Development of A Patient Decision Aid for Adults in China with Type 2 Diabetes Considering Add-on Antihyperglycemic Agents for Good Glycemic Control after Failure with Metformin Monotherapy

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Thesis submitted to the University of Ottawa

In partial fulfillment of the requirement for the

Doctorate of Philosophy Degree in Epidemiology

School of Epidemiology and Public Health

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Abstract

Patients with type 2 diabetes mellitus (T2DM) in whom metformin monotherapy is insufficient to achieve good glycemic control face challenges to choose among treatment options when considering treatment intensification. The objective was to develop a patient decision aid (PDA) prototype for these patients with T2DM in China in supporting them to make an informed decision. First, a patient decisional needs assessment was conducted at Fu Wai Hospital, China to gain insight into the values and preferences of patients in China in making this treatment decision. Second, a systematic review and network meta-analysis was conducted of the comparative efficacy and safety of eight antihyperglycemic classes combined with metformin in treating patients with T2DM. Third, the results of the first two objectives were integrated into developing a prototype of a PDA for patients with T2DM considering the addition of an agent after metformin monotherapy failure in achieving sufficient glucose control.

Executive Summary

Background: Diabetes Mellitus is a major cause of cardiovascular disease, blindness, amputations and kidney dialysis. Due to the progressive nature, most individuals with T2DM require pharmacological treatment intensification over their lifetime to maintain sufficient glycemic control. With the growing number of antihyperglycemic agents, patients face many treatment options after failure of metformin monotherapy, and these options can vary significantly in efficacy and safety. In this regard, clinical guidelines recommend a patient-centered approach for management of hyperglycemia. However, there are few tools, such as PDAs, in supporting patients and practitioners through the shared decision making process; in particular, in developing countries such as China. The objective of this study was to develop an evidence-based, culturally appropriate and theory-driven prototype of a PDA for patients with T2DM in China who need to decide among these treatment options.

Methods: There were three main components of the thesis. First, we conducted a patient decisional needs assessment at Fu Wai Hospital, China to gain insight into the values and preferences of patients with T2DM in China when considering treatment intensification. Guided by the Ottawa Decision Support Framework (ODSF), we developed interview guides that were culturally adapted in order to gather this information. The study was fully discussed and planned with the research team in China before the field interview occurred at Fu Wai Hospital, and included a training session and recruitment strategy. Content analyses were performed to summarize and classify patient decisional needs in major themes.

Second, we performed a systematic review and network meta-analysis of the comparative efficacy and safety of antihyperglycemic classes combined with metformin in treatment for T2DM. With the rapidly growing number of antihyperglycemic classes available, an appraisal of the evidence of the competing interventions between various classes is needed from a clinical perspective in order to provide treatment recommendations. A systematic review and Bayesian network meta-analysis of the treatment options were conducted to synthesize the outcomes of these options based on the latest evidence.

Third, the design and development of the PDA followed a systematic development process, guided by the International Patient Decision Aid Standards (IPDAS), in order to present a high quality and current information to patients in a comprehensible and transparent fashion. "Future users" on the steering committee, including Chinese patients with T2DM, family members and Chinese physicians and nurses who provide care to patients with diabetes, were involved in all steps of the development of the PDA.

Results: First, the patient needs assessment in China identified seven themes, including: patient values and preferences, patient experience in using the health care system, patient knowledge of medications, decisional conflict, factors related to decision conflict, role in decision-making and what patients need to make a better decision. In particular, the need for a patient decision aid was identified when patients expressed a wish to be more engaged in making a decision, and practitioners wanted tools to improve communication with patients about treatment options and outcomes. Second, the systematic review included a total of 204 randomized controlled trials providing an extensive evidence base for the Bayesian network meta-analysis in order to obtain the effect estimates for antihyperglycemic class comparisons for 23 efficacy and safety outcomes

of interest. There were eight antihyperglycemic drug classes of interest that were added to metformin, namely: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), basal and biphasic insulin, dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transport 2 inhibitors (SGLT-2 inhibitors). All of the eight classes significantly reduced HbA1c to varying degrees compared to metformin monotherapy. The eight classes varied in their effects on hypoglycemia, body weight, BMI, systolic and diastolic blood pressure, high and low density lipoprotein cholesterol. They also varied in their safety profiles on total adverse events, urogenital adverse events, and heart failure. Third, we incorporated the results of the first two objectives into developing a PDA for individuals with T2DM considering the addition of an add-on antihyperglycemic agent after metformin monotherapy failure to achieve sufficient blood glucose control. The PDA helps patients with T2DM to consider two aspects in the decision making process: first, understanding a glycose level (HbA1c) setting; and second, choosing an adjunct agent add-on to metformin.

Conclusions: We developed an evidence-based, culturally appropriate and theory-driven prototype of a patient decision aid. The patient decision aid meets the decisional needs for this population with type 2 diabetes mellitus in China, and is intended to bridge the knowledge gap between research and practice on patient-centred care for type 2 diabetes mellitus in China.

Acknowledgements

First and foremost, I would like to sincerely thank my advisor, Dr. George A Wells, for providing me the opportunity and motivating me to produce high quality research. George, you always encourage me to test the limits and go beyond my comfort zone in a positive and productive way, and I am very thankful for this. My sincere appreciation also extends to my co-advisor, Dr. Karine Toupin-April, for her insight and her helping in the field of qualitative research. I am incredibly thankful to my advisory committee members, Dr. Doug Coyle, Dr. Ronald J Sigal and Dr. Yue Chen, for their invaluable advice, constructive criticism, and ongoing support.

I would especially like to thank Dr. Guangwei Li and his team, and each of the patients who participated in the research study at Fu Wai Hospital China.

A huge thank you to Annie Bai for her detailed screening of the numerous articles. I would also like to thank the faculty and staff at the University of Ottawa, and in the School of Epidemiology and Public Health for their help and support.

I am so fortunate to have such an amazing and supportive family. Thank you to my beloved soulmate Wenli, my wife, inspiring me and always believing in me. Thank you to my daughter Chuhong for her encouragement and for being such an important part of my life. Last, but not least, thank you to my parents in law for their understanding and ongoing support.

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Table of Abbreviations

AASD:	Asian Association for the Study of Diabetes
AGI:	Alpha-glucosidase inhibitor
ADA:	American Diabetes Association
BMI:	Body mass index
CADTH:	Canadian Agency for Drugs and Technologies in Health
DIC:	Deviance information criterion
DM:	Diabetes Mellitus
DPP-4 inhibitors:	Dipeptidyl peptidase 4 inhibitors
EASD:	European Association for the Study of Diabetes
ESC:	European Society of Cardiology
GDM:	Gestational diabetes mellitus
GLP-1 RAs:	Glucagon-like-peptide-1 receptor agonists
GWAS:	Genome-wide Association Study
HbA1:	Hemoglobin A1c
IDF:	International Diabetes Federation
IGT:	Impaired glucose tolerance
INS-BA:	Basal insulin
INS-BI:	Biphasic insulin
IPDAS:	International Patient Decision Aids Standards
IQR:	Interquartile ranges

MEG:	Meglitinides
MD:	Mean difference
MET:	Metformin
MODY:	Maturity Onset Diabetes of the Young
NHFPC:	National Health and Family Planning Commission
NMA:	Network meta-analysis
OR:	Odds Ratios
PDA:	Patient Decision Aid
PICOS:	Population, interventions, and comparators, outcomes of interest and study design
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT:	Randomized controlled trial
ROB:	Risk of Bias
SD:	Standard deviations
SDM:	Shared decision making
SGLT-2 inhibitors:	Sodium-glucose co-transport 2 inhibitors
SNPs:	Single nucleotide polymorphisms
SUL:	Sulfonylurea
T2DM:	Type 2 Diabetes Mellitus
TCM:	Traditional Chinese Medicine
TZDs:	Thiazolidinediones
WHO:	World Health Organization

Chapter 1 Introduction

1.1 Rationale

Shared decision making in healthcare involves a patient sharing personal values and preferences and a clinician sharing the evidence-based information on up-to-date treatment options when they discuss clinical management options in order to find the option that best fits the patient's needs.[1] Tools that can facilitate the shared decision-making process between patients and clinicians, known as patient decisions aids (PDA), have been studied, developed and implemented. The fundamental aim of a PDA is to present the latest evidence-based information on various medical treatment options in an objective, comprehensive and understandable manner, as well as to take patient values and preferences into consideration when making the decision.

Decisions become more complex when uncertainties arise from both the patient's and clinician's perspectives. This is the case for the management of hyperglycemia in type 2 diabetes mellitus (T2DM). With an increasing array of novel antihyperglycemic agents and classes becoming available, the variety of possible treatment options increases accordingly. These options have different benefits and risks, as well as unclear comparative effectiveness and safety. In addition, the value of intensive glycaemic control (e.g., HbA1c<7%) for reducing the risk of macrovascular complications (e.g., heart attacks) is not as certain as it is for microvascular complications (e.g., retinopathy). Thus, clinical management of hyperglycemia must be customized to fit the individual patient situations.

Recognizing the complexity of this decision-making process, development of a decision tool to facilitate the shared decision making process and assist patients through the difficult treatment decisions is needed. Further, given that the number of patients with T2DM in China is projected by the International Diabetes Federation to rise to 140 million by 2030, a patient decision aid designed to be suitable for the Chinese population with diabetes is essential.

1.2 Objectives

This thesis was undertaken with three main objectives. First, to assess patient decisional needs through conducting patient face-to-face interviews and practitioner focus group and individual interviews at Fu Wai Hospital, Beijing China. These findings will be considered in the development of a PDA that will incorporate, in particular, patient values and preferences when adding antihyperglycemic agents. Second, to review and assess treatment options through performing a class-level systematic review and network meta-analysis of the comparative safety and efficacy of antihyperglycemic classes combined with metformin therapies in T2DM. The results from these network meta-analyses will be considered as the current evidence-based treatment options in the development of a PDA. Third, to develop a PDA for individuals with T2DM considering the addition of an add-on antihyperglycemic agent after metformin monotherapy failure to achieve sufficient blood glucose control.

1.3 Outline of chapters

Overviews of the content of each of the chapters are outlined below.

Chapter 1: Introduction

In Chapter 1, the rationale and objectives of the thesis are introduced, and a holistic view of the key tasks is provided.

Chapter 2: Background

In Chapter 2, pertinent background information on T2DM, together with the introduction of the concept of shared decision making and PDAs in the context of managing hyperglycemia in T2DM are presented. The epidemiology of diabetes in China is highlighted to provide a background to the importance of the thesis work related to diabetes in China.

Chapter 3: Patient decisional needs when adding antihyperglycemic agents after monotherapy failure in type 2 diabetes mellitus in China

In Chapter 3, the first objective is addressed. A description is provided of the process and procedures, as well as the results of the patient decisional needs when adding antihyperglycemic agents that were identified through patient face-to-face interviews and practitioner focus group and individual interviews at Fu Wai Hospital in China. The findings of the decisional needs assessment, in particular patient values and preferences, are thematically synthesized with the aim of incorporating them into the development of the patient decision aid.

Chapter 4: A systematic review and network meta-analysis to determine the comparative efficacy and safety of antihyperglycemic agents for patients with type 2 diabetes mellitus following failure with metformin monotherapy

The second objective is addressed in Chapter 4. In this chapter, the systematic review and network meta-analyses of randomized controlled trials are described, with the assessment of the latest evidence on the comparative efficacy and safety of adding antihyperglycemic agents for

patients with T2DM following metformin monotherapy failure. In the absence of head-to-head treatment comparisons, indirect comparisons are accomplished using a Bayesian network meta-analysis. The efficacy and safety estimates for each indirect comparison are obtained and optimal therapies are identified. The results will be incorporated into the development of the patient decision aid.

Chapter 5: Development of a patient decision aid for adults in China with type 2 diabetes mellitus considering add-on agents for good glucose control after failure with metformin treatment alone

In Chapter 5, the third and final objective is addressed. The development of a culturally appropriate and theory-driven PDA, following the International Patient Decision Aid Standards, for patients with T2DM in China is described. The patient decision aid includes the various treatment options with the pros and cons of each (Chapter 4), as well as considers patient decisional needs including values and preferences when considering treatment options (Chapter 3). The PDA helps patients with T2DM in going through the complex decision making process when adding medications in China.

