of those that were previously presented in this annex for age, sex, and race, or those that will be presented on urban/rural areas and geographic location.

## Distribution by area and geographic region

### *Urban/Rural*

Worldwide, the majority of diabetics reside in urban areas (246 million versus 136 million in rural areas) and this trend remains constant in the North America and Caribbean region where the percentage of diabetics (all types) in urban areas is 81.2% [2]. Though diabetics are less likely to reside in rural areas than in urban areas this is more likely a function of the overall population distribution between densely populated cities and sparsely populated rural areas. In fact, the prevalence of diabetes in rural areas of the US has been reported to be higher than in many urban areas. For example, in 1995 the self-reported prevalence of diabetes in non-metropolitan statistical areas of the US was 3.6% compared to 3.19% in central cities and 3.24% in all metropolitan statistical areas [29].

The prevalence of diabetes also varies significantly between rural regions with it generally being more common in the Southeast and Southwest (**Figure 1**), as well as Hawaii and Puerto Rico, and somewhat higher in Alaska which may be a reflection of differences in racial, socioeconomic, age, and lifestyle factors [30]. For those individuals with diabetes that do reside in rural areas, they are more likely to encounter difficulties in obtaining appropriate health care because of a lack of access to health care facilities, health care specialists, or distance to the nearest health clinic, and socioeconomic barriers such as poverty [31-32].

### *Geographic region*

The distribution of diabetes in the US varies by region and is especially high in an area that has been dubbed the "diabetes belt" [33]. In 2007 the Centers for Disease Control (CDC) produced estimates of the prevalence of diagnosed diabetes (all types) for every US county [34]

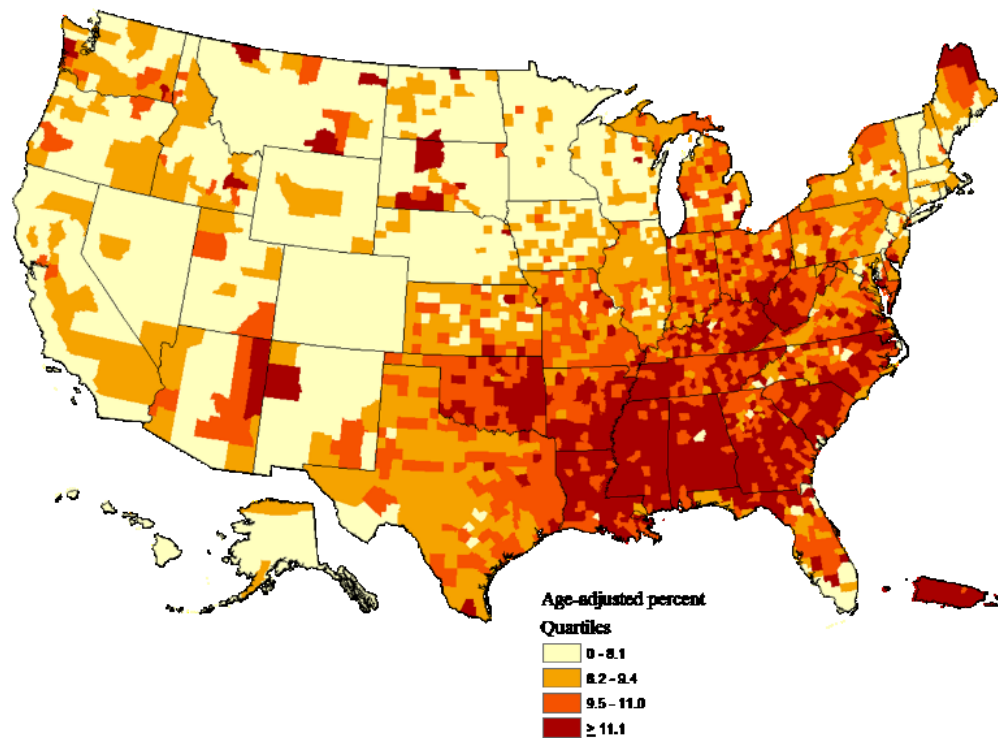


**Figure 1.** Age-adjusted county-level estimates of prevalence of diagnosed diabetes among US adults aged  $\geq 20$  years in 2011. Reproduced with permission from the CDC. Source: CDC [238].

and the majority of counties with a high prevalence of diabetes (greater than 11%) were concentrated in the Southeast region. This suggested the existence of a “diabetes belt” similar to the “stroke belt” identified in the 1960s [35]. Further analysis of this trend by Barker et al. [33] also identified counties in close proximity in the Southeast region that had an 11.0% or higher prevalence of diabetes that would also fall within, and confirmed the trend of a “diabetes belt”. Between 2004 and 2011 this distribution has remained. In 2011 (**Figures 1 and 2**) the age-adjusted county-level estimates of the prevalence of diagnosed diabetes and diagnosed diabetes incidence (all types) among US adults aged 20 years and older that were greater than or equal to 11.1%, or 11.3 per 1,000 population, respectively, were mainly concentrated in the Southeastern US.

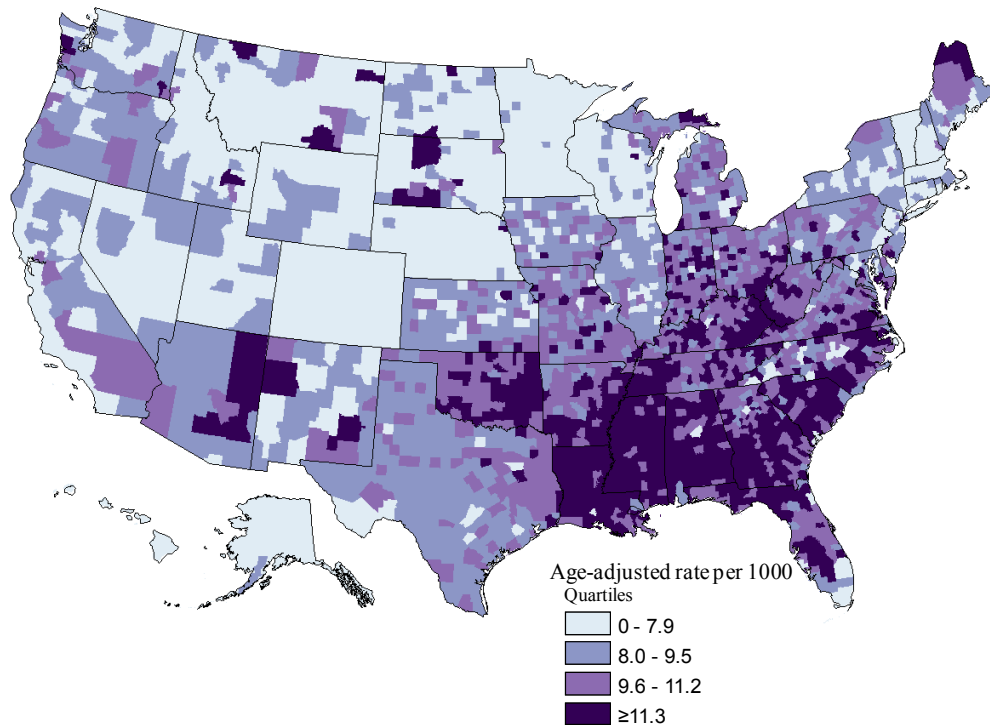


**Figure 2.** Age-adjusted county-level estimates of diagnosed diabetes incidence among US adults aged  $\geq 20$  years in 2011. Reproduced with permission from the CDC. Source: CDC [239].



## **RISK FACTORS, COMORBIDITY, AND MORTALITY**

### **Risk factors**

Several risk factors are associated with T2DM [36] and include, but are not limited to (see the *Diagnosis* section of this annex): a family history of diabetes; overweight and obesity; an unhealthy diet; a lack of physical activity; increasing age; hypertension; cardiovascular disease; race/ethnicity; impaired glucose tolerance; a history of gestational pregnancy; and, poor nutrition during pregnancy.

It should be noted that the development of T2DM is often a result of complex interactions between many factors including genetics/biology and SES. In addition, T2DM can be induced through other means such as exposure to some drugs or chemicals [37]. However, strong associations between some specific risk factors and diabetes have been demonstrated. For example, diabetes has been shown to be highly correlated with obesity (**Figure 3**) and low physical activity (**Figure 4**) with the distribution of both in the US showing a clear overlap with the distribution of diabetes (**Figures 1 and 2**).

### **Comorbidity and complications**

There are numerous comorbidities and complications associated with diabetes including: hypoglycemia, hyperglycemic crisis, hypertension, high cholesterol, heart disease, stroke, vision-related issues, neurological issues, falls and fractures, amputations, and renal disease. Many individuals will live with T2DM for several years without demonstrating symptoms however, during this time complications may already be developing [2] and contributing to poor health outcomes and greater morbidity and disability. Diabetes-related complications are more likely to occur in older adults and to compound other age-related conditions thus resulting, in many cases,

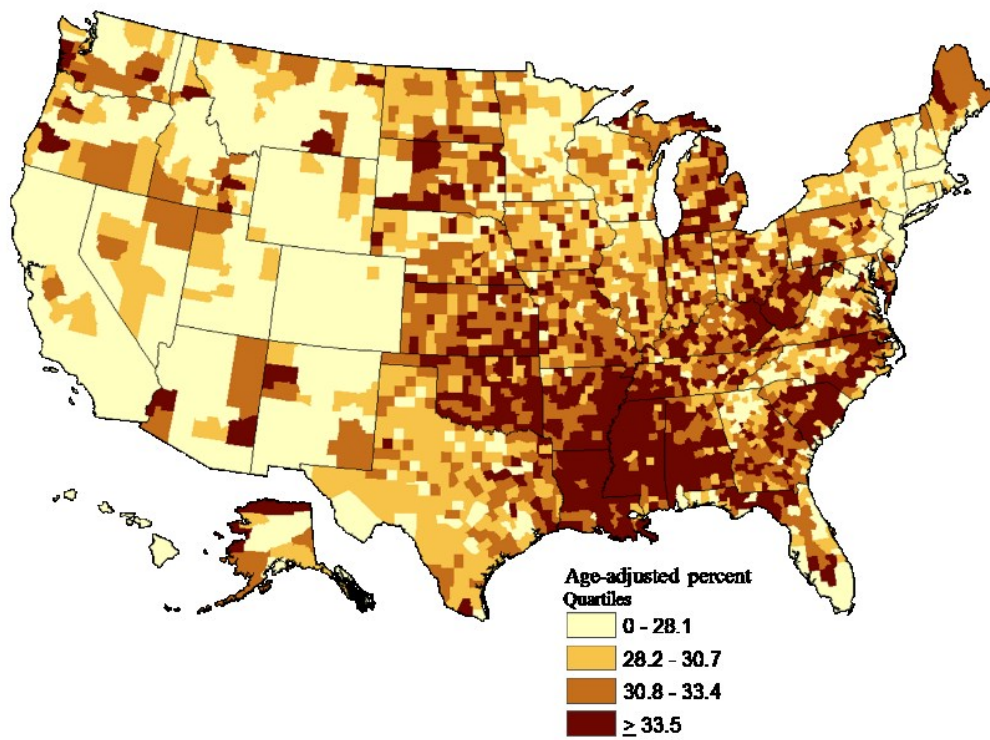


**Figure 3.** Age-adjusted county-level estimates of the prevalence of obesity among US adults aged  $\geq 20$  years in 2011. Reproduced with permission from the CDC. Source: CDC [240].