Chapter 6: Discussion

The key findings of each earlier step in the preceding chapters and the overall conclusions are summarized in Chapter 6, as well as the future research directions to further develop and refine, disseminate and implement the patient decision aid.

Chapter 2 Background

2.1 Diabetes mellitus

2.1.1 Diabetes mellitus and public health

Diabetes in Greek means excessive urination and *mellitus* refers to sweetness like honey. Clinically, diabetes mellitus is mainly characterized by higher-than-normal blood glucose levels or hyperglycemia. Today, the global trend of diabetes mellitus is sharply increasing. The International Diabetes Federation (IDF) estimates that more than 424 million adults lived with diabetes in 2017 and the figure is projected to reach 628 million by 2045, with disproportionate rates being reported in those regions experiencing rapid economic development, including China.[2]

Diabetes mellitus is a metabolic and endocrine disorder which can affect multi-organ systems in the human body.[3] More and more evidence from longitudinal studies shows that diabetes, in particular type 2 diabetes mellitus (T2DM), is a major cause of cardiovascular diseases, blindness, amputations, kidney failure and hospitalizations. Also, diabetes presents an increased risk of cancer, chronic liver disorders, psychiatric illness and other lingering medical conditions.[4-7] In 2017 over four million deaths worldwide resulted from diabetes, more than deaths from HIV/AIDS, tuberculosis and malaria combined.[2] Moreover, nearly half of those deaths occurred in persons under the age of 60; that is, during the ages of peak economic productivity. The globally estimated expenditure on diabetes has tripled from USD 232 billion in 2007 to USD 727 billion for healthcare alone in 2017.[2] As highlighted by the World Health

Organization (WHO), diabetes mellitus, along with three other non-communicable diseases (cardiovascular disease, cancer and respiratory disease), account for more than 70% deaths globally and urgently require global action plans for prevention and control.[8,9] To increase global awareness, November 14 has been designated as World Diabetes Day by the WHO (https://www.who.int/news-room/fact-sheets/detail/diabetes).

2.1.2 Diabetes mellitus classification, diagnosis and treatment

There are two classical types of diabetes mellitus, namely: insulin dependent diabetes mellitus (or type 1 diabetes mellitus (T1DM)) occurring in children; and non-insulin dependent diabetes mellitus (or T2DM) occurring in adults. Based on more recent epidemiological studies, age is no longer a hallmark to distinguish between the two types of diabetes.[10] From a broad etiological perspective, the WHO has recently classified diabetes into the following major categories:[11] type 1 diabetes mellitus, type 2 diabetes mellitus, other specific types (e.g., monogenic diabetes), hyperglycaemia first detected during pregnancy, hybrid forms of diabetes (e.g., ketosis prone type 2 diabetes) and unclassified diabetes (this category is used as a temporary classification when there is not a clear diagnostic category yet determined). Overall, type 2 diabetes mellitus accounts for up to 95% of all diabetes.[11,12]

Physiologically, fasting plasma glucose levels are maintained within a narrow range (e.g., between 10.5 and 13.9 mmol/L or between 70 and 100 mg/dl),[13] and any increased level in plasma following a meal, immediately stimulates insulin release from β cells in the pancreas. The temporary increase in plasma insulin efficiently facilitates increased transport of glucose into organs (liver and gut) and peripheral tissue (skeletal muscle); subsequently, plasma glucose

levels return to the normal fasting range within 2-3 hours after meals. Insulin is the main hormone that lowers blood glucose. Hyperglycemia can result from absolute insulin deficiency (in TIDM), or the combination of insulin resistance and relative insulin deficiency (as usually seen in T2DM).[14] A clinical diagnosis of diabetes can be made if the fasting plasma glucose level is ≥7 mmol/l (126 mg/dl); and/or 2-hour post-load plasma glucose level is ≥11.1 mmol/l (200 mg/dl); and/or HbA1c levels are ≥6.5% (48 mmol/mol) on two or more occasions.[12]

Prescribed lifestyle management (e.g., diet and exercise) is the first step for patients with newly diagnosed T2DM. Due to the progressive nature of T2DM, however, most patients eventually experience inadequate blood glucose control and require antihyperglycemic agents to maintain and control increased glucose levels. Currently, most guidelines[15-18] recommend a stepwise treatment approach with metformin as the initial monotherapy. In contrast, there are no universal recommendations regarding the addition of a second agent following the failure of monotherapy for the general population with T2DM. Today, an array of novel antihyperglycemic classes has become available on the market, including dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and sodium-glucose cotransporter-2 (SGLT-2) inhibitors.[16,18] These new antihyperglycemic agents include a mix of oral and injectable drugs along with differing side effects, efficacy and cost. Thus, pharmacologic treatment of T2DM must consider both clinical glucose targets, as well as patient preferences and values.

2.2 Diabetes mellitus in China

2.2.1 Overview of the healthcare system in China

In China, the health care system has progressed from the combined efforts of ongoing reforms in the political, economic and administrative systems.[19] Nationally, the major health authorities are the National Health and Family Planning Commission (NHFPC) and the State Administration of Traditional Chinese Medicine, which is overseen by the NHFPC. The healthcare system consists of four levels, namely: 1) National Health and Family Planning Commission; 2) provincial health bureaus; 3) municipal health bureaus; and 4) county health bureaus. The central government takes the lead in lawmaking and decision-making in the healthcare system, although an effort has been made on decentralization.[19]

In support of the health care services, three primary financial sources are in place: 1) government budget (tax-based); 2) insurance (e.g., social health insurance and private insurance); and 3) out-of-pocket. Each contributes to approximately one-third of the total expenditure. As it pertains to insurance, there are three basic medical insurance systems in China. First, the Urban Employee Basic Medical Insurance which is mandatory for all employees who work in urban areas, with premiums paid by both employers and employees. Second, the Urban Resident Basic Medical Insurance which is for urban residents, jointly financed by resident premiums and government. Third, the New Rural Cooperative Medical Scheme which covers rural residents enrolled voluntarily as families, jointly financed by resident premiums and the government.[19]

Based on the size and function, there is a three-tier hospital structure in China, namely: tier-1 hospital or primary hospital; tier-2 hospital; and tier-3 hospital. In general, a tier-1 hospital has

less than 100 beds and provides basic medical service in a community. In contrast, a tier-3 hospital has advanced medical devices and technologies, providing advanced medical service. Nearly all medical specialists and experts work at tier-3 hospitals.[19]

2.2.2 Diabetes mellitus in Asia and China

Asia accounts for more than 60% of the population with diabetes mellitus in the world. They also constitute the largest number of individuals with undiagnosed diabetes and the highest burden of diabetes-associated mortality.[2]

Before the 2000s, T2DM was considered a disease of developed countries and not a public heath priority in Asia, when most Asian countries reported a very low prevalence of diabetes, such as 0.86% in China in 1986[20] and 2.1% in India in 1979[21]. However, studies in early Asian immigrants showed that the incidence and prevalence of diabetes and prediabetes are significantly higher in Asian immigrants in comparison to their Caucasian counterparts.[22,23] A study[24] in the United States found that the prevalences of diabetes and prediabetes were 6.8% and 12.4%, respectively, in the first generation of Asian immigrations compared to the corresponding prevalences of 5.5% and 6.9% among Caucasians. The authors conjectured that relatively lower physical activity in the first generation may be one of the risk factors that needs to be addressed in Asian immigrants. Another study in Canada[25] examining the early onset of diabetes among immigrant populations showed that Asians developed diabetes earlier in comparison with their counterparts who had emigrated from the United Kingdom. A Household Income and Labour Dynamics study[26] in Australia found that Asian immigrants were more likely to report diabetes compared to native-born Australians. The research among Asian immigrants to

Western countries suggest that Asians may be more vulnerable to environmental and lifestyle changes as it relates to the development of diabetes.

Even when blood glucose levels do not meet the clinical diagnostic criteria for diabetes but are above the normal range, in addition to increased risk of diabetes, associated complications such as hyperlipidemia and cardiovascular disorders may occur.[27-29] The World Health Organization and the American Diabetes Association accordingly define this stage as intermediate hyperglycemia or a risk factor for future diabetes (prediabetes) but not the clinical entity of diabetes.[13, 30, 31] Prediabetes mainly includes two categories; impaired fasting glucose and impaired glucose tolerance.[13,32] Epidemiological studies in China showed that annually 10% of individuals with prediabetes progress to diabetes without intervention.[33,34] Other studies showed much lower rates of progress at 1.2% to 2.1% from prediabetes to diabetes after a 5-year follow up.[35] The methods and threshold for defining prediabetes between the studies may partially contribute to differences in progression from prediabetes to T2DM.[35] Consistently, lifestyle modification such as diet and exercise is the cornerstone to prevent or delay patients progressing from prediabetes to T2DM.[34-37]

Today, rapid economic growth in Asia, especially in China, has brought about some important changes from a public health perspective. For example, urbanization results in more people moving from rural regions, with less physical activity; and globalization introduces fast-food mass production. These changes in lifestyle, with high caloric intake and less-healthy diet, together with physical inactivity in Asia mirror the early Asian immigrants experience when they migrated into western countries.

The International Diabetes Federation predicts that of the ten countries with the largest number of adults with diabetes and prediabetes by 2045, five of them will be in Asia. The Director General of the WHO recently wrote a commentary paper[38] on "China's Burgeoning Epidemic of Diabetes-Associated Mortality" addressing the concern of diabetes in China.

2.2.3 Epidemiology of diabetes mellitus in China

China is becoming the global epicenter of diabetes. Recent epidemiological data indicated the estimated overall prevalence of diabetes in China was 11.6%,[39] corresponding to 114.4 million individuals with T2DM and surpassing India as the country with the largest number of people with diabetes in the world. The overall trend of diabetes in China continues to increase, with half of the adult population estimated to have prediabetes, forming a large of pool of the population (494 million) at risk for diabetes in the future.[39] The current burden of diabetes is one of the most costly chronic diseases in China. The total health expenditure, for example, required to deal with the great increase in diabetes amounted to approximately 110 billion USD on healthcare alone in 2017, placing China in the position of the country with the second largest healthcare cost on diabetes after the USA.[2] Variability in geographic and population vulnerability in China, combined with the rapid pace of change in lifestyle, is creating new challenges for public health to prevent and control the emerging epidemic of T2DM.

2.2.3.1 Trends of diabetes and prediabetes in China

Thousands of years ago, traditional Chinese medicine recognized a cluster of relevant clinical manifestations and described them as "Xiaoke Zheng" or "Three Excess and One Loss": polyuria, polydipsia, polyphagia and emaciation (or unexpected weight loss). Based on the *Yin*

and *Yang* balance principal in the traditional medicine, "Xiaoke Zheng" is associated with *Yin* deficiency, resulting in a dynamic imbalance between *Yin* and *Yang* in the human body. *Yin* represents body fluids and its deficiency over time leads to endogenous dryness-heat, reflecting blood stasis and phlegm.[40-42] The traditional Chinese medicine treatment on "Xiaoke Zheng" depends on clinical manifestations. Even for two people with diabetes at the same glycemic levels, traditional medicine may interpret their symptoms and treat them differently. For example, one patient with a rounded face and overweight or obese may mainly suffer from the deficiency of *Yin* (e.g., phlegm and heat stasis). The other patient with weight loss and fatigue may mainly suffer from the deficiency of both *Yin* and *Qi* (energy).[42] Under traditional Chinese medicine of *Yin* and *Yang* balance, a variety of traditional herbs have been used to deal with "Xiaoke Zheng",[43,44] which is named Diabetes Mellitus in the modern world.

Not until the last three decades, T2DM was not a health priority in China and was considered a disease appearing only among the upper classes and rich.[36] The prevalences of T2DM and prediabetes were estimated at 0.9% and 0.8% in 1980 respectively, and at 1.04% and 0.68 % respectively in 1986.[20,45,46] In 1994, Pan and Li et al[46] reported results from a national population-based survey with 224,251 individuals aged 25-64 years across 19 provinces. Using the 1985 WHO criteria, the study estimated the prevalence of diabetes and prediabetes at 2.5% and 3.5% respectively, and these figures have tripled within one decade.[20] Interestingly, the spike of diabetes was parallel with the rapid economic growth under the reform policy in the mid-1990s in China.[47] Analysis of the risk factors associated with increased diabetes showed that high annual income, less physical activity, family history of diabetes and age were all independent risk factors contributing to diabetes.[46] This is the earliest modern epidemiological

research in China, using the WHO standard of diagnosis and methods for data collection and analyses. Although the prevalence of diabetes increased in China, it was lower than that reported in Western countries, such as the prevalence of 7.8% in 1994 in the USA[48] and 5.2% in 1995 in Canada.[49]

In 2007, Yang et al[50] recruited a nationally representative sample of 46,239 individuals aged 20 years or older and screened these individuals using the 1999 WHO diagnostic criteria. The overall prevalences of diabetes and prediabetes were reported at 9.7% and 15.5% respectively. These rates had increased dramatically not only in adults, but also in the younger population. For example, diabetes and prediabetes rates were estimated at 3.2% and 9.0% respectively, for the age group 20-39 years in 2007,[50] in comparison with the figures at 0.24% and 1.4% for the same age groups in 1994.[46] In interpreting the increased trends, the authors assumed rapid economic growth, urbanization, lifestyle changes, increased overweight and obesity and aging population were all contributors. Geographically, there is an imbalance in the increase in diabetes reported, with a higher proportion being reported in urban areas than in rural areas. People migrated from rural to urban areas for greater opportunities, becoming accustomed to less physical activity and to a high-calorie-food lifestyle.[51,52]

The latest Chinese national survey on diabetes[39] was conducted in 2013, with approximately 98,658 adult participants. Results of the survey showed that the prevalence of diabetes was estimated at 11.6%, continuing the rapid increase of diabetes in the country compared to the estimate in 2007.[50] Even more concerning from the public health perspective, the survey reported prediabetes at 50.1%, with 40% of these in the age group 19-29 years.[39]

This latest survey added hemoglobin A1c (HbA1c) to the screening tests for diabetes and prediabetes diagnosis as recently recommended by the American Diabetes Association and WHO.[30,32] There are variations among different ethnicities when applying HbA1c for diagnostic purpose, such as 6.3% (6.2% to 6.4%) being considered the best indicator for diagnoses of diabetes in Chinese adults.[53] This may partially explain some overestimated case counts in comparison with previous epidemiological data in China. However, the recent figures are comparable to, or higher than, those in Western Countries using the same diagnostic methods. For instance, the 2020 National Diabetes Statistics Report provided by the United States Centers for Disease Control, which added HbA1c as a diagnostic test, estimated the prevalence of diabetes and prediabetes at 10.5% and 34.5% respectively.[54]

The pathophysiology of T2DM involves the impairment of both insulin action (insulin resistance) and insulin relative deficiency, in conjunction with genetic factors. Chronic hyperglycemia, hyperinsulinemia, as well as adipose tissue and inflammation, all interact in the complex pathophysiology of T2DM and contribute to the underlying mechanisms of diabetic complications.[6,7] Following by the identification of leptin in 1994[55] and tumor necrosis factor-alpha in 1993,[56] adipose tissue was recognized as an endocrine organ, rather than simple energy storage, and an excess of adipose tissue is associated with a variety of adverse metabolic effects such as insulin resistance, hyperglycemia, hypertension and inflammation.[57] Inflammation as a bridge between obesity and T2DM, not only results in insulin resistance, but also contributes to insulin deficit via impairing islet function.[58]

Other types of diabetes mellitus

There is less epidemiological information about type 1 diabetes mellitus (T1DM) in China, compared to T2DM. A recent national population based registry study[59] provided several interesting findings: 1) the overall incidence of T1DM for cases under 14 years of age was estimated at 1.93 per 100,000 person years during 2010-13, in comparison with 0.51 during 1985-1994 time period; 2) most (65.3%) newly diagnosed cases were in adulthood, with an estimated 9,605 cases per year occurring among those over 15 years old; 3) a high proportion of diabetic ketoacidosis was reported within a six-month period since the diagnosis onset with 51.4% for those under 15 years old and 40.1% for all ages. Nearly half of newly diagnosed patients with T1DM have experienced diabetic ketoacidosis, which is quite significant because ketoacidosis is life threatening but manageable clinically and often preventable. Overall, the trend in T1DM is increasing and more adults are being diagnosed with T1DM.[59]

Gestational diabetes mellitus (GDM) is usually diagnosed among women in their second or third trimester of pregnancy. If pregnant women in their first trimester are diagnosed as diabetes, they are considered as having pre-existing diabetes.[13] Until recent years, GDM has not attracted public health attention in China. It is estimated approximately 20% of pregnant Chinese women with GDM, most of them with high body mass index.[60] Women with GDM present a 7 times increased risk of T2DM in their later life compared to those without GDM.[61] As well, even mild maternal hyperglycemia poses a higher risk of cardiovascular disease in the offspring.[62-65] There are approximately 16 million births annually in China and the prevention and control of GMD among pregnant women requires a medical and societal effort.[62]

Other specific types of diabetes include cases in which the cause of diabetes is relatively clear, such as glucocorticoid drug-induced diabetes, or monogenic maturity-onset diabetes of the young (MODY).[13]

2.2.3.2 Risk factors associated with increased type 2 diabetes mellitus

Recent studies have shown that some factors which may be associated with increase in diabetes in Asia, especially in China, differ between Asian and Caucasian populations.

Age

T2DM in the young has been reported to be increasing globally; however, the rate of increase is higher in the Asian population.[39,66] Currently diabetes in China includes a high proportion of young adults, with approximately 15-23% of newly diagnosed cases with T2DM aged less than 44 years old.[39,67] The trends have increased dramatically among the young population in the country. Taking the age group 30-39 as an example, the prevalence of diabetes and prediabetes were estimated at 6.6% and 47.1% respectively in 2013,[39] in comparison with prevalences of 0.24% and 1.4% respectively in 1997.[46]

In comparison with late-onset T2DM, early-onset diabetes tends to have a more aggressive course, with higher risks of diabetes-associated mortality and morbidity (e.g., cardiovascular disease and renal disease).[68-70] Studies in China have shown that young individuals with early-onset diabetes commonly presented with poor blood glucose control (HbA1c > 7% or > 53 mmol/mol)[71] and cardiovascular-risk profiles similar to those of patients with late-onset diabetes.[39,67] In Asia, a multi-country collaborative study[68] found that individuals with young-

onset T2DM (defined as onset of diabetes prior to the age of 40 years old) presented with similar dyslipidemia metabolic characteristics, but with worse glucose control, compared to their counterparts with late-onset diabetes. In other words, although this group is younger, it seems to lack the natural advantages of youth.

Today, prevalences of diabetes and prediabetes in the young population in China are comparable to, or even higher than figures reported in Western countries. For example, the prevalences of diabetes and prediabetes were reported at 5.9% and 28.8% respectively in China[72] compared to 4.6%, and 23.7% respectively in the United States, for individuals under 44 years of age.[54] This may indicate that Chinese are prone to develop diabetes at a younger age.

Sex

Sex differences in T2DM in youth have been reported. Studies in the western countries showed that more than two-thirds of children and adolescents diagnosed with type 2 diabetes were girls, partially resulting from the influence of sex hormone during puberty.[142,143] However, studies in Asia reported more boys than girls were diagnosed with type 2 diabetes,[144] highlighting the complexity of race/ethnicity as risk factors for T2DM in youth. Sex differences in cardiovascular diseases in T2DM have shown that women with T2DM presented greater risk of cardiovascular diseases than their male counterparts. A study [145] in UK reported that the excess risk of a cardiovascular event in T2DM was greater in women (HR: 1.96, 95%CI 1.60, 2.41) than in men (HR: 1.33, 95%CI 1.18, 1.51). A recent prospective cohort study[5] in China showed that T2DM significantly increased the risk for death from cardiovascular disease (RR: 2.13, 95%CI 2.01 to

2.26), and the risk is higher in women with T2DM (RR: 2.36, 95%CI 2.18 to 2.56) than men with T2DM (RR: 1.93, 95%CI 1.77 to 2.10). Studies on sex-based efficacy of antihyperglycemic agents for T2DM are few in number. One study reported that women with T2DM had a 25% reduction in GLP-1 response to an oral glucose tolerance test, which may suggest the sex-based efficacy of medications exist in T2DM, given that higher GLP-1 responses are associated with better insulin secretion.[146] Currently, sex and gender differences in T2DM have not been epidemiologically described well.[147] More research is warranted to provide insight into understanding whether T2DM progression, clinical presentation and treatment are based on a sex and gender background.

Overweight and obesity

The prevalence of overweight and obesity in China have increased. One study found that the overall prevalence of overweight and obesity were, respectively, 24.1% and 2.6% in men, and 26.1% and 5.0% in women.[73] These rates have sharply increased in comparison with the corresponding prevalences of 9.9% and 0.8% in men and 12.9% and 1.9% in women five years earlier.[74] Furthermore, individuals become overweight/obese at a younger age compared to a decade earlier (e.g., beginning at 30 years versus 45 years of age).[73,75,76]

Geographically, the overall prevalence of diabetes is higher in urban than in rural locales in China.[73] Intrestingly, individuals with overweight and obesity are more commonly reported among those who live in rural regions than in urban regions in the country.[75] The distributions of overweight and obesity also vary by ethic groups. For example, a recent study that recruited 15.8

million men aged 15-49 years in China found that the prevalence of overweight and obesity combined varied by ethnic groups with 34% in Han, 43.7% in Mongolian and 43% in Manchu.[76] Body mass index (BMI) is a common indicator for body weight in relation to height and is defined as an individual's weight (kilograms) over height squared (meters). It is recommended that for Asians, a BMI> 28kg/m^2 is obese and a BMI> 24 kg/m^2 is overweight; whereas for Caucasians the corresponding BMI ranges are > 30 kg/m^2 and 25 kg/m^2, respectively.[77] Studies[78] suggest that the risk of diabetes in the Chinese population appears to increase at a BMI around 23 kg/ m^2. Moreover, even for those Asians with normal body weight, the risk is still greater than in Caucasians because body fat tends to be concentrated around the waistlines, or as abdominal fat (android fat), which is strongly associated with insulin resistance and diabetes, independent of BMI.[79,80] In a randomized trial conducted in Da Qing, China, Pan et al and Li et al[36,37] reported that individuals with impaired glucose tolerance randomized to diet and/or exercise interventions had significantly reduced risks of developing diabetes in later life even among those with normal body weight. This is partially explained by the fact that Chinese individuals commonly have significant amounts of visceral adiposity, even at BMIs that would be considered within normal limits. Using the China Health and Nutrition Survey Data between 1993 and 2009, it was found that Chinese adults have become more overweight and obese over the past 17 years, characterized by abdominal obesity.[81] Abdominal obesity, compared to peripheral obesity, is more associated with insulin resistance, inflammation and T2DM.[82-84] As well, studies suggested that insulin sensitivity among those with higher amounts of abdominal fat, even with a normal body weight, can be improved up to 79% with exercise and diet.[84] Genetically, abdominal fat is approximately 5% higher in Asians for any given BMI level in comparison with Caucasians.[85]

Physical activity and diet

There is consistent evidence that regular physical activity, for example, at least 30 minutes walking every day, can reduce the risk of developing T2DM and associated mortality.[36,37,86-89]

The earliest and largest randomized controlled trial of diet and exercise on preventing T2DM was the China Da Qing Diabetes Prevention Study.[36,37,89] Briefly, the Da Qing study recruited approximately 110,600 individuals from the city of Da Qing, in the northern part of China. Through an oral glucose tolerance screening test, 577 individuals were diagnosed with impaired glucose tolerance (IGT), or prediabetes. This cluster randomized controlled trial, with randomization by clinics, was performed in four groups: Exercise Group; Diet Group; Exercise and Diet Group; and Control Group. For exercise intervention, participants were encouraged to increase their leisure physical activity by at least 1 unit/day (e.g., 30 minutes walking every day). For diet intervention, participants were encouraged to increase their vegetable intake, and decrease sugar and alcohol use, with approximately 25-30kcal/kg body weight per day, including 55-65% carbohydrate, 10-15% protein and 25-30% fat. Over a six-year intervention, the incidence of diabetes was reduced by 31%-46% among the intervention groups in comparison with that in the control group.[36] After a 23-year follow-up, individuals initially assigned to the intervention groups continued to show significantly lower mortality in comparison with those in the control group;[36,37,89] with most of the excess mortality in those who had developed diabetes. This highlights the conclusion that simple exercise and diet can prevent diabetes and associated mortality.