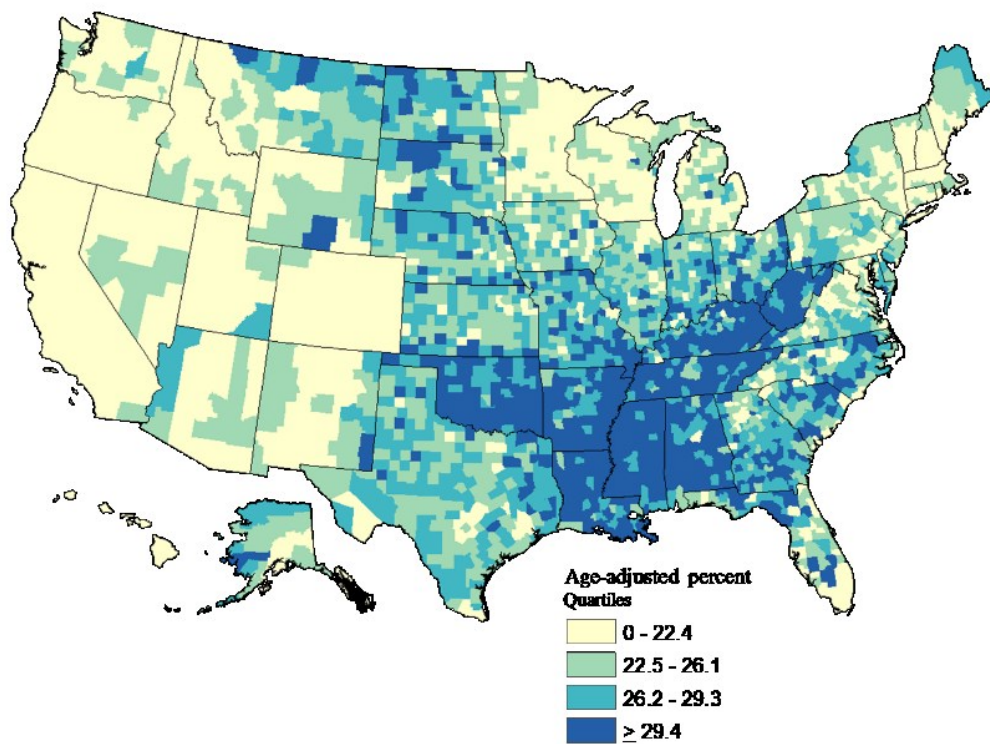


**Figure 4.** Age-adjusted county-level estimates of leisure-time physical inactivity among US adults aged  $\geq 20$  years in 2011. Reproduced with permission from the CDC. Source: CDC [241].

in physical disability and functional impairment, cognitive dysfunction, falls and fractures, depression, pressure ulcers, impaired vision and hearing, unrecognised and under-treated pain, and death [38].

The following are brief descriptions and US statistical information for common comorbidities and complications associated with T2DM:

### *Hypoglycaemia*

Hypoglycaemia is a condition characterized by abnormally low blood glucose levels, usually less than 70 milligrams per decilitre (mg/dl), which if left untreated can lead to seizure or unconsciousness (including coma) and death [37, 39]. Risk factors for hypoglycaemia in diabetes include the use of insulin or insulin secretagogues, duration of diabetes, antecedent hypoglycaemia, erratic meals, exercise, and renal insufficiency [40]. In 2011 approximately 282,000 emergency room visits for adults aged 18 years or older in the US had hypoglycaemia as the first-listed diagnosis and diabetes as another diagnosis [4].

### *Hyperglycaemic crisis*

Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are the two most serious acute metabolic complications of diabetes. Although they have important differences both occur because of a lack of insulin effect and are manifestations of the same underlying insulin deficiency [41]. DKA is characterized by uncontrolled hyperglycaemia, metabolic acidosis, and increased total body ketone concentration [42] and although more common in Type 1 diabetes, Type 2 diabetics are at risk of DKA as a result of the stress of trauma, surgery, serious infections, or cardiovascular emergencies [43]. HHS is characterized by

severe hyperglycaemia, hyperosmolality, and dehydration in the absence of significant ketoacidosis [42] and is more likely to occur in Type 2 diabetics because of the presence of some insulin secretion [41]. Both DKA and HHS carry significant likelihood of morbidity and mortality including cerebral oedema, permanent neurological injury, and death [41].

In 2011 approximately 175,000 emergency room visits in the US for patients of all ages had DKA and HHS as the first-listed diagnosis and in 2010 hyperglycaemic crises caused 2,361 deaths among adults aged 20 years or older [4]. The number of hospital discharges with DKA as the first-listed diagnosis increased from approximately 80,000 discharges in 1988 to approximately 140,000 in 2009 [44], and the age-adjusted hospital discharge rate per 10,000 population consistently increased by 43.8% (from 3.2 to 4.6 per 10,000 population) from 1988 to 2009 [45]. The average length of stay (LOS) of hospital discharges with DKA as the first-listed diagnosis decreased from 5.7 to 3.4 days over the same time period [46].

### *Hypertension*

Hypertension is the most common condition seen in primary care settings and is associated with MI, stroke, renal failure, and death if not detected early and treated appropriately [47]. Hypertension is also often found to coexist with T2DM which itself is a risk factor for cardiovascular disease and other conditions such as renal failure. From 2009 to 2012, 71% of US adults aged 18 years or older with diagnosed diabetes (all types) had blood pressure greater than or equal to 140/90 millimeters of mercury (mmHg) or used prescription medications to lower high blood pressure [4]. According to the American Diabetes Association (ADA) [37], people with diabetes and hypertension should be treated to a systolic blood pressure goal of 140 mmHg, though lower systolic targets such as 130 mmHg may be appropriate for certain individuals, and to a diastolic blood pressure of 80 mmHg.

### *Dyslipidemia*

Diabetic dyslipidemia is characterized by elevated triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, and increased numbers of small low-density lipoprotein (LDL) particles [48] which put diabetic individuals at greater risk of cardiovascular disease [37]. From 2009 to 2012, 65% of adults aged 18 years or older with diagnosed diabetes (all types) had blood LDL cholesterol greater than or equal to 100 mg/dl or used cholesterol-lowering medications [4].

### *Cardiovascular disease and stroke*

Cardiovascular disease and stroke are the primary causes of death and disability among people with T2DM (refer to **Chapters 2 and 3** of this thesis for more detailed information on cardiovascular disease, T2DM, and the association of TZD pharmacotherapy with cardiovascular events). Globally, in some populations cardiovascular disease accounts for more than 50% of diabetes-related deaths [2]. It has been estimated that in the US at least 65% of diabetics die from some form of heart disease or stroke, and that adults with diabetes are two to four times more likely to have cardiovascular disease or a stroke than adults without diabetes [49].

From 1997 to 2011 the number of US diabetics (all types) aged 35 years or older with self-reported heart disease or stroke increased from 4.2 million to 7.6 million, and in 2011, 5.0 million reported having coronary heart disease, 3.7 million reported having another heart disease or condition, and 2.1 million reported having had a stroke [50]. In 2010, after adjusting for population age differences, hospitalization rates were 1.8 times higher for MI among US adults aged 20 years or older with diagnosed diabetes than among adults without diagnosed diabetes, and 1.5 times higher for stroke [4]. With respect to mortality, after adjusting for population age

differences cardiovascular disease death rates were approximately 1.7 times higher among US adults aged 18 years or older with diagnosed diabetes than among adults without diagnosed diabetes from 2003 to 2006 [4].

### *Vision-related issues*

Diabetic retinopathy, which is characterised by damage to the retina provoked by microvascular changes resulting from diabetes, can lead to blindness and is the leading cause of vision-loss in young and middle-aged adults [51]. It can be classified into two types [52]:

- non-proliferative: the early state of the disease where the blood vessels in the retina are weakened causing microaneurysms and potential swelling of the macula; and
- proliferative: the more advanced form of the disease where circulatory issues deprive the retina of oxygen leading to the formation of new blood vessels that may leak into the vitreous and cloud vision. Other complications may include detachment of the retina, glaucoma, severe vision loss, and blindness.

Persistently high levels of blood glucose together with high blood pressure and high cholesterol are the main causes of retinopathy [2].

A pooled analysis [53] found that worldwide, approximately 93 million people have diabetic retinopathy, 17 million with the proliferative form, 21 million with diabetic macular oedema, and 28 million with vision-threatening diabetic retinopathy. In the US, from 1997 to 2011 the number of adults with diagnosed diabetes (all types) who reported visual impairment (defined as trouble seeing even with glasses or contact lenses) increased from 2.7 million to 4.0 million [54]. From 2005 to 2008, 4.2 million diabetics (all types) aged 40 years or older (or

28.5% of diabetics) had diagnosed diabetic retinopathy [4]. During this same timeframe 655,000 diabetics (or 4.4% of diabetics) had advanced diabetic retinopathy, including clinically significant macular oedema and proliferative diabetic retinopathy [4].

### *Neurological issues and amputations*

Diabetic peripheral neuropathy (of which there are various forms that may affect different parts of the nervous system and may present with diverse clinical manifestations) is one of the most common microvascular complications of diabetes and is a consequence of exposure to high blood glucose levels over an extended period of time resulting in damage to peripheral nerves [55]. It has been estimated that up to 50% of diabetic peripheral neuropathies may be asymptomatic where patients cannot detect injuries to their feet leading to ulcerations, amputation (greater than 80% of amputations follow a foot ulcer or injury), and significant reduction in quality of life [56-57]. In the US, approximately 60% of non-traumatic lower-limb amputations among people aged 20 years or older occur in people with diagnosed diabetes and in 2010 alone approximately 73,000 non-traumatic lower-limb amputations were performed in diabetic adults [4].