The Da Qing results were further confirmed among different ethnic populations in randomized controlled trials, such as the Finnish Diabetes Prevention Study in 2001,[87] the US Diabetes Prevention Program Study in 2002,[90,91] the Japanese Study in 2005,[92] and the Indian Diabetes Prevention Program Study in 2006.[93] Results from the Da Qing study have been widely cited, including the Task Force on Diabetes and Cardiovascular Disease of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD),[94] the American Diabetes Association[95] and the World Health Organization.[31] In 2013, the Asian Association for the Study of Diabetes (AASD) established a research award for Epidemiology of Diabetes in Asia in the name of Dr. Xiaoren Pan, who was a designer and pioneer of the China Da Qing Diabetes Study, in recognition of his significant contribution of our understanding of epidemiology for the prevention of diabetes in the world (link: http://www.aa-sd.org/awards/pan.html).

Diet is another important factor. It is well known that high caloric intake is associated with increased risk of diabetes. Not only is the quantity, but also the quality of food (higher glycemic load) is associated with the risk of diabetes. The consumption of white rice is significantly higher in China and other Asian countries compared to Western countries. Researchers explored whether this major staple food in China contributed to the increasing incidence of diabetes in the country. Some studies have shown that the more rice consumed, then the higher risk of T2DM.[96-98] In contrast, other studies have suggested no correlation between white rice intake and diabetes.[99,100] Some have even indicated a negative correlation.[101,102] More research is needed in this field in order to provide an evidence-based guidance.

Smoking

Smoking is a common risk factor for diabetes, cardiovascular diseases, respiratory diseases and cancers which together account for more than 70% of all fatalities in the world.[9] Despite the widely disseminated recommendations for tobacco cessation, the prevention and control of smoking in Asia is sub-optimal, and more than 50% of men in China and Korea are smokers.[103]

Evidence consistently shows that smoking is associated with an increased risk of diabetes. In China, a prospective study on the association between smoking and T2DM with obesity found that the risk for diabetes is more than four times higher in current smokers compared to non-smokers (hazard ratio (HR) 4.16, 95% CI: 2.77-6.24), and smoking coupled with abdominal obesity increased the risk of diabetes beyond either smoking or abdominal obesity alone.[104] A 14-year follow-up study in Korea found an adjusted HR for diabetes of 1.55 (95% CI: 1.51-1.60) for men and women smoking 20 cigarettes or more per day in comparison with non-smokers.[105] Studies in Japan reported that the more cigarettes consumed, then the higher the risk for diabetes.[106] Recent systematic reviews have confirmed that active smoking is associated with a 44% greater likelihood of developing T2DM in comparison with non-smoking.[107,108] In addition, smoking is associated with increased inflammation and oxidative stress, both of which are risk factors for diabetes.[109]

Smoking is a significant and independent risk factor for macrovascular diseases among individuals with T2DM. Clinically, the Asian population has greater risk of stroke (especially hemorrhagic stroke), while the Caucasian population has more coronary heart disease or ischemic heart disease.[5,110] Although any amount of smoking increases the risk of stroke,[111] this

risk is particularly increased among those diabetic smokers with more than 15 cigarettes per day.[112,113] Nevertheless, the mechanisms underlying the different excess risks due to diabetes between Asian and Western populations remains unclear.

Compared to macrovascular diseases, the effect of smoking on microvascular diseases (e.g., retinopathy and neuropathy) among patients with diabetes is less clear and requires further research.[114,115]

Acohol

Studies suggest that moderate alcohol consumption is associated with lowering risk of T2DM, but it is controversial since outcomes differ by sex.[148,149] Some studies reported that the risk reduction was specific to women,[148] while others suggested the risk reduction was only observed to men.[149] A systematic review, that included 1.9 million individuals from 38 observational studies, found that moderate alcohol drinkers significantly reduced the risk of T2DM in women and the non-Asian population.[150] Recently, a prospective cohort study in China provided some interesting findings between alcohol consumption and T2DM in the Chinese population.[151] The study recruited 500,000 adults from five urban and five rural regions and followed them for seven years. The results indicated that alcohol initiation at a late age and a short drinking duration were associated with a lower risk of T2DM.[151] The authors noted in the limitations that few women were current drinders and the results were inconlusionve for women.

Genetics

Genetically, T2DM is highly heterogeneous. The recent move from focusing on individual candidate genes to Genome-wide Association Study (GWAS) has provided greater insight into understanding the complexity of the pathophysiological mechanisms of T2DM at the molecular level, by replicating those identified single nucleotide polymorphisms (SNPs) and comparing genetic heterogeneities across different ethnic groups. Globally, GWAS has identified more than 250 SNPs associated with T2DM, some being associated with insulin resistance and others with β-cell dysfunction.[116-118] Most of these SNPs were initially identified and reported in Caucasian populations.[116,117,119,120]

In replication studies conducted in China of 25 SNPs from the GWAS showed that lean patients with T2DM present with more SNPs, in comparison with obese patients with T2DM. In addition, the isolated genes (e.g., TCF2) in the lean patients are mainly associated with β-cell function or insulin secretory capacity.[79] Through replicating GWAS identified SNPs among different ethnic groups, it helped to understand the genetic influence on different populations. For example, the variance of CENTD2 gene has an independent effect on the risk of T2DM in the Chinese population.[120] Genetic variations associated with insulin resistance such as the adiponectin gene and the SIRT1 gene have been observed for patients with diabetes in China.[121,122] Based on genetic research, some preliminary clinical trials have begun to explore the clinical implications of genotype on the efficacy of antihyperglycemic drugs among patients with T2DM in China, including some selected genes associated with insulin resistance and β cell function.[123]

Epigenetics

Neither environmental influence nor genetic influence alone can fully explain the current epidemic of T2DM in Asia and in China.

Although Conrad Waddington initially coined the term "Epigenetics" in 1942,[124] it was not well recognized until recent decades in studies of T2DM at the molecular level. The "thrifty genes" theory explains the environmental and genetic interaction that may contribute to the epidemic of obesity and diabetes.[125] An early study[126] investigated the correlation between famine and glucose tolerance for people born during the famine of 1944 to 1945 in the Netherlands. The study found that exposure to famine in utero likely resulted in impaired glucose tolerance, especially in those who became obese in later life. One study[127] used Chinese national nutrition and health survey collected on 7,874 adults born during the Chinese famine period between 1954 and 1964 and showed that adults who were exposed to the famine in fetal life had significantly increased risk of metabolic syndrome when compared with those without the exposure (odds ratio (OR) 3.13, 95%CI: 1.24, 7.89). Another study in East China found that adults who experienced famine either during fetal life (OR 1.53, 95%CI: 1.09, 2.14) or childhood (OR 1.82, 95%CI: 1.21, 2.73) had a greater risk of diabetes compared to their counterparts without exposure to famine.[128]

Furthermore, the SEARCH for Diabetes in Youth Study and others showed that exposure to maternal diabetic intrauterine environment was strongly associated with the development of T2DM at a younger age.[129,130]

Research has explored other factors that may be related to the epidemic of T2DM in China. A cross-sectional study[131] explored the relationship between breastfeeding and diabetes among 9,128 women aged 40-81 years. The results showed that mothers who had breastfeed were less likely to develop diabetes in their later lives, compared to those who did not breastfeed. Within the first 12 months of the baby's life, the longer a mother breastfed, the lower the risk of developing diabetes in her later life. Although the physiological mechanisms remain unclear, some observational studies suggested that lactation can improve insulin sensitivity and lower glucose concentrations through the influence of the hypothalamic-pituitary axis on hormone levels.[132,133]

In summary, type 2 diabetes in the young Asian population has increased faster than their counterparts in the non-Asian population. Sex and gender-based differences in T2DM have not been widely studied from an epidemiological perspective. Some data in the non-Asian population suggested that more girls than boys were diagnosed with T2DM under the age of 18 years, but studies in Asia found the opposite results, indicating a complex relationship of race/ethnicity and T2DM in youth. Other risk factors such as alcohol consumption may result in different impacts in T2DM by sex dimeshoph and by race/ethnicity. Consistently, diabetes-associated cardiovascular mortality was higher in women than men regardless on their race/ethnicity. Clinically, the Asian population in T2DM mainly manifested with hemorrhagic stroke, while non-Asian in T2DM commonly presented coronary heart disease or ischemic heart disease. The GWAS has identified genetic variations in T2DM by race/ethnicity that suggests race/ethnicity-based efficacy of antihyperglycemic agents in humans with T2DM. More research

is needed to study the diversities by sex and race in predisposition, progress, clinical manifestation and treatment for patients with T2DM.

2.2.4 Management of diabetes mellitus in China

Clinical guidelines for the management of diabetes in China are updated and consistent with the guidelines endorsed by the WHO and other developed counties.[15,18,134] The 2019 Chinese diabetes guidelines[135] indicated that the following antihyperglycemic classes were commercially available in China: biguanide (e.g., metformin), sulfonylureas (e.g., gliburide), meglitinides (e.g., repaglinide), dipeptidly peptidase-4 inhibitors (e.g., sitagliptin), thiazolidinedioznes (e.g., rosiglitazone), alpha-glucosidase inhibitors (e.g., acarbose), glucagon-like-peptide-1 receptor agonists (e.g., liraglutide), sodium-glucose co-transporter 2 inhibitors (e.g., dapagliflozin), and insulin (e.g., rapid-acting insulin analogues, regular insulin, intermediate-acting insulin, long-acting insulin analogues, premixed insulin and premixed insulin analogues).

Consistent with guidelines published by the WHO and developed countries,[15,18,134] the 2019 guideline in China recommends that patients could add an adjunct antihyperglycemic agent, as described above, after their glucose levels were insufficiently controlled with initial metformin monotherapy.[135] In addition, the 2019 guidelines also introduced Traditional Chinese Medicine (TCM) as treatment options for patients with T2DM.[135]

2.3 Shared decision making in management of hyperglycemia in T2DM

2.3.1 Shared decision making

Shared Decision making (SDM) is "a collaborative process by which patients and clinicians work together in a deliberative dialogue… to identify reasonable management options that best fit and address the unique situation of the patients".[1] SDM becomes more useful in clinical service when uncertainties arise in both patients and practitioners in choosing a treatment among the various options. Since Banting and Best first isolated insulin, for example, there has been no controversy among either physicians or patients that insulin is the standard of care for T1DM. In contrast, the current pharmacologic therapy for patients with T2DM is heterogeneous and complex. The growing diversity of antihyperglycemic agents provides various treatment options after patients treated with metformin alone fail in achieving sufficient glucose control. However, each treatment presents different degrees of effectiveness and side effects. Furthermore, there is a lack of information on the comparative efficacy and safety among antihyperglycemic agents combined with metformin. On the other hand, the cut-off value of intensive glycemic control is clear for diabetes-associated microvascular complications (e.g., HbA1c $\leq$7%) but it is relatively unclear for diabetes-associated macrovascular complications.[15] Recognizing these uncertainties in the decision making process, the American Diabetes Association (ADA) and the EASD jointly introduced in 2012 the concept of a patient-centered approach, or shared decision-making, on the management of hyperglycemia in T2DM.[15,136] Ideally, physicians and patients communicate regarding treatment options, such as the pros and cons for each of the available treatments, and together choose a treatment based on an individual's unique situation and needs.