In 2007, there were approximately 113,000 hospital discharges of diabetic patients (all types across all age groups) in the US for ulcers/inflammation/infections and approximately 75,000 hospital discharges for neuropathy [58]. In addition, approximately 84,000 hospital discharges were for peripheral arterial disease [58] a condition caused by plaque build-up in the arteries that can also present symptoms and complications similar to diabetic neuropathies such as foot wounds and amputations [59].



### *Falls and fractures*

Falls and fractures are often the result of the complications of diabetes (e.g. hypo- and hyperglycaemic events, retinopathy, neuropathy) in combination with other comorbidities (e.g. neurological disorders, pharmacological side effects from drugs used in the treatment of other disorders or drugs used in the treatment of T2DM [which were explored in relation to treatment with TZD drugs in **Chapters 2** and **4** of this thesis] ), and/or age-related conditions (e.g. dementia, hearing loss, poor balance) and are especially prevalent in elderly populations [60]. For example, the annual incidence rates of falls in the elderly with diabetes have been estimated at 39% in those over 65 years [61] and 35% in those over 55 years [62]. In addition, other conditions directly related to bone health, fractures, and falls such as osteoporosis and bone loss may also be associated with diabetes (see **Chapter 2** and reviews such as Schwartz and Sellmeyer [63] and Abdulameer et al. [64]).

### *Renal disease*

Diabetes is one of the leading causes of renal disease and nephropathy which is caused by damage to small blood vessels leading to less efficient, or failure of, renal function, and nephropathy is more common in diabetics [2]. In nephropathy high levels of blood glucose cause the kidneys to filter too much blood leading to microalbuminuria early on in the disease and later macroalbuminuria, which may be followed by end-stage renal disease: kidney failure necessitating dialysis and kidney transplant [37]. In 2011, diabetes was listed as the primary cause of kidney failure in 44% of all new cases in the US and 49,677 diabetics across all age groups began treatment for kidney failure due to diabetes [4]. In addition, a total of 228,924

people of all ages with kidney failure due to diabetes were living on chronic dialysis or with a kidney transplant [4].

## **Mortality**

### *Global*

Globally, diabetes and its complications are major causes of early death with cardiovascular disease, as previously mentioned, being a leading cause. Worldwide approximately 5.1 million people between the ages of 20 and 79 years died from diabetes in 2013 accounting for 8.4% of the global all-cause mortality among people in this age group, and 48% of these deaths were in persons under the age of 60 [2]. It should be noted however, that many diabetes-related deaths are underreported.

### *United States*

From 2003 to 2006, rates of death from all causes were approximately 1.5 times higher among US adults aged 18 years or older with a diagnosis of diabetes than among adults without diagnosed diabetes after adjusting for population age differences [4]. In 2010, diabetes (all types) was the seventh leading cause of death in the US based on 69,071 death certificates in which diabetes was listed as the underlying cause of death [4]. In addition, diabetes was mentioned as a cause of death in a total of 234,051 certificates in 2010. Using a modelling approach [65-66] the IDF [2] estimated that in 2013, approximately 192,725 Americans died from diabetes (all types), one of the highest numbers of deaths due to diabetes of any country in the world.

It should be noted when interpreting the above estimates that diabetes is most likely underreported as a cause of death. Some studies have found that approximately 35% to 40% of people with diabetes who died had diabetes listed anywhere on the death certificate and approximately 10% to 15% had it listed as the underlying cause of death [4]. In addition, direct comparisons between CDC estimates (based on number of death-certificates) and modelled IDF estimations (based on WHO life tables for the expected number of deaths, country-specific diabetes prevalence by age and sex, and age and sex-specific relative risks of death for persons with diabetes compared to those without diabetes) are not possible due to the different statistical techniques used.

## **DURATION AND TREATMENT PATTERNS**

### **Duration of diabetes**

In 2011, approximately 61.2% of American adults aged 18 to 79 years with diabetes (all types), or 11.4 million Americans, reported having had diabetes for 10 years or less [67], at least 10 million of which are assumed to have T2DM. Only 6.8% of diabetics reported having diabetes for more than 30 years. From 1997 to 2011, the mean duration increased from 10.8 to 11.4 years, but the median duration did not show a consistent trend during this period [68].

### *Age*

From 1997 to 2011, the median duration of diabetes (all types) for adults aged 18 to 79 years in the US was longest among adults aged 65 to 79 years and shortest among adults aged 18 to 44 years [69]. In 2011, the median duration of diabetes was 5.2 years among adults aged 18 to

44 years, 6.7 years among adults aged 45 to 64 years, and 9.8 years among adults aged 65 to 79 years [69].

### *Sex*

From 1997 to 2011, the median duration of diabetes (all types) among males aged 18 to 79 years in the US showed little or no change [70]. Among US females the median duration of diabetes declined until 2004 and then increased and in general, was higher than in males. In 2011, the median duration was 8.3 years for females and 7.0 years for males [70] which may again be a function of the longer life span of females.

### *Race*

From 1997 to 2011, no consistent trend in the median diabetes duration (all types) was observed for non-Hispanic black adults aged 18 to 79 years in the US [71]. For non-Hispanic white adults the median duration of diabetes decreased from 1997 to 2003 and then increased, and median duration increased from 1997 to 2011 for Hispanic adults. The median duration of diabetes was similar across groups throughout the entire study period and in 2011, the median duration was 8.1 years for non-Hispanic blacks, 7.6 years for non-Hispanic whites, and 7.2 years for Hispanics [71]. It should be noted that this analysis did not include American Indian/Alaska Native or Asian adults presumably because it was survey-based and the sample size of respondents from these races was insufficient for analysis.

## Treatment patterns

T2DM is frequently treated through a combination of medications and lifestyle changes (see the *Treatment Guidelines and Standards* and *T2DM Drug Classes* sections of this annex).

With respect to pharmacotherapy, from 2010 to 2012 the number of US adults using diabetes medication (for all types of diabetes) varied between those using insulin alone, those using insulin in combination with an oral antihyperglycaemic agent (OHA), and those using only oral medication (**Table 3**). However, the majority of diabetics were treated with OHAs which is a reflection of the high proportion of Type 2 diabetics in the population. Only 14% of the population was not using either insulin or an OHA [4].

An analysis of the use of antidiabetic drugs in the US from nationally projected data on prescriptions for adults dispensed from retail pharmacies [72] found that in 2012, 154.5 million prescriptions were dispensed, 78.4% of which were for non-insulin medications. Single-ingredient metformin was used by 72.3% of non-insulin drug users and more than 25% of the remaining non-insulin prescriptions were for sulphonylureas (nearly all were for glipizide, glimepiride, or glyburide). Patients undergoing concomitant therapy were most likely to be using metformin in conjunction with one or more drugs from another class (**Table 4**) with the highest percentages for metformin in combination with sulphonylureas (61%), TZDs (66.6% - mostly pioglitazone), and dipeptidyl peptidase 4 (DPP-4) inhibitors (65.1%).

**Table 3.** Treatment of diabetes (all types) among people aged 18 years or older with diagnosed diabetes in the US from 2010 to 2012 [1]<sup>1</sup>.

| <b>Treatment</b>                   | <b>Number of adults using diabetes medication* (million)</b> | <b>Percentage using diabetes medication (unadjusted)</b> |
|------------------------------------|--------------------------------------------------------------|----------------------------------------------------------|
| <b>Insulin only</b>                | 2.9                                                          | 14.0                                                     |
| <b>Insulin and oral medication</b> | 3.1                                                          | 14.7                                                     |
| <b>Oral medication only</b>        | 11.9                                                         | 59.9                                                     |
| <b>No pharmacotherapy</b>          | 3.0                                                          | 14.4                                                     |

<sup>1</sup> Adapted from CDC [4]. Based on 2010–2012 National Health Interview Survey data.

\*Does not add to the total number of adults with diagnosed diabetes because of the different data sources and methods used to obtain the estimates.

**Table 4.** Concomitant therapy among the most common antidiabetic drug classes used in the US in 2012<sup>1</sup>.

| <b>Drug Class Concomitant Use with Other Therapies (%)<sup>2</sup></b> |                      |                   |                       |                         |             |                      |                                          |                                          |
|------------------------------------------------------------------------|----------------------|-------------------|-----------------------|-------------------------|-------------|----------------------|------------------------------------------|------------------------------------------|
|                                                                        | <b>No other drug</b> | <b>Biguanides</b> | <b>Sulphonylureas</b> | <b>DPP-4 inhibitors</b> | <b>TZDs</b> | <b>GLP-1 analogs</b> | <b>Insulin, analog human Long-acting</b> | <b>Insulin, analog human Fast-acting</b> |
| <b>Biguanides</b>                                                      | 44.9                 | -                 | 22.1                  | 22.0                    | 8.0         | 4.0                  | 9.7                                      | 2.4                                      |
| <b>Sulphonylureas</b>                                                  | 28.0                 | 61.0              | -                     | 15.4                    | 9.4         | 3.7                  | 10.3                                     | 1.9                                      |
| <b>DPP-4 inhibitors</b>                                                | 25.5                 | 65.1              | 16.4                  | -                       | 5.3         | 1.3                  | 8.7                                      | 2.7                                      |
| <b>TZDs</b>                                                            | 19.4                 | 66.6              | 28.5                  | 14.9                    | -           | 5.6                  | 7.9                                      | <1.0                                     |
| <b>GLP-1 analogs</b>                                                   | 37.3                 | 51.9              | 17.3                  | 5.5                     | 8.7         | -                    | 18.7                                     | 3.2                                      |
| <b>Insulin, analog human</b>                                           |                      |                   |                       |                         |             |                      |                                          |                                          |
| <b>Long-acting</b>                                                     | 32.7                 | 31.7              | 12.3                  | 9.7                     | 3.1         | 4.8                  | -                                        | 31.4                                     |
| <b>Fast-acting</b>                                                     | 25.7                 | 16.1              | 4.6                   | 6.2                     | < 1.0       | 1.7                  | 64.1                                     | -                                        |

<sup>1</sup>Adapted from Hampp et al [72]. Source data from Encuity Research Answer Generator.

<sup>2</sup>Row totals may exceed 100% as a result of patients using more than two antidiabetic drugs.

DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; TZD: thiazolidinediones

## INTERACTIONS WITH THE HEALTH CARE SYSTEM AND COSTS

### Interactions with the health care system

#### *Emergency department visits*

In the US the number of Emergency Department (ED) visits with diabetes (all types) as an any-listed diagnosis increased from 9,464,000 visits in 2006 to 11,492,000 in 2009 [73]. In adults aged 18 years or older diabetes mellitus with complications was the most common first-listed diagnosis followed by chest pain and heart failure (**Table 5**) [74]. From 2006 to 2009, visit rates were highest among persons aged 75 years or older and lowest among those aged 45-64 years [75], though there were no obvious differences between sexes during this time period [76]. In 2009 however, age-adjusted ED visit rates among adult diabetics (all types) were higher among females (66.9 per 100 diabetic adults) than males (47.0 per 100 diabetic adults) [76]. The age-adjusted ED visit rates among adults aged 18 years or older increased from 41.0 per 1,000 adults in 2006, to 47.4 per 1,000 adults in 2009 [77].

#### *Hospitalization*

In 2010, among hospital discharges with diabetes as an any-listed diagnosis in US adults aged 18 years or older, the top five categories of first-listed diagnoses were circulatory diseases (24.1%), diabetes (11%), respiratory diseases (10.1%), diseases of the digestive system (9.8%), and diseases of the genitourinary system (7%) [78]. Overall, the age-adjusted hospital discharge rates for diabetes as an any-listed diagnosis decreased from 379.4 per 1,000 diabetic population in 1988 to 223.7 in 2009 [79].



**Table 5.** Distribution of first-listed diagnoses among ED visits with diabetes as any-listed diagnosis in adults aged 18 years or older in the US in 2009.<sup>1</sup>

| <b>Diagnosis</b>                                                                      | <b>Number (thousands)</b> | <b>Percent</b> |
|---------------------------------------------------------------------------------------|---------------------------|----------------|
| <b>Diabetes mellitus with complications</b>                                           | 733.6                     | 6.4            |
| <b>Nonspecific chest pain</b>                                                         | 617.1                     | 5.4            |
| <b>Congestive heart failure; non-hypertensive</b>                                     | 396.4                     | 3.5            |
| <b>Abdominal pain</b>                                                                 | 333.0                     | 2.9            |
| <b>Urinary tract infections</b>                                                       | 317.9                     | 2.8            |
| <b>Skin and subcutaneous tissue infections</b>                                        | 312.5                     | 2.7            |
| <b>Chronic obstructive pulmonary disease and bronchiectasis</b>                       | 290.0                     | 2.5            |
| <b>Pneumonia (except that caused by tuberculosis or sexually transmitted disease)</b> | 281.0                     | 2.5            |
| <b>Superficial injury—contusion</b>                                                   | 265.1                     | 2.3            |
| <b>Diabetes mellitus without complication</b>                                         | 256.9                     | 2.3            |
| <b>Other</b>                                                                          | 7,588.0                   | 66.6           |
| <b>TOTAL</b>                                                                          | <b>11,391.6</b>           | <b>100.0</b>   |

<sup>1</sup>Adapted from CDC [74].

From 1988 to 2009, the number of hospital discharges in the US with diabetes as the first-listed diagnosis increased from 454,000 to 688,000 [80] but the average LOS decreased from 8.2 days to 5.0 days [81]. Throughout the period discharge rates (per 1,000 diabetic population) were higher among people aged 44 years or younger and those aged 75 years or older than other age groups [82], but age-adjusted rates were similar among males and females [83]. Age-adjusted rates were however, higher among blacks than whites where in 2009 the age-adjusted hospital discharge rate was 1.8 times higher among blacks (59.4 versus. 32.7 per 1,000 diabetic population, respectively) [84]. It should be noted that discharge rates for race in this analysis are most likely underestimated since a substantial proportion of discharges were missing racial classification and missing values were not imputed. Overall, the age-adjusted hospital discharge rates for diabetes as a first-listed diagnosis for the entire diabetic population decreased between 1988 and 2009 and was 46.7 per 1,000 diabetic population in 2009 [85].

## **Costs and expenditures**

### *Global*

The costs associated with diabetes to individuals, families, governments, and societies are numerous and can be a considerable burden. These costs include increased health care costs, loss of productivity, and disability. Worldwide health spending on diabetes, including costs to health care systems, to diabetics, and to their families, accounted for 10.8% of total health expenditure in 2013 [2]. Monetized (in US dollars [USD]), the global health spending to treat diabetes and manage complications totalled at least \$548 billion [2]. This number is projected to exceed \$627 billion by 2035. In 2013 health spending for diabetes was not evenly distributed across age groups. It is estimated that 76% of global health expenditure on diabetes was for people between

the ages of 50 and 79 years and that this number will continue to grow with the aging global population.

### *United States*

A recent study on the economic burden of diagnosed and undiagnosed diabetes, gestational diabetes, and prediabetes in the US [86] found that the combined economic burden for all ages exceeded \$322 billion (USD) in 2012; \$244 billion of which was related to excess medical costs and \$78 billion as a result of reduced productivity. This represents an estimated economic burden exceeding \$1,000 for each American in 2012 and is 48% higher than in 2007. The burden per case averaged \$10,970 for diagnosed diabetes and \$4,030 for undiagnosed diabetes [86].

Similar costs were estimated by the ADA [87] who found that the total direct and indirect costs of diagnosed diabetes (but not prediabetes) in 2012 totalled \$245 billion. Direct medical costs represented \$176 billion of this figure with the largest components related to hospital inpatient care (43%), prescription medications to treat complications (18%), antidiabetic medications and diabetes supplies (12%), physician office visits (9%), and nursing facility stays (8%). The medical burden per person with diabetes averaged approximately \$13,700 per year, of which approximately \$7,900 was attributed to diabetes [87]. Indirect costs represented \$69 billion of the \$245 billion total and included absenteeism (7%) and reduced productivity (30%) for those who were employed, reduced productivity for those not in the labour force (4%), inability to work as a result of disease-related disability (32%), and lost productive capacity due to early mortality (27%) [87]. A large proportion of this burden can again be attributed to the ageing US population as 39% of the population was over 50 years of age in 2013 [36]. However,

even after adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than people without diabetes in 2012 [4].

## **TREATMENT GUIDELINES AND STANDARDS**

The following treatment guidelines and standards summarize, for the most part, those recommended by the ADA for 2014 [37]. References are provided where the ADA has adopted the recommendations, guidelines, or standards of other organizations or committees, or where additional information has been included.

### **Classification**

Diabetes may be classified into one of four treatment/type categories:

- **Type 1:**  $\beta$ -cell destruction leading to insulin dependence (in most cases);
- **Type 2:** a progressive insulin secretion defect combined with insulin resistance;
- **Other:** induced by drugs or chemicals or resulting from other causes such as genetic defects or diseases of the exocrine pancreas; or
- **Gestational:** a diagnosis of diabetes during pregnancy that is not clearly overt diabetes.

Although the onset of Type 1 is usually during childhood versus during adulthood for T2DM, the ADA has noted that some patients cannot be clearly classified as Type 1 or Type 2 diabetic since clinical presentation and disease progression can vary considerably in both types.

## Diagnosis

The diagnosis of diabetes is usually based on plasma glucose criteria, either fasting plasma glucose (FPG) or 2-h plasma glucose (2-h PG) after a 75-g oral glucose tolerance test (OGTT) [88], though a third more recent option is measuring glycated hemoglobin (A1C) level [89]. It should be noted that one test may be used as an alternative to another in the following list however, for each, repeated testing should occur in the absence of unequivocal hyperglycaemia to confirm the result.

The criteria for the diagnosis of diabetes are:

- FPG  $\geq$  126 mg/dL (7.0 mmol/L)
  - Fasting is defined as no caloric intake for at least 8 h;

or,

- 2-h PG  $\geq$  200 mg/dL (11.1 mmol/L) during an OGTT
  - This test should be performed as described by the WHO [90] using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water;

or,

- A1C  $\geq$  6.5%
  - This test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) reference assay;

or,

- a random PG  $\geq 200$  mg/dL (11.1 mmol/L)
  - In situations where a patient exhibits classic symptoms of hyperglycaemia or hyperglycaemic crisis.

Testing is recommended for all adults who are overweight (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup> or at a lower BMI for some at-risk ethnic groups - see below) and have additional risk factors such as: physical inactivity; a first-degree relative with diabetes; are of a high-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander); are a woman who delivered a baby weighing greater than 9 lbs or were diagnosed with gestational diabetes; hypertension ( $\geq 140/90$  mmHg or on therapy for hypertension); HDL cholesterol level  $< 35$  mg/dL (0.90 mmol/L) and/or a triglyceride level  $> 250$  mg/dL (2.82 mmol/L); are a woman with polycystic ovarian syndrome; A1C  $\geq 5.7\%$ , impaired glucose tolerance, or impaired fasting glucose on previous testing; other clinical conditions associated with insulin resistance (e.g. severe obesity); and/or, a history of cardiovascular disease.

In the absence of the above criteria the ADA recommends that testing for diabetes should begin at 45 years of age. If results are normal, testing should be repeated at least every 3 years with consideration of more frequent testing depending on initial results (e.g. those with prediabetes should be tested yearly) and risk status.

## **Glycaemic control**

The primary goal of both the treatment and management of T2DM is to obtain and maintain glycaemic control. The two primary techniques for assessing glycaemic control are patient self-monitoring of blood glucose or interstitial glucose, and monitoring of A1C by physicians. With respect to A1C levels (which demonstrate a correlation with mean plasma

glucose levels) [91] the ADA [37] recommends that a reasonable goal for many non-pregnant adults is less than 7%. This has been shown to reduce microvascular complications and if implemented soon enough, long-term reductions in macrovascular disease. More stringent goals (< 6.5%) may be recommended for patients with a shorter duration of diabetes, long life expectancy, and no significant complications such as cardiovascular disease, and less stringent goals (< 8%) may be recommended for patients with a history of severe hypoglycaemia, a limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions with longstanding diabetes.

### **Lifestyle changes and education**

Although glycaemic control is a major focus in the management of patients with T2DM, both the ADA and European Association for the Study of Diabetes (EASD) recommend [92] that this should always be in the context of a comprehensive cardiovascular risk factor reduction program (due to associations between T2DM and cardiovascular disease) that includes smoking cessation, blood pressure control, lipid management, antiplatelet therapy (in some circumstances), and the adoption of healthy lifestyle habits.