2.3.2 Patient decision aids

Tools, such as patient decision aids (PDA), have been designed to facilitate the shared decision-making process, and to support communication between physicians and patients when choosing a treatment option to best fit the patient's needs.[1] Recently, a Cochrane Collaboration systematic review of 105 randomized controlled trials of PDA studies for a variety of health conditions found that PDAs, in comparison with usual care, could help patients to improve their knowledge of diseases and help them to set up more realistic expectations of the treatment, and reduce decisional conflict.[137] In 2003, an International Patient Decision Aids Standards (IPDAS) collaboration was established, led by Drs Glyn Enwyn of the United Kingdom and Dawn Stacey of Canada. The IPDAS has developed a quality criteria framework to guide systematic development and assessment of PDAs,[138,139] including knowledge translation from two perspectives: 1) the latest evidence-based medicine supporting available treatment options with the pros and cons of each option; and 2) patient decisional needs supporting their values and preferences in the context of the patient's cultural background.

2.3.3 Shared decision making and patient decision aids in China

For the first time, the 2018 diabetes guidelines in China recommended a patient-centered approach to the management of hyperglycemia.[53] However, few studies of SDM were available in China and research in this field for hyperglycemia is still in its infancy.[140] From a broad literature search, only one PDA study of any kind for the Chinese population was identified. This PDA which involved choosing a statin, was initially developed by the Mayo Clinic in the United States, and was tested on Chinese patients with cardiovascular disease.[141] Although informative, the patient values and preferences are context-specific (or depending on different diseases). As

well, the values and preferences in other countries may not be applicable to the population in China. It is essential to develop a PDA in China by taking Chinese culture into account for patients with T2DM.

To our knowledge, the current research is the first study which will develop a PDA for patients with T2DM in China who consider adding antihyperglycemic medications to metformin monotherapy in China.

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Chapter 3 Patient decisional needs when adding antihyperglycemic agents after monotherapy failure in type 2 diabetes mellitus in China

Note: A manuscript based on Chapter 3 has recently been accepted for publication (Appendix 3G): Zheng H, Toupin-April K, An Y, He S, Sigal RJ, Coyle D, Wells GA*, Li G*, Patient decisional needs when considering treatment intensification for type 2 diabetes: A qualitative study in China. Volume 170, December 2020. Diabetes Research and Clinical Practice (link: https://www.sciencedirect.com/science/article/abs/pii/S0168822720307245).

3.1 Introduction

Recent studies in China have found that only 50% of patients with type 2 diabetes mellitus (T2DM) continue to take their prescribed antihyperglycemic agents for one year.[1,2] It is important to explore why such a high proportion of patients with diabetes discontinue or change their treatment regimens. Patients' values or preferences on choosing medications are rooted in their culture. In particular, patients with diabetes in China may seek therapies for their disease from both western medicine and traditional Chinese medicine.[3] As well, physicians in China have hectic clinical practice schedules and are unlikely to provide as much information as every individual patient needs during a clinical visit.[4,5] If we know a patient's important concerns on choosing medications, they could be addressed more efficiently and effectively to better serve the patient's medical needs.

Although the latest Chinese guidelines for patients with diabetes introduced the concept of a patient-centered approach,[6] research in this field is still in its early development in China.

Huang[7] conducted a broad literature search on shared decision making in the Chinese population and found 14 relevant studies; however, none of these studies was conducted among Chinese patients who live in China. To our knowledge, no studies identified the decisional needs of patients with T2DM in China to support them in their decision-making when considering adding antihyperglycemic agents after monotherapy failure of glucose control. This highlights the need to identify patient decisional needs. Ideally these needs should be identified directly from the patients, as well as taking into consideration the perspectives of their practitioners.[8]

The objective of this study was to identify patient decisional needs, from both the patients' and practitioners' perspectives, when considering adding antihyperglycemic agents after monotherapy failure to achieve adequate glucose control for patients with type 2 diabetes mellitus in China.

The study was conducted at the Fu Wai Hospital in Beijing, China and the study, including two data collection interview guides, received ethics approval from the Office of Research Ethnics and Integrity, University of Ottawa (H01-18-02), as well as Fu Wai Hospital, Beijing, China (#2018-1051).

3.2 Methods

Based on the Ottawa Decision Support Framework and the Decisional Needs Assessment in Populations,[9-13] nine steps were formulated in order to identify the patient decisional needs of patients with T2DM in China, namely: 1) define the objective of the needs assessment; 2)

identify the participants; 3) identify the rationale or purpose of the needs assessment; 4) identify the information to be collected; 5) select the methods for collecting the information; 6) develop data collection tools; 7) select the sample, sample size and sampling procedure; 8) develop a schedule; and 9) conduct the needs assessment and perform the analysis. We elaborate on each of these steps below.

3.2.1 Define the objective of the needs assessment

The primary objective was to describe the decision support needs of patients in China with T2DM when adding on antihyperglycemic agents to achieve good glucose control after monotherapy failure to achieve the glucose target. Patient decisional needs were assessed from both the patients' and practitioners' perspectives.

3.2.2 Identify the participants

Participants included patients with T2DM, and practitioners who provided clinical care to patients with diabetes in Fu Wai Hospital, Beijing, China.

The type of patient participants included those who were taking antihyerglycemic agents which were either western medicine or traditional Chinese medicine, or both. However, patients with severe underlying medical conditions, including diabetes-associated kidney dialysis, amputation or advanced stage of retinopathy, were excluded, given that they may have different decision support needs regarding glucose control, in comparison with patients with relatively mild diabetes-associated complications.

The practitioners included physicians and nurses who provided direct care to patients with T2DM at the Fu Wai Hospital, and had a minimum of one-year clinical experience.

3.2.3 Identify the rationale or purpose of the needs assessment

Identifying the decision-making issues that patients feel are important would be the first step in developing services to meet patients' decisional needs when adding antihyperglycemic agents to achieve adequate glucose control for patients with T2DM. Based on our search of the available literature, no such needs assessment was found for the population with T2DM in China.

This decisional needs assessment study is the first of three key tasks to achieve the overall research aim to develop a culturally appropriate and theory-driven patient decision aid (PDA) for adults with T2DM in China.

3.2.4 Identify the information to be collected

Guided by the Decisional Needs Assessment in Populations,[9-13] we developed interview guides for patient and practitioner interviews respectively. The guides collected information on the patients' experience living with T2DM, values and preferences with their health care options, knowledge of medications, decision-making about adding on antihyperglycemic medications, decisional conflict (i.e., uncertainty about the best choice), and decision support needs. As well, the practitioners' perceptions regarding patient decisional needs were assessed when adding on antihyperglycemic medications. In addition, we reviewed the relevant literature and based on discussions within the research team we added questions to the interview guides. For example, we added questions about what physicians explain to their patients when adding

antihyperglycemic medications, and what patients would choose if they have to choose a medication today, in order to help patients clarify their concerns when adding antihyperglycemic agents.[14] We also asked practitioners how much time, on average, they spend with a patient in the clinic.

We used open and close-ended questions to allow the formulation of answers potentially related to patients' concerns when adding medications, rather than a selection from a set of fixed answers, since we wanted to collect as broad information as possible.

3.2.5 Select the methods for collecting the information

Two methods were used to collect the information of patient decisional needs in China. First, semi-structured individual interviews were conducted with individual patient face-to-face interviews for collection of the information concerning their decision support needs when adding antiphyerglycemic agents. Second, focus group interviews were conducted with practitioners for collecting information of the practitioners' perceptions regarding patient decisional needs when adding antihyperglycemic agents in China. We also conducted individual interviews for those practitioners who were not available for the focus group interviews.

3.2.6 Develop data collection tools

Guided by the Decisional Needs Assessment in Populations,[9,13] two interview guides were developed: one for patient interviews (Appendix 3A) and the other for practitioner interviews (Appendix 3B). The interview guides included open- and close-ended questions. Interview guides were developed in English and translated into Chinese. They were then modified to

ensure relevance and acceptability in the Chinese context through discussions with the Chinese research team members at Fu Wai Hospital**.** The initial responses to questions were recorded on paper and then recorded in a spreadsheet (Excel) and coded for further analyses.

3.2.7 Select the sample, sample size and sampling procedure

Sample: Patients who were taking at least one antihyperglycemic agent were eligible because we wanted to learn about patients' actual experiences of making decisions on adding medications. In other words, they had made the decision to add an antihyperglycemic agent. However, those with severe diabetes-associated medical conditions such as kidney dialysis, amputation, or advanced stage of retinopathy were excluded.

Sample size: Based on Guest's field study,[15,16] data saturation likely occurs within the first 12 patient interviews and first 4 practitioner focus groups (5 to 7 practitioners per group). To help ensure that saturation was achieved, the plan was to recruit approximately 25 to 35 patients, since patients attending a tier 3 level hospital, such as the Fu Wai Hospital, come from across the country and a wide diversity of backgrounds is expected. A purposive sampling process was followed in which a sample of patients with diverse characteristics was selected. As well, the plan was to recruit approximately 20 to 30 practitioners.

Sampling procedure: Patient face-to-face interviews: A research assistant, who was not directly involved with the patients' care, selected a convenience sample of patients at Fu Wai Hospital with the goal of identifying a diverse sample of patients based on their histories and severity of diabetes and various demographic characteristics such as age, sex and geographic distribution.

The research assistant identified eligible outpatients from the hospital registry system two days before the clinic visit, and eligible inpatients two days prior to the interview. She communicated with the patients by phone and explained the study project, using the study's information sheet (Appendix 3C) and consent form (Appendix 3D). Patients were informed that there was no obligation on their part to participate in the study, and that their medical care would not be affected. If the patient agreed and signed the consent form (either over the phone or on the clinical visit day), a time to meet with the interview team was arranged on the day of the outpatient clinic visit, or at a convenient time for the inpatients. Face-to-face interviews of approximately 40 minutes were conducted in a private meeting room in June 2018.

Practitioner focus groups: Practitioners in the Department of Endocrinology at Fu Wai Hospital with more than one year of clinical experience in treating patients with diabetes were eligible. These included nurses, endocrinologists and other specialists trained in different medical fields such as cardiovascular disease. The research assistant identified eligible practitioners and explained the study project using the study information sheet (Appendix 3E). If the practitioner provided informed consent (Appendix 3F), he/she was added to a list for a focus group if they were available at the scheduled time. Focus groups took approximately one hour in a clinic conference room during working hours. Practitioners who were not available for the focus groups participated in individual interviews in the same conference room.

3.2.8 Develop a schedule

A tier-3 level hospital (i.e., hospital with various specialties), Fu Wai Hospital, was selected for the study in China mainly for two reasons: 1) patients with T2DM who visited this level of

hospital generally come from across the country and presented with more diverse backgrounds than other lower level hospitals; and 2) practitioners in such tier-3 level hospitals have experience treating patients with diverse backgrounds and were more likely to engage in a research study.

The PhD candidate (H.Z.) planned to conduct the interviews over a two-week period at Fu Wai Hospital, Beijing, China. A detailed plan of the activities during this two-week period was developed and discussed with his thesis supervisor, the Thesis Advisory Committee and colleagues at Fu Wai Hospital (table below): a training session with the research team members in Fu Wai Hospital on the interview process would be conducted on the first day; the research assistant (RA) at Fu Wai Hospital would contact participants (i.e., patients and practitioners) two days prior to the date of the interview, introduce the study and provide the information sheet; and the location for the interview was arranged in advance, in particular, considering the convenience for the outpatients on the day of their clinic visit.

Week	T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F
June	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
RA call		x			x	x	x	x	x				x			
Training	x	x														
Patients interview					x	x	x	x	x			x	x	x	x	
Practitioner interview					x	x	x	x	x			x	x	x	x	
Practitioner focus group													x		x	
Daily data analysis					x	x	x	x	x	x	x	x	x	x	x	

"X" indicates interview activities in that working day.