Lifestyle changes, such as those focusing on physical activity and nutrition [93-94], and education are critical aspects of effective management of T2DM. It is recommended that all patients receive standardized general diabetes education with a specific focus on dietary interventions and the importance of increasing physical activity [95]. Modest weight loss of 5% to 10% has been demonstrated to be an achievable and realistic goal for preventing T2DM in susceptible individuals and for improving glycaemic and metabolic control in Type 2 diabetics [96]. The ADA recommends [37] a target weight loss of 7% of bodyweight along with increasing

physical activity to at least 150 minutes/week of moderate activity (e.g. walking) to prevent, delay, and manage T2DM. The ADA also recommends [37] that diabetics monitor carbohydrate intake and quality (e.g. carbohydrate intake from vegetables, fruits, whole grains, legumes, and dairy products is advised over intake from other carbohydrate sources, especially those that contain added fats, sugars, or sodium), substitute low-glycaemic load foods for higher-glycaemic load foods (as this may modestly improve glycaemic control), moderate alcohol intake if they choose to drink alcohol (alcohol consumption may place people with diabetes at increased risk for delayed hypoglycaemia, especially for diabetics taking insulin or insulin secretagogues), and follow recommendations for the general population for fat intake and sodium intake (< 2,300 mg/day) unless comorbidities such as cardiovascular disease warrant further reductions or dietary changes.

It should be noted that highly motivated patients with A1C levels already near target (e.g. < 7.5%) at diagnosis may be given the opportunity to engage in the lifestyle changes described above for a period of 3 to 6 months before initiating pharmacotherapy (which in most cases begins with metformin, see below) [95].

## **Pharmacotherapy**

Several pharmacotherapy options are available to treat T2DM (see the *T2DM Drug Classes* section below and the tables referred to therein for a brief description of each drug class and a list of drugs of each class found in the Cerner Health Facts<sup>®</sup> dataset) and treatment regimes may include monotherapy, dual combination therapy, triple combination therapy, or combination injectable therapy (**Figure 5**). To select the most appropriate treatment for a patient, the ADA [37] recommends that a patient-centered approach be used to guide choice of drug(s) taking into



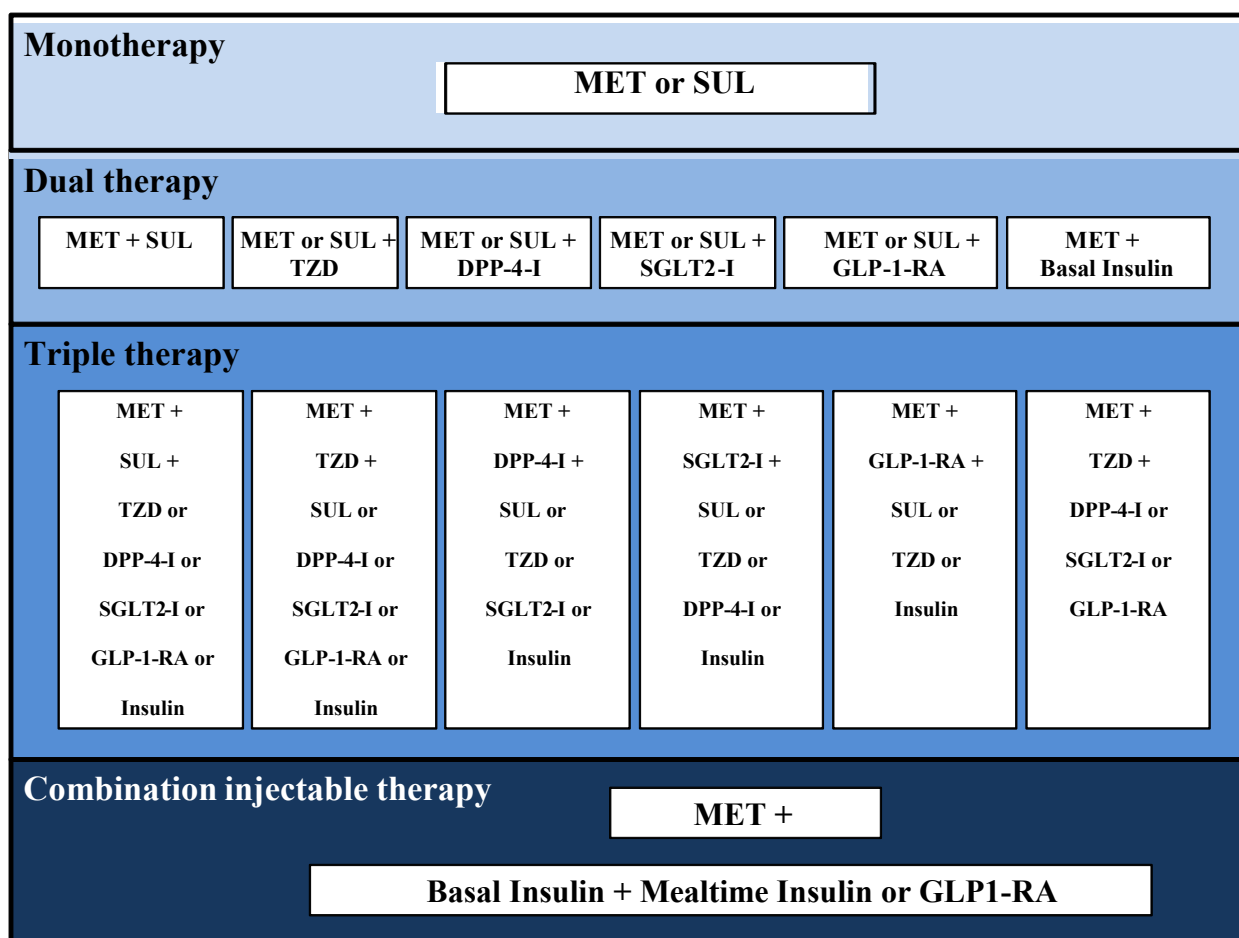


**Figure 5.** ADA and EASD recommendations for pharmacotherapy and treatment sequence for T2DM adapted to recognize that sulphonylureas may also be considered a first line treatment, especially in patients who do not tolerate metformin. Potential sequences progress vertically (but may also move horizontally depending on patient circumstances) and move from monotherapy to dual monotherapy where metformin is combined with another antidiabetic agent or basal insulin, to triple therapy where metformin is combined with two antihyperglycaemics or insulin, to combination injectable therapy with insulin. Adapted from Inzucchi et al. [92] DPP-4-I: dipeptidyl peptidase-4 inhibitor; GPL-1-RA: glucagon-like peptide-1 receptor agonists; MET: metformin; SGLT2-I: sodium-glucose co-transporter-2; SUL: sulphonylurea; TZD: thiazolidinediones.

consideration efficacy, cost, side effect profile, effects on weight, patient comorbidities, hypoglycaemia risk, and patient preferences.

### *Initial drug therapy*

According to ADA guidelines [37, 95] metformin monotherapy is the preferred initial pharmacological treatment for T2DM (**Figure 5 - Monotherapy**) so long as it isn't contraindicated or not tolerated by the patient, because of its low cost, proven safety record, lack of weight gain, and possible cardiovascular benefits [92]. Though sulphonylureas are also recognized as a first line treatment, especially in cases where patients are intolerant to metformin (e.g. patients with liver or kidney disease) and it is estimated that approximately 20-30% of diabetic patients will begin treatment on sulphonylurea monotherapy. In some cases, insulin may instead be recommended as an initial treatment for newly diagnosed patients who are markedly symptomatic and/or have elevated blood glucose or A1C levels, with or without additional drug therapy. If noninsulin monotherapy (e.g. metformin described above) at the maximum tolerated dose does not achieve or maintain glycaemic targets over 3 months, a second oral agent (see **Figure 5 - Dual therapy and the T2DM Drug Classes** section below), a glucagon-like peptide 1 (GLP-1) receptor agonist, or insulin may be added.

### *Combination therapy*

Initial combination therapy with metformin or sulphonylurea plus a second agent (**Figure 5 - Dual therapy**) may allow patients to achieve A1C targets more quickly than sequential therapy (e.g. moving from metformin to another drug) and this approach may be considered, and is frequently used for diabetics with baseline A1C levels well above target ( $\geq 9\%$ ) who are

unlikely to attain targets using monotherapy alone [92]. In addition, a third agent (**Figure 5 - Triple therapy**) such as a sodium-glucose co-transporter-2 (SGLT2) inhibitor (approved for use in monotherapy but frequently used with metformin or other drugs such as sulphonylureas as a second or third-line agent) may be added [92].

### *Injectable combination therapy*

Glycaemic control may remain poor for some patients even when using three antihyperglycaemic drugs in combination, especially for some long-standing diabetics who demonstrate diminished insulin secretion capacity [92]. It should be noted as well that due to the progressive nature of T2DM, insulin therapy is eventually required for many patients [37]. The ADA and EASD [92] recommend that basal insulin therapy should be considered for patients not achieving A1C targets, despite extensive combination therapy.

The 2012 ADA and EASD position statement [95] recommended that after basal insulin (usually in combination with metformin and for some patients an additional agent), an alternative may be simpler but less flexible premixed formulations of intermediate and short/rapid-acting insulins in fixed ratios [97]. Updated guidelines [92] however recognize the effectiveness of combining GLP-1 receptor agonists (both shorter-acting and weekly formulations) with basal insulin over the addition of prandial insulin [98-100]. The ADA and EASD also note in the updated guidelines [37] that for patients with uncontrolled diabetes who are already using basal insulin in combination with one or more OHAs, that the addition of a GLP-1 receptor agonist or mealtime insulin (**Figure 5 - Combination injectable therapy**) could be the logical progression of the treatment regimen. However, they also note that such combination injection regimes may

come with significant expense and complexity for patients and that appropriate patient support and education is required.

## T2DM DRUG CLASSES

### Insulin

In T2DM pancreatic  $\beta$ -cell dysfunction is progressive and on average 40-80% of patients with T2DM will require insulin within 10 years of diagnosis [101-102]. Insulin is primarily available in injectable form (by syringe, pen, or pump) though new forms are being developed. A previously marketed inhalable insulin, Exubera, was approved for use in the US in January of 2006 but was withdrawn from the market by the manufacturer (Pfizer) in 2007 due to poor sales and lung cancer concerns [103]. More recently, the US Food and Drug Administration (US FDA) [104] approved a new form of rapid-acting inhalation insulin (Afrezza approved in June 2014) but is requiring further post-market studies due to continuing concerns with respiratory side effects including lung cancer.