Face-to-face interviews and focus group interviews were all conducted during the working day. At the end of each interview, the two interviewers [H.Z., Y.A. (Yali An, research team member at Fu Wai Hospital)] reached consensus on the discussions that took place. If there were any discrepancies, they reviewed their initial notes or transcripts and discussed the participant responses during the interview in order to reach consensus. Audio recording was not used because it was not deemed acceptable by local authorities at Fu Wai Hospital, due to the cultural context and participants' concerns.

3.2.9 Conduct the needs assessment and perform the analysis

Content analysis

The evaluation of the text data was guided by content analysis.[17] First, the two interviewers (H.Z, Y.A.) independently reviewed open-ended question response (text data) line by line and identified any potential ideas in the phrases, sentences or paragraphs. They created a code or a phrase. Each code described the meaning of the text data with its idea in simple words. The two reviewers compared the coded transcripts. If any discrepancy occurred, both interviewers reviewed their initial text data to check their coding, and then discussed the issue and reached consensus. This was done after each face-to-face interview. The interviews were conducted and this process followed until data saturation was achieved. This was defined as the point at which no new ideas could be generated or contributed to existing ideas or codes in subsequent face-to-face interviews. Next, following a similar process, the two interviewers would independently generate a second level set of codes based on the list of initial codes, by merging the initial codes with similar meanings. Each second-level code described the meaning of the combined text data with its idea in simple words. The second-level coded transcripts were compared. If any

discrepancy occurred, both reviewers reviewed the initial text data to check their first level coding, and then openly discussed the issue and reached consensus. Otherwise, the research team made a final decision.

Finally, the codes were tabulated and sorted to identify a range of categories or themes. The codes and their interactions were considered as representing the main categories or themes associated with the study purpose of identifying patient decision making needs.

Statistical analysis

The characteristics of the study participants were described using percentages for the categorical variables and means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables. In situations where subgroups of patients were compared on categorical variables, the Fisher's exact test was used. Patients' knowledge score was computed by dividing the number of questions answered correctly by the total number of questions. The maximum score for each medicine was 3 (1 for knowing the advantage; 1 for knowing the disadvantage; and 1 for knowing the risk), and for a patient with more than one medication, the average of the knowledge scores was calculated.

3.3 Results

3.3.1 Study participants

In total, 35 patients with type 2 diabetes participated in the semi-structured individual interviews, and 28 practitioners providing care to patients with diabetes participated in semi-structured individual interviews and focus group interviews at Fu Wai Hospital. The 35 patients interviewed, came to Fu Wai Hospital from a wide range of geographic regions in China (Figure

3.1). Of the 28 practitioners, 12 practitioners participated in two focus group sessions, 6 in each, and sixteen participated in individual interviews. Only 2 of the 37 patients invited declined because of cancelled clinic visits, and one of the 29 practitioners invited did not participate because of time commitments.

Figure 3.1: Geographic distribution of the interviewed patients in China *

*gray indicates the provinces where the participants residence

Table 3.1: Characteristics of the patients interviewed

Patient characteristic	Percentage (n=35)
Age (years)	
30-39	5.7
40-49	5.7
50-59	31.5
60+	57.1
Sex	
Male	54.3
Female	45.7
Monthly income (RMB) *	
≤ 3000	25.7
3000 – 5000	31.4
5000 – 9000	20.0
> 9000	22.9
Median (IQR[+])	5000 (3000, 8300)

Occupation	
Managers (CEO, Manager, Self-employed)	8.7
Professionals (Accountant, Architecture, Businessman, Teacher)	11.7
Technicians and Associate Professionals (Civil servant, Finance, Technician, Real estate)	20.1
Services and Sales Workers (Policeman)	2.9
Craft and Related Trades Workers (Blue-collar Worker)	8.6
Other: Housewife	5.7
Retirement	40.0
Residence region	
Beijing	51.4
Hai Nan	2.9
He Nan	2.9
He Bei	2.9
Hei Long Jiang	11.4
Ji Lin	5.7
Jiang Su	2.9
Nei Meng	5.7
Shan Dong	5.7
Shan Xi	8.6
DM duration	
≤ 5 years	21.6
6 - 9 years	27.0
10 - 15 years	27.0
> 15 years	24.3
Median (IQR)	11 (6.0, 9.0)
HbA1c	
≤ 6.5%	25.7
6.6-7.3%	25.7
7.4-8.7%	25.7
> 8.7%	20.0
Median (IQR)	7.7 (6.0,8.1)
Insurance coverage	
Urban Employee Basic Medical Insurance	14.3
Urban Resident Basic Medical Insurance/New Rural Cooperative Medical System	60.0
Self-payment	14.3
Other	11.4
Education	
No school	5.7
Primary School	14.3
High school	22.9
College	28.6
University	20.0
Graduate Degree	8.6
DM treatment	
Metformin	82.9
Insulin	62.9
GLP-1 analogue	22.9
DPP-4 inhibitor	14.3
Acarbose	20.0
Traditional Chinese Medicine	8.6
Sulfonylureas	5.8
Meglitinides	2.9

* The unit is Chinese Yuan (RMB) in China. One US dollar is equal about 6 RMB.

Twenty-eight practitioners participated in the study: 17 physicians and 11 nurses. Their mean age was 35 years (SD 7.7 years), and most were female (23/28). Physicians typically spent an average of 11 to 15 minutes per clinical visit (Table 3.2).

Table 3.2: Characteristics of the practitioners interviewed

Professional characteristic		**Percentage**
Age (years)	(N=28)	
	20-29	32.1
	30-39	42.8
	40-49	25.0
Sex	(N=28)	
	Male	17.9
	Female	82.1
Department	(N=28)	
	Cardiovascular	10.7
	Endocrinology	32.1
	General Practitioner	17.9
	Nurse	39.3
Patients seen per day	(n=16 physicians)	
	5-10	31.2
	11-20	18.8
	21-30	25.0
	> 30	25.0
Time per patient	(n=16 physicians)	
	4-10 minutes	12.5
	11-15 minutes	56.3
	>15 minutes	25.0

3.3.2 Thematic summary

Based on the Ottawa Decision Support Framework,[9-13] seven thematic categories were identified, namely: (1) patient experience in using the health care system; (2) patient knowledge and exchange about their medications; (3) decision conflict (uncertainty about the best choice); (4) factors potentially relevant to decisional conflict; (5) patient values and preferences; (6) role in decision making; and (7) patient decision support. Each of these themes is described below.

3.3.2.1 Patient experience in using the health care system

Patients' Perspective:

All but one patient reported having tried different types of medications for diabetes, including Western medicine and traditional Chinese medicine (TCM). Most patients perceived Western medicine as being more effective and less safe in comparison with TCM. Most of the patients using TCM mentioned using them as a holistic treatment for body functions and not necessarily to reduce high blood sugar.

> *"When my blood sugar level was high, I used Western medications. When my blood sugar [was] back to normal, I preferred to take Traditional Chinese medications because the newspapers said they were made of herbs and they had no side effects." (Patient 10)*

Almost half of the patients reported visiting different hospitals and consulting with different physicians. Patients reported trusting health care services provided in larger hospitals or tier-3 level hospitals, and they indicated believing medical advice from specialists more than from general practitioners outside of tier-3 level hospitals. Nearly all patients reported consulting

specialists and/or renowned experts in diabetes. Few patients mentioned going to see a general practitioner in his/her community.

> *"I lived in a small town (in the northern part of Jilin province). I came to Fu Wai hospital because this is a tier-3 level famous hospital and had very well-known experts in diabetes. I did not trust the doctors in my small town and there was no advanced medical devices like here." (Patient 6)*

Younger (p=0.005) and more educated (p=0.045) patients were more likely to report visiting multiple hospitals than older and less educated individuals. The most common sources of information for patients were newspapers, magazines, internet, social media and friends, as well as information available in hospitals.

3.3.2.2 Patient knowledge and exchange of information about their medications

Patients' perspective:

Most patients could not correctly answer one-third of the questions about their current antihyperglycemic medications. In general, patients who took TCM were more likely to have less knowledge of their medications (p=0.02).

Some patients also mentioned that practitioners did not provide them with information on the side effects of new drugs.

> *"I had diabetes less than two years and I changed medications many times for diabetes. Every time we added or changed medication, my doctor could not explain its side effects to me." (Patient 20)*

Practitioners' perspective:

Some of the practitioners revealed that patients have expectations of the pharmacological treatment for diabetes which were not realistic. In fact, more than half of practitioners reported that their patients were looking for various types of medications to cure type 2 diabetes, often after hearing about treatments which were reported to be effective in the media.

> *"Patients often came to the clinic and asked for medicine (either Western medicine or Traditional Chinese medicine) to cure the disease of* type 2 diabetes*. Sometimes, they provide the names of the medicines because they got them from their friends or heard it on TV, or sometimes, they just ask if there are new medicines available." (Practitioner 7)*

3.3.2.3 Decisional conflict (uncertainty about the best choice)

Patients' perspective:

Given that all the patients were taking at least one antihyperglycemic medication, we asked about their feelings when adding medications to their existing regimen. Although most patients reported that they accepted adding medications, a few patients reported concerns and negative feelings such as feeling distressed or upset, worried about what could go wrong, wavering between choices or changing their mind.

> *"my doctor gave me a new drug (for diabetes), but I read some drug company's report on the drug later which mentioned a lot of side effects of this drug. So, I did not know what to do and came to the big hospital to ask the expert." (Patient 26)*

Practitioners' perspective:

As with patients, most practitioners reported their patients were receptive to add-on medications. However, they mentioned that many patients were uncertain about what to do. Most practitioners

also observed patients' concerns and negative feelings related to adding medications such as: questioning why they should add medication; being distressed or upset; delaying the decision; worrying about what could go wrong; and feeling physically stressed. Fewer practitioners observed other more serious patients' concerns and negative feelings such as: refusing to accept the change of treatment; crying and sadness; and reducing the dosage or stopping the prescribed medications without informing their physicians.

> *"A patient came to the clinic with high glucose level. The patient started to use insulin to control hyperglycemia at the local hospital, but he heard that once he would begin insulin, it would become addictive. So the patient came to our hospital" (Practitioner 11)*

3.3.2.4 Factors potentially related to decisional conflict

Patients' perspective:

When asked about factors that may result in decisional conflict, most patients expressed confusion due to the diversity of information on antihyperglycemic medications being provided from various sources such as television, newspapers, internet other social media and friends. Interviewed patients complained that they were lacking reliable information on risks and benefits of the antihyperglycemic drugs that they were interested in possibly taking. Nearly all patients reported that consulting specialists and/or renowned experts in tier-3 level hospitals made their decision easier because they trusted their recommendations.

> *"In my hometown, my doctor asked me to take metformin, but the newspaper said the drug harms kidney function, so I took Traditional Chinese Medication, but my blood sugar is very high, then I came to the big hospital to find a good drug." (Patient 15)*

In addition, some patients felt unsupported by their families in making decisions. Some also mentioned the lack of financial support to pay for drugs that are not covered by their insurance, which then has an impact on decision-making.

> *"I am obese and have diabetes. I heard a new drug can reduce weight and blood sugar, but the drug was expensive and was not covered by my insurance. I want to use it, but my family members did not support me financially to use this new drug." (Patient 11)*

Some felt pressure from others, such as friends with diabetes, to use a novel medication for diabetes.

> *"My friend with diabetes had started to take a new drug for diabetes and he said the drug was very effective and had no side effects. He said I should use it, but the doctor in my hometown said the drug was not good in my case. So, I came to the big hospital to see famous experts." (Patient 18)*

Practitioners' perspective:

The confusion felt by patients about the information on medications was echoed by the practitioners. Nearly all practitioners mentioned that their patients did not know which source of information was more reliable and which information they could trust.

Practitioners reported that their patients were influenced largely by the pressure from others to make decisions that were not necessarily appropriate for them, which would lead to uncertainty.

> *"If a patient knows that some of his friends with diabetes are taking a new medication, or if a drug was advertised frequently on television, or had an attractive drug name, patients often*

confuse whether they should or should not use the new drug and they may then not know what to do." (Practitioner 3)

"Patients need more support in decision-making from their families. Also, if some medications are not covered by a patient's current insurance plan or covered partially, family members have to pay out-of-pocket and they will make a big decision." (Practitioner 10)

A trust relationship between patients and practitioners:

Consistently, both patients and practitioners identified a "trust" relationship between a patient and a practitioner is critical when adding antihyperglycemic medication. Interviewed practitioners noted that their patients often accepted to add-on antihyperglycemic medication when these were prescribed by consulting specialists and/or renowned experts in tier-3 level hospitals.

"I came to the big hospital and saw famous doctors for diabetes. If they asked me to take some medication I would do it, but I may not do it if the doctor at my small hometown suggested it to me." (Patient 7)

"Sometimes, we may prescribe the same medication that the patient had been told previously by his or her doctor at local hospital. Patients accepted them when we introduced it." (Practitioner 5).

3.3.2.5 Patient values and preferences

Patients' perspective:

Most patients were concerned about adverse effects, specifically on kidneys and the liver. They also worried about medication effectiveness.

"My doctor gave me metformin, but the newspaper said the drug was harmful to kidney and liver function, so I really worried about the drug not being good for me." (Patient 22)

Other common patient worries included: weight gain and hypoglycemia; daily frequency of medication administration; the cost of therapies; and insurance coverage. Notably, female patients were more concerned about weight gain than male patients. Patients with higher incomes were more concerned about the effectiveness of the drugs compared to patients with lower incomes. For example, more women than men were concerned about weight gain ($p=0.003$), and the higher the income, the more concern about the effectiveness of the medication ($p=0.05$).

Most patients reported that their physicians seldom asked about their concerns when adding medications.

"*I have type 2 diabetes for more than seven years. When adding medications, my doctor just told me that my blood sugar level was high, and I needed to add medications. I worried for my kidney and liver function, but my doctor did not ask my worries when he gave the medication*." *(Patient 12)*

Patients with a short duration of diabetes were more likely to be asked ($p=0.04$).

Practitioners' perspective:

Patient concerns were largely echoed by practitioners. Most practitioners noted their patients were often concerned about the safety of medications, in particular: the impact on kidney and liver function; the convenience of administration; and the cost of medications. However, only a few practitioners felt that patients were concerned about medication effectiveness.

"Most patients in clinic asked about the negative impact of medicines on kidney and liver function because they often heard from the newspapers and TV that some new drugs had no side

effects on kidneys and liver. Patients asked more often about side effects than efficacy of medicines." (Practitioner 19)

3.3.2.6 Role in decision-making

Patients' perspective:

One-third of patients mentioned that they were actively involved in their decisions about add-on medications. One-third mentioned they simply agreed with their health care providers' recommendations. One-third mentioned that the decisions were made by their family members, relatives, friends or even other patients with diabetes. Nearly all patients reported that they were capable of making a decision.

Practitioners' perspective:

Practitioners, in general, perceived that a large majority (e.g., almost two-thirds) of medical decisions were made by physicians and patient's family members and friends combined, without the patients. Few practitioners perceived that patients had the ability to make decisions.

"Patients' family members play a very important role in decision making, especially for those patients with low income and/or low education. Family members sometimes support patients not only emotionally but also financially." (Practitioner 25).

3.3.2.7 Patient decision support

Patients' perspective:

Most of the interviewed patients wished to have reliable information on risks and benefits of medications. They wanted to be more engaged in decision-making and to express their concerns about treatment options to practitioners when choosing to add on medications.

Practitioners' perspective:

When practitioners were asked how they could help patients to make a sound clinical decision about adding diabetes medications, practitioners noted that their own knowledge about new medications was important because patients often asked about them. Most practitioners said they needed to improve their communication skills and suggested that some examples of successful cases may be good ideas to facilitate the knowledge translation especially during a clinical visit.

> *"It was challenge to clearly explain benefits and risks of medications to patients in such a short clinical visit time period, and it would be better to have successful cases as examples or other simple tools to help explain information to patients when adding medications" (Practitioner 2)*

In addition, half of the practitioners reported that the support from the patient's family was important for making decision.

3.4 Discussion

A patient-centered approach of hyperglycemic management for patient with T2DM has been increasingly recognized in China,[6] however, little is known about patient decisional needs for treatment of diabetes in China.[7] To our knowledge, this is the first study that explored decisional needs for adults with T2DM who considered adding antihyperglycemic agents, from both the patients' and practitioners' perspectives.

Interviewed patients presented a diversity of personal experiences of T2DM treatment, including using a variety of Western medications and traditional Chinese medications, with many of them

visiting different hospitals and consulting different physicians, especially specialists in diabetes at tier-3 level hospitals.

Most patients did not know their HbA1c levels and had little knowledge about their medications, illustrated by only one-third of the interviewed patients being able to correctly answer questions about their medications. Coincidently, our results echoed the 2019 standards of medical care for T2DM in China "the overall proportion of patients who were aware of their diabetes condition was 38.6%".[6] Also, patients who took traditional medications were more likely, in general, to show less knowledge of their medications. Consistent with patients' low knowledge, some of the practitioners revealed that patients had expectations of the pharmacological treatment for diabetes that were not realistic, such as thinking that some medications could cure type 2 diabetes. Some patients also mentioned that practitioners did not provide them with information on the side effects of new drugs, and they were lacking reliable information on risks and benefits of antihyperglycemic drugs, which may partially explain their low level of knowledge of the risk-benefit features of the medications.

Although most patients reported that they accepted adding medications, some patients expressed concerns and negative feelings and practitioners reported these concerns and negative feelings among their patients. These appear to be related to a patient's confusion due to the contradictory information from various sources and ultimately trusting recommendations of experts in tier-3 level hospitals. Other factors that may have played a role included the lack of decision-making support and financial support from their families, as well as pressure from friends and relatives.

Patients' trust of experts working in tier-3 level hospitals is an element that helped them make a decision and follow the advice of the professionals. But this trust ideally should go beyond tier-3 level hospitals and also exist at the tier-2 and tier-1 level hospitals. It is well known that renowned experts or specialists commonly practise at large hospitals or tier-3 levels such as Fu Wai Hospital, however there are only 30,000 specialists to deal with 120 million patients with diabetes in China.[18] As indicated in our results, specialists can only spend approximately 10-15 minutes per patient visit. Other studies in China even showed that physicians spend less than 10 minutes per patient during clinical visits.[7] Today, there is a "trust crisis" in the health care system in China.[7,19,20] The ongoing health care reform is intended to focus primarily on patient-centered medical care and to improve the patient and practitioner relationship in the country.[21]

Patient values and preferences when adding on antihyperglycemic agents were largely consistent between patients and practitioners, often focusing on the safety, cost and the convenience of medications. These values may change depending on individuals' socioeconomic and demographic characteristics; for instance, the perception of weight gain associated with using antihyperglycemic agents seems more concerning to females than males. In our results, practitioners did not rank drug effectiveness as high as patients which is similar to a study in Malaysia finding that patients focused more on the treatment side effects and physicians focused more on the efficacy when they consider a treatment.[8] Furthermore, it seems that the higher patient's income, the more they cared about the effectiveness of the medications as well.

Making a decision when adding medications involves physicians, patients and other individuals which include family members or relatives, spouses, friends or even other patients with diabetes.

Although patient values and preferences were recognized, they were rarely communicated, and most physicians simply told patients that their blood glucose level was high and that they needed to add medications. Following failure with metformin monotherapy, patients face many treatment options and physicians can choose one or another medication depending on each individual patient needs. At this stage, there is no single "best" treatment for T2DM and the communication between patients, family members and physicians becomes critical to consider individual patient values and preferences.[22] Such communication is essential for this shared decision-making process to happen. However, communication is not optimal. In fact, most practitioners during the interviews indicated they wished to improve their communication with patients, which is consistent with other studies which showed that physicians in China require better communication skills because of minimal patient communication training in medical school.[23]

Of note, most patients wish to engage more in making decision. These findings are similar to a study which showed that Chinese patients desired greater involvement in medical decision making.[7] For patients to be able to play a role in a shared decision-making process, they need understandable information about the specific condition and associated treatment options. Using tools such as PDAs and decision coaching[24,25] may help prepare patients, family members, and others to engage in decision-making by providing them with evidence-based information about treatment options and having open conversations with practitioners about patients' values and preferences.

Strengths and limitations

To our knowledge, this is the first study to investigate patient needs among individuals with type 2 diabetes in China and provides an in-depth exploration of the needs, from both patient and practitioner perspectives. Some limitations should be considered. First, we could not analyze the results separately for outpatients and inpatients because of the small numbers of inpatients (5/35). Second, the two focus group sessions included both physicians and nurses with the goal of including a diverse selection of practitioners, and the numbers were too small for a separate analysis by physicians versus nurses. Third, the study had no audio transcription of interviews, although the two interviewers (H.Z., Y.A) reviewed notes and reached consensus at the end of each interview while the information was fresh in their minds. Fourth, age and sex were important demographic characteristics in T2DM, but the specific subgroups by age or sex would not be large enough to provide meaningful interpretations. Finally, the values and preferences are specific to patients with T2DM in China and are not necessarily generalizable to other countries and healthcare systems.

Conclusion

The findings from our study suggest that patients with T2DM in China have suboptimal knowledge of antihyperglycemic medications, although they visit various hospitals and see different physicians. Patients want more consistent and clear information on treatment options and wish to be more engaged in making a decision regarding their treatment. On the other hand, practitioners indicated a willingness to participate in a shared decision making process with patients, a sentiment that was also identified in other studies in China. A PDA may help to

facilitate this shared decision making for patients who fail metformin monotherapy and are considering add-on antihyperglycemic medications.

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Chapter 4 A systematic review and network meta-analysis to determine the comparative efficacy and safety of antihyperglycemic agents for patients with type 2 diabetes mellitus following failure with metformin monotherapy

4.1 Introduction

Adequate glucose control is an important component of clinical management of diabetes since hyperglycemia is associated with increased risk of diabetic complications.[1,2] For example, a one percentage point increase in hemoglobin A1c (HbA1c) is associated with approximately a 30% increase in risk in mortality for patients with type 2 diabetes mellitus (T2DM).[3] Current guidelines[4-6] recommend metformin as a first line treatment along with lifestyle modifications. Due to the progressive nature of T2DM, most patients require more than one antihyperglycemic agent over their lifetime in order to maintain near-normal glucose targets or good glucose control.[7] After patients with metformin monotherapy fail to achieve sufficient glucose control, the guidelines recommend to add another agent, but no specific antihyperglycemic agent or class is endorsed for patients with T2DM, with the exception for those who already have comorbid cardiovascular or renal diseases,[4-6,8] in which case the SGLT2 inhibitors (empagliflozin) and GLP-1 receptor agonists (liraglutide) are specifically recommended. Despite the rapidly growing diversity of pharmacologic options, there is a paucity of head-to-head comparisons between these therapies that can be considered as add-on to metformin. This gap in the evidence-based medicine has given impetus for the current research.

A previous systematic review and network meta-analysis (NMA) was conducted in 2016.[9] This study assessed the relative efficacy and safety, in particular, of novel antihyperglycemic classes, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors, glucagon-like-peptide-1 receptor agonists (GLP-1 RAs), and dipeptidyl peptidase-4 (DPP-4) inhibitors all combined with metformin.[9] The results from the NMAs showed that: all selected classes significantly reduced HbA1c compared to metformin monotherapy; GLP-1 RAs were superior to DPP-4 inhibitors in HbA1c control; SGLT-2 inhibitors and GLP-1 RAs were superior to other treatments in reduction of body weight and systolic blood pressure; and GLP-1 RAs increased the risk of total adverse events and withdrawals due to adverse events. Due to limited data, SGLT-2 inhibitors did not show a significantly increased risk of urogenital adverse events.[9] An updated analysis is required to incorporate the numerous randomized controlled trials (RCTs) completed and published since the last review in 2016, and to assess the efficacy and safety of all antihyperglycemic classes and not limited to selected classes.[9] Although some recently conducted NMAs provided indirect comparisons of antihyperglycemic agents combined with metformin, they often included only a small number of RCTs (e.g., 12 RCTs[10]), included few antihyperglycemic classes,[10-12] and/or included a limited number of clinical outcomes.[10-12]

The objective of this study was to comprehensively compare efficacy and safety of all antihyperglycemic classes combined with metformin for patients with type 2 diabetes in whom there was inadequate glycemic control with metformin monotherapy.