Several types of insulin are available (see **Table 6**) based on different characteristics of action [105]:

- **Regular or Short-acting:** onset within 30 minutes, peaktime from 2 to 3 hours after injection, and duration approximately 3 to 6 hours;
- **Rapid-acting:** onset is approximately 15 minutes, peaktime after approximately 1 hour, and duration approximately 2 to 4 hours;

**Table 6.** Insulin prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Insulin Type            | Generic Name               | Brand Name <sup>1</sup>       |
|-------------------------|----------------------------|-------------------------------|
| Regular or short-acting | Insulin - regular          | Velosulin*                    |
|                         |                            | Insulin Purified Regular Pork |
| Rapid-acting            | Insulin aspart             | Novolog                       |
|                         |                            | NovoRapid                     |
|                         | Insulin lispro             | Humalog                       |
|                         |                            | Lispro PRC                    |
| Intermediate-acting     | Isophane or insulin zinc   | Apidra                        |
|                         |                            | Humulin                       |
|                         |                            | Insulin Pork Mix              |
|                         | Neutral protamine hagedorn | Lente                         |
|                         |                            | Novolin                       |
|                         |                            | Novolinset                    |
|                         |                            | Iletin                        |
|                         |                            | Insulin NPH Pork              |
| Long-acting             | Insulin glargine           | Lantus                        |
|                         | Insulin detemir            | Levemir                       |
| Inhalation              | Insulin inhalation         | Exubera**                     |

<sup>1</sup> Insulin is in injectable form unless otherwise indicated.

\*No longer available in the US.

\*\*Withdrawn from the US market in 2007 due to poor sales.

- **Intermediate-acting:** onset approximately 2 to 4 hours after injection, peaktime 4 to 12 hours later, and duration approximately 12 to 18 hours; and
- **Long-acting:** onset several hours after injection, lowers glucose levels consistently over a 24-hour period.

Normally a “basal” insulin is used for initial therapy (either intermediate-acting, long-acting, or insulin detemir formulations) to provide uniform insulin coverage day and night, followed by prandial insulin therapy with shorter-acting insulin before meals (usually rapid insulin analogs if glycaemic targets cannot be achieved) [95]. Insulin may also be used in conjunction with other hypoglycaemic agent (**Figure 5**).

#### *Mechanism of action*

Insulin acts through the activation of insulin receptors to increase glucose uptake and decrease hepatic glucose production [106-107].

#### *Advantages*

Insulins have been shown to be universally effective with a theoretically unlimited efficacy [95]. Some studies, such as the United Kingdom Prospective Diabetes Study (UKPDS), have shown an association between insulin use and decreased microvascular risk [101, 108-111], as well as macrovascular disease during long-term follow-up [111-112].

### *Disadvantages*

Disadvantages to insulin use include an increased risk of hypoglycaemia and weight gain (though the risks are lessened with basal insulin analogs compared to neutral protamine hagedorn [NPH] insulin and pre-mixed insulin [113]), potential mitogenic effects [114], and the requirement for injections which require training and may be associated with stigma for some patients [95]. The cost of insulin depends on the type, for example, analogs are more expensive than human insulins, and the dosage.

### **Biguanides**

As previously mentioned, metformin monotherapy is a preferred initial pharmacological treatment for T2DM. Metformin (**Table 7**) is currently the only marketed biguanide class antidiabetic drug (phenformin was withdrawn from the US market for lactic acidosis in 1978 [115], another drug in the class buformin was never marketed in the US) and is available in oral tablet form either as a monotherapy or in a fixed-dose tablet with other antidiabetic medications (e.g. sulphonylureas, TZDs, DPP-4 inhibitors, meglitinides). Metformin may also be used with other hypoglycaemic agents and insulin (**Figure 5**).

### *Mechanism of action*

Although there have been many studies investigating the mechanism of action of metformin it is still not completely understood. It is thought that metformin activates adenosine monophosphate (AMP)-activated protein kinase (AMPK) which is a master regulator of cellular

**Table 7.** Biguanide class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                          | Generic Name                                         | Brand Name <sup>1</sup>                               |
|--------------------------------------------------|------------------------------------------------------|-------------------------------------------------------|
| <b>Biguanide monotherapy</b>                     | Metformin hydrochloride                              | Metformin hydrochloride*                              |
|                                                  |                                                      | Apo metformin                                         |
|                                                  |                                                      | Dom metformin                                         |
|                                                  |                                                      | GMD metformin                                         |
|                                                  |                                                      | Gen metformin                                         |
|                                                  |                                                      | Med metformin                                         |
|                                                  |                                                      | Novo metformin                                        |
|                                                  |                                                      | Nu metformin                                          |
|                                                  |                                                      | PMS metformin                                         |
|                                                  |                                                      | Phl metformin                                         |
|                                                  |                                                      | Ratio metformin                                       |
|                                                  |                                                      | Rho metformin                                         |
|                                                  |                                                      | Rhoxal metformin                                      |
|                                                  |                                                      | Riva metformin                                        |
|                                                  |                                                      | Riomet                                                |
|                                                  |                                                      | Fortamet                                              |
|                                                  |                                                      | Glucophage                                            |
|                                                  |                                                      | Glumetza                                              |
|                                                  |                                                      | Glycon                                                |
| <b>Biguanide combination therapy<sup>2</sup></b> | Metformin hydrochloridehydrochloride - Glipizide     | Glipizide - metformin hydrochloride*                  |
|                                                  |                                                      | Metaglip                                              |
|                                                  | Metformin hydrochloride - Glyburide                  | Metformin hydrochloride - Glyburide*                  |
|                                                  |                                                      | Glucovance                                            |
|                                                  | Metformin hydrochloride - Pioglitazone hydrochloride | Metformin hydrochloride - Pioglitazone hydrochloride* |
|                                                  |                                                      | Actoplus Met                                          |
|                                                  |                                                      | Actoplus Met XR                                       |
|                                                  | Metformin hydrochloride - Rosiglitazone maleate      | Metformin hydrochloride - Rosiglitazone maleate*      |
|                                                  |                                                      | Avandamet                                             |
|                                                  | Metformin hydrochloride - Linagliptin                | Jentadueto                                            |
|                                                  | Metformin hydrochloride - Repaglinide                | Prandimet                                             |
|                                                  | Metformin hydrochloride - Saxagliptin hydrochloride  | Kombiglyze XR                                         |
|                                                  | Metformin hydrochloride - Sitagliptin phosphate      | Janumet                                               |
|                                                  |                                                      | Janumet XR                                            |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup>Both drugs in combination in one oral tablet.

\*Marketed generic version of the drug.



energy homeostasis, through decreases in hepatic energy [116]. An upstream AMPK kinase, LKB1, also leads to reduction of gluconeogenic gene transcription [117-119] potentially due to sensitization to insulin through AMPK-mediated decreases in hepatic lipid content [120-121]. In addition, metformin has been shown to non-competitively inhibit the enzyme mitochondrial glycerophosphate dehydrogenase which results in an altered hepatocellular redox state, reduced conversion of lactate and glycerol to glucose, and decreased hepatic gluconeogenesis [122].

### *Advantages*

Metformin is considered to be one of the most effective drugs for treating T2DM because it has been used extensively and has been shown to reduce hepatic gluconeogenesis without increasing insulin secretion, causing weight gain, or posing a risk of hypoglycaemia [95, 123-124]. Some studies, such as the UKPDS [111, 125], have also shown associations between metformin and decreases in cardiovascular disease events such as MI. The cost associated with metformin prescription is also low compared to other hypoglycaemic agents [126].

### *Disadvantages*

Disadvantages of metformin include gastrointestinal side effects such as diarrhea and abdominal cramping [127], risk of lactic acidosis especially in patients with impaired kidney function (though this is rare for metformin compared to other biguanides such as phenformin) [128-129], and vitamin B12 deficiency [130].

## Sulphonylureas

The insulin secretagogue sulphonylureas were the first OHAs introduced in the US for the treatment of T2DM [131]. The first-generation drugs in this class were introduced in the 1950s but are now rarely used [132] (chlorpropamide was however used in the UKPDS [112]) with second- and third-generation drugs (**Table 8**) having largely replaced them because of greater effectiveness and more favourable safety profiles [132-135]. Sulphonylureas may be used in monotherapy as an oral tablet, or in conjunction with other OHAs (e.g. as an add-on or in a combination tablet with metformin [**Table 8**]), GLP-1 receptor agonists, or insulin (**Figure 5**)

### *Mechanism of action*

Secretagogue drugs such as sulphonylureas bind to sulphonylurea receptors to close adenosine triphosphate (ATP)-dependent potassium ( $K_{ATP}$ ) channels on  $\beta$ -cell plasma membranes and stimulate insulin secretion [136].

### *Advantages*

One main advantage to sulphonylurea class drugs is that they have been used extensively for many years and are therefore well-studied and have predictable effects [95]. In addition, they have a low cost for patients [126] and have been demonstrated to decrease microvascular risk in some large-scale studies such as the UKPDS [112].

**Table 8.** Sulphonylurea class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                        | Generation | Generic Name                             | Brand Name <sup>1</sup>                   |
|------------------------------------------------|------------|------------------------------------------|-------------------------------------------|
| Sulphonylurea monotherapy                      | First      | Acetohexamide                            | Acetohexamide*                            |
|                                                |            |                                          | Dymelor                                   |
|                                                |            | Chlorpropamide                           | Chlorpropamide*                           |
|                                                |            |                                          | Diabinese                                 |
|                                                |            |                                          | Novo-Propamide                            |
|                                                |            | Tolbutamide                              | Tolbutamide*                              |
|                                                |            |                                          | Apo-Tolbutamide                           |
|                                                |            |                                          | Novo-Butamide                             |
|                                                |            |                                          | Orinase                                   |
|                                                |            |                                          | Tol-Tab                                   |
|                                                |            | Tolazamide                               | Tolazamide*                               |
|                                                |            |                                          | Tolinase                                  |
|                                                | Second     | Glipizide                                | Glipizide*                                |
|                                                |            |                                          | Glucotrol                                 |
|                                                |            | Gliclazide                               | Gliclazide*                               |
|                                                |            |                                          | Diamicon                                  |
|                                                |            | Glyburide                                | Glyburide*                                |
|                                                |            |                                          | Glyburide (micronized)                    |
|                                                |            |                                          | Diabeta                                   |
|                                                |            |                                          | Euglucon                                  |
|                                                |            |                                          | Gen Glybe                                 |
|                                                |            |                                          | Glycron                                   |
|                                                |            |                                          | Glynase                                   |
|                                                |            |                                          | Med Glybe                                 |
|                                                |            |                                          | Micronase                                 |
|                                                |            | Glimepiride                              | Glimepiride*                              |
|                                                |            |                                          | Amaryl                                    |
| Sulphonylurea combination therapy <sup>2</sup> |            | Glipizide - metformin hydrochloride      | Glipizide - metformin hydrochloride*      |
|                                                |            |                                          | Metaglip                                  |
|                                                |            | Glyburide - metformin hydrochloride      | Glyburide - metformin hydrochloride*      |
|                                                |            |                                          | Glucovance                                |
|                                                |            | Glimepiride - pioglitazone hydrochloride | Glimepiride - pioglitazone hydrochloride* |
|                                                |            |                                          | Duetact                                   |
|                                                |            | Glimepiride - rosiglitazone maleate      | Avandaryl                                 |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup>Both drugs in combination in one oral tablet.

\*Marketed generic version of the drug.

### *Disadvantages*

Sulphonylureas may cause hypoglycaemia, though the risk is greater for the first-generation sulphonylureas than the newer generation drugs [134]. They have also been associated with weight gain that is more pronounced with second-generation sulphonylureas than with metformin, but less pronounced compared with TZDs [137]. It has also been shown that sulphonylureas may blunt myocardial ischemic preconditioning [137-139] and may elevate cardiovascular risk [140]. Sulphonylureas have been associated with low durability compared to other hypoglycaemic agents such as rosiglitazone and metformin [141].

### **Thiazolidinediones**

TZDs, which have been covered in-depth in this thesis, are a class of OHAs used alone or in combination with other OHAs such as metformin or sulphonylureas (glimepiride) in a combination tablet (**Table 9**) or in conjunction with other drugs such as GLP-1 receptor agonists, or insulin (**Figure 5**). First marketed in the late 1990s this drug class was praised for delivering glycaemic control and physiological effects comparable to, and in some cases, better than, other established first-line treatments such as metformin and second-line treatments such as sulphonylureas, but has been fraught by associations with hepatotoxicity (troglitazone), adverse cardiovascular effects (rosiglitazone), bone fractures (pioglitazone), and bladder cancer (pioglitazone) (see **Chapter 2** and references therein).

**Table 9.** TZD class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                    | Generic Name                                         | Brand Name <sup>1</sup>                              |
|--------------------------------------------|------------------------------------------------------|------------------------------------------------------|
| <b>TZD monotherapy</b>                     | Rosiglitazone                                        | Avandia                                              |
|                                            | Pioglitazone                                         | Pioglitazone hydrochloride*                          |
|                                            |                                                      | Actos                                                |
|                                            | Troglitazone                                         | Rezulin                                              |
| <b>TZD combination therapy<sup>2</sup></b> | Rosiglitazone maleate - Glimepiride                  | Avandaryl                                            |
|                                            | Rosiglitazone maleate - Metformin hydrochloride      | Rosiglitazone maleate - Metformin hydrochloride*     |
|                                            |                                                      | Avandamet                                            |
|                                            | Pioglitazone hydrochloride - Glimepiride             | Pioglitazone hydrochloride - Glimepiride             |
|                                            |                                                      | Duetact                                              |
|                                            | Pioglitazone hydrochloride - Metformin hydrochloride | Pioglitazone hydrochloride - metformin hydrochloride |
|                                            |                                                      | Actoplus Met                                         |
|                                            |                                                      | Actoplus Met XR                                      |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup>Both drugs in combination in one oral tablet.

\*Marketed generic version of the drug.

TZD: thiazolidinedione.

### *Mechanism of action*

TZDs are ligands of PPAR $\gamma$  and ligand-binding results in the activation of pathways responsible for glycaemic control and lipid homeostasis [142-144]. TZDs have also been shown to help preserve  $\beta$ -cell function and to confer other effects through a variety of other mechanisms (e.g. binding to the  $\alpha$  subtype PPAR in addition to PPAR $\gamma$ ) such as reducing inflammation [95, 145] (refer to **Chapter 2** for more detail).

### *Advantages*

Advantages of TZDs include effectiveness, a lack of hypoglycaemia, increases in HDL cholesterol levels, lowered triglyceride levels (pioglitazone), potential positive cardiovascular effects (pioglitazone), and potential uses in the treatment of cancer and other diseases and conditions such as polycystic ovarian syndrome and Cushing's disease (see **Chapter 2** and references therein for an overview of the positive effects of TZD class drugs).

### *Disadvantages*

TZDs, and especially rosiglitazone, remain controversial due to their association with several adverse effects. Well known side-effects include weight gain and oedema for all TZDs and hepatotoxicity associated with early TZD drugs (troglitazone was removed from the US market in 2000 for hepatotoxicity). In addition there are potential associations with heart failure and MI (rosiglitazone), increases in LDL cholesterol levels (rosiglitazone), bone fractures (pioglitazone), and bladder cancer (pioglitazone) (see **Chapter 2** and references therein for a detailed overview of adverse effects of TZD class drugs). TZDs also have a higher cost for patients than other OHAs such as metformin or sulphonylureas [126].

## DPP-4 inhibitors

DPP-4 inhibitors are a relatively new class of antidiabetic drugs with the first agent, sitagliptin, approved by the US FDA in 2006 [146]. DPP-4 inhibitors, also referred to as gliptins, are highly selective incretin-based therapies that improve glucose control [147] and are considered a third-line treatment of T2DM (**Figure 5**). They may be used in monotherapy as an oral tablet (sitagliptin, linagliptin, saxagliptin, and alogliptin in the US; vildagliptin is not approved in the US) or in conjunction with other OHAs as an add-on or in a combination tablet with metformin (**Table 10**), or with insulin (**Figure 5**).

**Table 10.** DPP-4 inhibitor class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                      | Generic Name                          | Brand Name <sup>1</sup> |
|----------------------------------------------|---------------------------------------|-------------------------|
| <b>DPP-4 monotherapy</b>                     | Linagliptin                           | Tradjenta               |
|                                              | Saxagliptin hydrochloride             | Onglyza                 |
|                                              | Sitagliptin phosphate                 | Januvia                 |
| <b>DPP-4 combination therapy<sup>2</sup></b> | Linagliptin - Metformin hydrochloride | Jentadueto              |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup>Both drugs in combination in one oral tablet.

DPP-4: dipeptidyl peptidase-4.

### *Mechanism of action*

DPP-4 inhibitor class drugs inhibit DPP-4 activity in the peripheral plasma. This inhibition prevents the inactivation of the incretin hormone glucagon-like peptide (GLP)-1 in the peripheral circulation leading to increased insulin secretion and decreased glucagon secretion [147]. As a result, increased glucose utilization occurs and hepatic glucose production is

decreased, which in turn, through reductions in postprandial and fasting glucose concentrations, reduces A1C levels [147].

### *Advantages*

DPP-4 inhibitors have been found to be well-tolerated by patients with no reports of severe hypoglycaemia [148].

### *Disadvantages*

Some, but not all studies [e.g. 149], have found generally modest A1C efficacy with DPP-4 inhibitors [e.g. 148]. Adverse effects reported include urticaria/angioedema [e.g. 150-154], potential increase in MI risk with long-term use [155], and pancreatitis, though the associations between DPP-4 inhibitors and pancreatitis are still unclear [156]. DPP-4 inhibitors also have a higher cost for patients than other OHAs such as metformin or sulphonylureas [126].

## **GLP-1 receptor agonists**

The injectable GLP-1 receptor agonists (in the US these are exenatide, liraglutide, and the recently approved albiglutide, and dulaglutide [157-158]; **Table 11**) are a second class of incretins in addition to DPP-4 inhibitors [159]. GLP-1 receptor agonists are approved for monotherapy in the US, for use with metformin alone, in third-line therapy with sulphonylureas or TZDs, and as an add-on to basal insulin [100] (**Figure 5**). At the time of the analyses for this thesis they were not yet widely used in primary care [160].



**Table 11.** Injectable GLP-1 agonist class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                | Generic Name            | Brand Name |
|----------------------------------------|-------------------------|------------|
| GLP-1 agonist monotherapy <sup>1</sup> | Exenatide               | Bydureon   |
|                                        |                         | Byetta     |
|                                        | Liraglutide recombinant | Victoza    |

<sup>1</sup> GLP-1 agonists are not currently used in a combined formulation with other drugs.  
GLP-1: glucagon-like peptide 1.

### *Mechanism of action*

The incretins, glucose-dependent intestinal polypeptide and GLP-1 receptor agonists, account for approximately 70% of  $\beta$ -cell insulin secretion and both are required for normal glucose tolerance [161]. GLP-1 receptor agonists mimic human GLP-1[159] and activate GLP-1 receptors which are located in several tissues in the human body, including the pancreas [162]. Doing so inhibits glucagon release, increases insulin secretion, decreases gastric emptying, and decreases blood glucose levels in addition to increasing satiety and therefore reducing food intake [163-164].

### *Advantages*

Because GLP-1 receptor agonists stimulate insulin release and inhibit glucagon secretion in a glucose-dependent fashion the risk of hypoglycaemia is low [165]. GLP-1 receptor agonists are also associated with weight reduction [166], potentially improved  $\beta$ -cell function [167], and may have cardioprotective effects [168].

### *Disadvantages*

Several adverse effects have been reported for GLP-1 receptor agonists. These include gastrointestinal side effects such as nausea and vomiting [169] as well reports of acute pancreatitis, though results from large-scale studies have been conflicting [e.g. 170]. Concerns have also been raised regarding C-cell hyperplasia/medullary thyroid tumours in animal models [171-172], however, these effects have not been seen in human studies [173]. Other disadvantages for patients include the injectable route of GLP-1 receptor agonists which requires training and education, in addition to their high cost [95].

### **Meglitinides**

The meglitinide analogues (repaglinide and nateglinide; **Table 12**) are short-acting insulin secretagogues, first approved in 1997 (repaglinide; nateglinide followed in 2000) in the US, that target the progressive loss of early phase prandial insulin secretion [174]. Meglitinides may be used in monotherapy as an oral tablet, in addition to metformin or combined into one oral tablet with metformin (**Table 12**), or used in place of sulphonylureas in patients with irregular meal schedules or who develop late postprandial hypoglycaemia on a sulphonylurea [92]. Repaglinide has also been shown to be effective when combined with pioglitazone [175].

### *Mechanism of action*

Meglitinides act in a glucose-dependent manner to close  $K_{ATP}$  channels on  $\beta$ -cell plasma membranes to increase insulin secretion [176-177], similar to sulphonylureas, though binding by meglitinides occurs at a different site on the cell surface itself [178].

**Table 12.** Meglitinide class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                            | Generic Name                          | Brand Name <sup>1</sup> |
|----------------------------------------------------|---------------------------------------|-------------------------|
| <b>Meglitinide monotherapy</b>                     | Nateglinide                           | Nateglinide*            |
|                                                    |                                       | Starlix                 |
|                                                    | Repaglinide                           | Repaglinide*            |
|                                                    |                                       | Prandin                 |
|                                                    |                                       | NovoNorm                |
| <b>Meglitinide combination therapy<sup>2</sup></b> | Metformin hydrochloride - Repaglinide | Prandimet               |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup>Both drugs in combination in one oral tablet.

\*Marketed generic version of the drug.

### *Advantages*

Advantages of meglitinides include decreases in postprandial glucose excursions and dosing flexibility, though it should be noted that they require a frequent dosing schedule [92].

### *Disadvantages*

Similar to sulphonylureas, meglitinides may cause hypoglycaemia which is the most commonly reported adverse event [174], as well as blunting myocardial ischemic preconditioning [95]. They have been also associated with modest weight gain greater than metformin [179]. Meglitinides have a moderate cost compared to other OHAs [95].

### **$\alpha$ -glucosidase inhibitors**

The  $\alpha$ -glucosidase inhibitors (acarbose, miglitol, voglibose) have been studied extensively in Europe and Japan, though only acarbose and miglitol (approved by the US FDA in 1996 [180-181] are available in the US (**Table 13**).  $\alpha$ -glucosidase inhibitors are oral antidiabetic

**Table 13.**  $\alpha$ -glucosidase inhibitor class drugs prescribed within the total Type 2 diabetic population in the Cerner Health Facts<sup>®</sup> database for the treatment of T2DM between 2000 and 2012.

| Therapy                                                                  | Generic Name | Brand Name <sup>1</sup> |
|--------------------------------------------------------------------------|--------------|-------------------------|
| <b><math>\alpha</math>-glucosidase inhibitor monotherapy<sup>2</sup></b> | Acarbose     | Acarbose*               |
|                                                                          |              | Prandase                |
|                                                                          |              | Precose                 |
|                                                                          | Miglitol     | Glyset                  |

<sup>1</sup>Drugs are in tablet form unless otherwise indicated.

<sup>2</sup> $\alpha$ -glucosidase inhibitors are not currently used in a combined formulation with other drugs.

\*Marketed generic version of the drug.

drugs that are primarily used in monotherapy [182], but may be used as an add-on therapy to other hypoglycaemic drugs such as metformin [183] or sulphonylureas [180], though add-on therapy may present a risk of hypoglycaemia when combined with some medications (see below).

### *Mechanism of action*

The  $\alpha$ -glucosidase inhibitor class drugs act by inhibiting intestinal  $\alpha$ -glucosidase (they are poorly absorbed by the gut, e.g. < 1% for acarbose [184]) to slow intestinal carbohydrate digestion and absorption of ingested disaccharides, and reduce postprandial glycaemia [185].

### *Advantages*

Because of their mechanism of action  $\alpha$ -glucosidase inhibitors are nonsystemic and are therefore not associated with drug-induced hypoglycaemia unless used in combination with exogenously administered insulin or an insulin secretagogue (e.g. sulphonylureas or meglitinides) [181].  $\alpha$ -glucosidase inhibitors have been demonstrated to decrease postprandial glucose excursions [92] and may potentially decrease adverse cardiovascular events and hypertension

[186-188].  $\alpha$ -glucosidase inhibitors have a moderate cost for patients compared with other antidiabetic drugs [92].

### *Disadvantages*

Disadvantages to  $\alpha$ -glucosidase inhibitors include generally modest A1C efficacy compared to placebo [189-191] or other OHAs such as metformin or sulphonylureas [180, 189], though more recent studies have found that efficacy is comparable to that of metformin [e.g. 192]. In addition they have been associated with gastrointestinal side effects such as abdominal pain, flatulence, and diarrhea [191]. For patients,  $\alpha$ -glucosidase inhibitors require a frequent dosing schedule [92].

### **Bile acid sequestrants**

Bile acid sequestrants were originally developed as lipid-lowering agents for the treatment of hypercholesterolemia but were subsequently discovered to improve glycaemic control in patients with T2DM [e.g. 193-196]. To date, colesevelam is the only bile acid sequestrant approved in the US (in 2000) for improving glycaemic control in adults with T2DM [197]. Colesevelam is approved for use (in oral form) in monotherapy and as an adjunct therapy to other antidiabetic drugs such as sulphonylureas and insulin, and cholesterol-reducing drugs such as statins [181, 198]. Bile acid sequestrants were not found in the Cerner Health Facts<sup>®</sup> dataset for the treatment of T2DM during the study timeframe of this thesis.

### *Mechanism of action*

Bile acid sequestrants bind bile acids in the intestinal tract to increase hepatic bile acid production [92]. Although the mechanism of action of bile acid sequestrants with respect to glucose-lowering effects is not fully understood, recent studies have suggested that it may be mediated via increased secretion of the incretin hormones [199].

### *Advantages*

Colesevelam has been associated with decreased LDL cholesterol levels and a low risk of hypoglycaemia [200-201].

### *Disadvantages*

Bile acid sequestrants such as colesevelam show generally modest A1C efficacy and may cause gastrointestinal issues, primarily constipation [195], increases in triglyceride levels [200-201], and may decrease absorption of other medications [92]. In addition they have a high cost for patients compared to other hypoglycaemic drugs [92].

### **Dopamine-2 agonists**

The dopamine-2 agonist and ergot alkaloid bromocriptine is at present only available in the US for use as an antihyperglycaemic agent and was approved by the US FDA in 2009 for use in the treatment of T2DM [202]. Prior to approval for the treatment of T2DM, bromocriptine has been used extensively in the treatment of hyperprolactinemia-associated dysfunctions, acromegaly, and Parkinsonism [203]. Bromocriptine is administered in oral tablet form as a

monotherapy, but has also been shown to be effective as an add-on treatment to metformin, sulfonylureas, or TZDs [202]. Dopamine-2 agonists were not found in the Cerner Health Facts<sup>®</sup> dataset for the treatment of T2DM during the study timeframe of this thesis.

### *Mechanism of action*

Although well established in the treatment of Parkinsonism, the mechanism of action of bromocriptine in the treatment of T2DM is currently unclear. It is thought to potentially increase dopaminergic neurotransmission by resetting the circadian dopamine signal which modulates hypothalamic regulation of metabolism and increases insulin sensitivity [204].

### *Advantages*

Bromocriptine has been demonstrated to have a low risk of hypoglycaemia [202, 205], decreases blood pressure [206], and reduces the risk of adverse cardiovascular events in safety trials [206-208].

### *Disadvantages*

The use of bromocriptine in treating T2DM is relatively recent therefore there is little safety information with respect to bromocriptine use in conjunction with other antidiabetic drugs [205]. In addition, efficacy in reducing A1C levels has been shown to be generally modest [204-205, 209]. Side effects reported with bromocriptine include dizziness, headache, nausea, vomiting, fatigue, and rhinitis [209]. The cost of bromocriptine is also higher for patients than other antidiabetic drugs such as metformin [92].

## **Amylin mimetics**

Amylin mimetics, of which pramlintide is currently the only marketed drug in the US (first approved in 2005), are synthetic analogs of the human amylin hormone that are used to improve postprandial and overall glycaemic control in patients with either Type 1 or T2DM [210]. Pramlintide, which is in injectable form, is approved for use as an adjunct to insulin in patients who have failed to achieve glycaemic control despite optimal insulin therapy [211], with or without combination therapy with a sulfonylurea and/or metformin [212]. Amylin mimetics were not found in the Cerner Health Facts<sup>®</sup> dataset for the treatment of T2DM during the study timeframe of this thesis.

### *Mechanism of action*

Amylin has been shown to be co-secreted with insulin from pancreatic  $\beta$ -cells in response to a glucose challenge [213]. Amylin mimetics such as pramlintide activate amylin receptors to decrease glucagon secretion and slow gastric emptying, thereby suppressing hepatic glucose production, while also increasing satiety [214-215].

### *Advantages*

Pramlintide has been demonstrated to decrease postprandial glucose excursions [216], have a low rate of hypoglycaemia (if insulin dose is simultaneously reduced) [92, 217], and to reduce weight [218].



### *Disadvantages*

One disadvantage of amylin mimetic therapy is that the efficacy of pramlintide in achieving A1C levels has been shown to be modest in some studies [e.g. 217, 219], though not all [e.g. 220]. In addition, there are currently no data on the safety and efficacy of oral agents and injectable noninsulin therapies such as pramlintide in hospital [37]. Outside of the hospital setting, gastrointestinal side effects such as nausea and vomiting have been reported [218] but were generally more severe for Type 1 diabetics [212]. Like other injectable medications, pramlintide requires patient training and education as it also requires a frequent dosing schedule [95]. It should also be noted that for patients pramlintide has a high cost compared to other hypoglycaemic agents [132].

### **SGLT2 inhibitors**

SGLT2 inhibitors are a newly developed class of OHAs that target the kidneys. Canagliflozin was the first SGLT2 inhibitor approved for the treatment of T2DM in the US in 2013 [221], followed by dapagliflozin (Forxiga) in 2014 [222] and empagliflozin (Jardiance) also in 2014 [223]. SGLT2 inhibitors are approved for use in the US for monotherapy and combination therapy with other antidiabetic drugs. SGLT2 inhibitors were not found in the Cerner Health Facts<sup>®</sup> dataset for the treatment of T2DM during the study timeframe of this thesis.

### *Mechanism of action*

SGLT2 inhibitors decrease hyperglycaemia independently of insulin by inhibiting SGLT2 in the proximal nephron of the kidneys leading to reduced glucose reabsorption and increased urinary glucose excretion [224-226].

### *Advantages*

Advantages of SGLT2 inhibitors include low risk of hypoglycaemia [227], mild weight loss of approximately 2 kg compared with placebo [228-229], decreased blood pressure [230], and effectiveness at all stages of T2DM [92].

### *Disadvantages*

Disadvantages of SGLT2 inhibitors include genitourinary infections in men and women [231-233], polyuria, volume depletion, hypotension, and dizziness (particularly in older adults) [234], increased LDL cholesterol levels [231, 235], increased creatinine levels [236-237], and high cost for patients [92].

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