4.2 Methods

4.2.1 Scope and protocol

The initial systematic review and network-meta analysis was designed in support of the clinical evidence needs of the Canadian Agency for Drugs and Technologies in Health (CADTH).[9,13] The study was registered with the International Prospective Register of Systematic Reviews (register number CRD42016038144), and it followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14] The update to this systematic review was conducted following the same procedures and processes as the original review, however only the RCTs which involved patients with T2DM for whom there was inadequate glycemic control and antihyperglycemic agents were added on to metformin were selected and considered in the NMA. That is, the RCTs of interest were restricted to the population of patients with T2DM for whom there was inadequate glycemic control, who were randomized to either an antihyperglycemic agent plus metformin vs metformin or an antihyperglycemic agent plus metformin vs another antihyperglycemic agent plus metformin.

4.2.2 Literature search strategy

Following a structured search strategy, which was developed and tested through an iterative process by an experienced medical information specialist in consultation with the research team,[9] the current systematic review was executed to include citations up to 10 October 2018 using the OVID platform search for the following databases: Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Embase Classic + Embase. Cochrane CENTRAL on Wiley was searched, as well as PubMed for the most recent and unindexed citations.

Literature search strategies used a combination of controlled vocabulary (e.g., "Diabetes Mellitus, Type 2", "Hypoglycemic Agents", "Dipeptidyl-Peptidase IV Inhibitors") and keywords (e.g., "T2DM", "anti-diabetic", "DPP 4 inhibitors", "SGLT 2 inhibitors"). Vocabulary and syntax were adjusted across databases. The 2008 sensitivity- and precision-maximizing version of the Cochrane highly sensitive search strategy was used to identify randomized controlled trials. When possible, animal-only and opinion-pieces were removed from the search results.

Specific details on the literature search strategies are available in Appendix 4A.

4.2.3 Selection criteria

Studies were eligible for inclusion in the updated systematic review if they met the population, interventions, comparators, outcomes of interest and study design (PICOS) criteria as outlined in Table 4.1. The population of interest was adults with T2DM on metformin pharmacotherapy with insufficient glucose control. The diagnosis of T2DM was made if the fasting plasma glucose level was ≥ 7mmol/l (126 mg/dl), and /or 2-hour post-load plasma glucose level was ≥ 11.1mmol/l (200 mg/dl) and/ or HbA1c ≥ 6.5% on at least two occasions.[6] Interventions included agents from any of the following eight antihyperglycemic classes: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), basal and biphasic insulin, dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), glucagon-like-peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transport 2 inhibitors (SGLT-2 inhibitors). The comparators included regimens combining any antihyperglycemic agents, as described above, with metformin. The outcomes of interest were based on clinical relevance and data availability including HbA1c, non-severe hypoglycemia, severe hypoglycemia, body weight, body mass

index, systolic blood pressure, diastolic blood pressure, low density lipoprotein cholesterol, total cholesterol, high density lipoprotein cholesterol, total adverse events, serious adverse events, withdrawals due to adverse events, urogenital adverse events, heart failure, renal adverse events, bone fractures, all-cause mortality, cardiovascular mortality, fatal stroke, unstable angina, transient ischemic attack and pancreatitis. The eligible study design was the randomized controlled trial. Exclusion criteria included: a treatment duration less than 4 weeks; language of full-text publication was not English; and participants with mixed background therapies and results were not reported separately or no results were reported for the subgroup of metformin users.

Table 4.1: Population, intervention, comparator, outcome and study designs of interest

Population	Adults with type 2 diabetes on metformin with inadequate glycemic control [a]	
Interventions and Comparators [b]	**SGLT-2 inhibitors**	canagliflozin, dapagliflozin, empagliflozin
	GLP-1 analogues	dulaglutide, exenatide, liraglutide
	DPP-4 inhibitors	alogliptin, linagliptin, saxagliptin, sitagliptin
	Sulfonylureas	chlorpropamide, gliclazide, glimepiride, glyburide, tolbutamide
	Insulin	Regular insulin, pork insulin, insulin aspart, insulin lispro, insulin glulisine, insulin NPH, insulin detemir, insulin glargine, mixed regular insulin/insulin NPH, mixed insulin lispro/lispro protamine and mixed insulin aspart/aspart protamine
	Metformin	
	Placebo	

Outcomes	**Clinical benefits** [c, d]	Reduction in: • All-cause mortality • Fatal and non-fatal myocardial infarction • Fatal and non-fatal stroke • Unstable angina • Hospitalization for unstable angina • Heart failure • Transient ischemic attack • Coronary revascularization procedure • Blood pressure • Body weight • Body mass index • Hemoglobin A1c
	Clinical harms	• Total adverse events • Serious adverse events • Withdrawals due to adverse events
	Other notable harms	• Hypoglycemia • Urogenital adverse events • Renal adverse events • Lipids • Ketoacidosis • Bone fractures • Bladder cancer • Pancreatitis • Pancreatic cancer

A1C = glycated hemoglobin; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; NPH = neutral protamine Hagedorn; SGLT-2 = sodium-glucose cotransporter-2; TBC = to be confirmed.

[a] In the previous CADTH review, inadequate control was defined as hemoglobin A1C > 6.5% or fasting plasma glucose > 7 mmol/L or two-hour post-prandial glucose > 10 mmol/L.

[b] Interventions may include regimens combining the above drugs with metformin, a sulfonylurea, insulin product and/or other drug (e.g., pioglitazone) as indicated in the Health Canada product monographs. Other agents (including meglitinides, alpha-glucosidase inhibitors, thiazolidinediones or insulin degludec) may also be included as comparators in the network meta-analysis.

[c] Based on a reduction in events, or a change in clinical measurement signifying improvement or clinical benefit.

[d] A decrease in weight will be considered a clinical benefit, while an increase in weight will be considered a harm.

Standardized methods and customized forms in DistillerSR, an online systematic review software tool (https://distillercer.com/products /distillers-systematic-review-software/), were utilized. This maximized efficiency and effectiveness in the review process and facilitated consistency and transparency across reviewers for literature screening, selection, and data extraction.

Two reviewers (H.Z. the PhD candidate and A.B. a research assistant) independently reviewed and selected studies identified by the search strategies at the title and abstract stage of the screening. Full text articles of these studies were then retrieved and assessed in a similar fashion at the second level full text screen. Any disagreements were resolved by consensus between the two reviewers when possible; otherwise, the third reviewer (G.A.W. the thesis supervisor) was considered final. As noted earlier, only the RCTs which involved patients with T2DM for whom there was inadequate glycemic control and antihyperglycemic agents were added on to metformin were selected and considered in this NMA. That is, the RCTs of interest were restricted to the population of patients with T2DM for whom there was inadequate glycemic control, who were randomized to either an antihyperglycemic agent plus metformin vs metformin or an antihyperglycemic agent plus metformin vs another antihyperglycemic agent plus metformin. Detailed selection criteria are listed in Table 4.2.

Table 4.2: Detailed selection criteria for identifying eligible randomized controlled trials

Inclusion Criteria	**Study was included if:**
	The design was randomized controlled trial.
	It was published in English.
	Study participants must have inadequately controlled type 2 diabetes and received a second-line drug as an add-on to metformin monotherapy.
	Studies employed a combination of metformin and any other antihyperglycemic medication.
	Studies were included regardless of metformin dosage at baseline or treatment history prior to the metformin.
Exclusion Criteria	**Study was excluded if:**
	Treatment duration was less than 4 weeks.
	Reported only in abstract format.
	Not all participants in the study population had type 2 diabetes, and results for the participants with diabetes were not reported separately.
	Crossover study design and the first period results are not available.
	Intervention was not an antihyperglycemic medication.
	Participants with mixed background therapies and results were not reported separately.

4.2.4 Data extraction

Two reviewers (H.Z., A.B.) independently extracted data from eligible RCTs using the online systematic review software tools with pre-designed data extraction forms in DistillerSR. During the data extraction process, any disagreements were resolved by consensus when possible; otherwise, the third reviewer's opinion (G.A.W.) was considered final.

For eligible studies, the initial publication for each unique study was usually considered for data extraction. If multiple publications for a single RCT were found, we extracted the most recently adjudicated data for each outcome specified in the protocol that involved the population of interest (either the overall population or subgroup of interest). For example, companion publications reported additional outcomes from the primary study. Furthermore, when published studies did not report an outcome of interest, we reviewed and extracted data of interest from clinical trial registry records reporting study results (e.g., clinicaltrials.gov). For studies included in previous reviews, a *de novo* data extraction process for those outcomes and baseline characteristics that had not been previously assessed was implemented (e.g., total cholesterol, systolic blood pressure), following the same methods and procedures as for studies identified in the literature search.

If a study reported outcomes at multiple time points, the outcome for the longest time point within the formal randomization period of the trial was selected. When data were not available in a publication in text format, the first reviewer (H.Z.) extracted the data from figures using WebPlotDigitizer (www.arohatgi.info.WebPotDigitizer) and the second reviewer (A.B.) verified the data to help ensure the accuracy of the data extraction.

For some notable harm outcomes such as bone fractures, urogenital adverse events and renal adverse events, the total number of outcomes or the total number of patients with at least one outcome, or both during the treatment period were extracted. In preparing for the analysis, patients experiencing some types of study-reported outcomes needed to be combined to generate a total number of patients with the outcome of interest. For example, for the outcome "urogenital adverse events", patients with urinary tract infections and genital mycotic infections were separately reported and needed to be combined to create a total number of patients with urogenital adverse events. When patients needed to be combined, the number of patients experiencing any one of the outcomes were summed together. This approach was used given the fact that most studies did not report whether the same patients experienced more than one type of outcome.

The outcomes of all-cause mortality, cardiovascular mortality and fatal myocardial infarction or stroke were inferred to be zero if the studies explicitly stated that no fatalities occurred.

For each RCT, data extraction included: 1) basic characteristics of trial participants, inclusion and exclusion criteria, outcome definitions such as hypoglycemia and baseline characteristics; 2) interventions studied, including dosing, and background therapy; 3) results of the clinical benefit and harm outcomes of interest; and 4) study design characteristics in order to assess the risk of bias.

4.2.5 Risk of bias assessment

The quality of studies was assessed independently by two reviewers (H.Z., A.B. or S.A. a research assistant) using the Cochrane Collaboration's Risk of Bias (ROB) tool.[15] This ROB tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other issues (excluded for this assessment). A form was created in line with the Cochrane Collaboration's ROB template. The first part of the form describes what was reported in the study; and the second part assigns a judgment relevant to the risk of bias for that entry by replying to a pre-specified question about the adequacy of the study associated with the entry, including a judgment of whether it is 'LOW' risk of bias, 'HIGH' risk of bias and 'UNCLEAR' or unknown risk of bias. Blinding was assessed separately for objective outcomes and subjective outcomes, given that objective outcomes in unblinded studies may be prone to less risk of bias than subjective outcomes because they tend to be less person dependent and more based on standardized criteria or equipment output such as laboratory testing results of HbA1c.

For each study, the initial publication was the primary source of information. When additional information was available in other publications related to this study, such as study protocol, companion publication and clinical trial register records, it was used in the ROB assessment.

Following the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) of quality of evidence (https://www.gradeworkinggroup.org/), we further assessed the overall risk of bias for each study by clarifying the study either as "High ROB" or as "Not High

ROB". In our assessment, we classified a study as "High ROB" if any one of the five domains of bias is identified as high risk; otherwise the study is classified as "Not High ROB".

Any disagreements on the ROB assessment were solved by consensus between the two reviewers when possible; otherwise, the judgment of a third reviewer (G.A.W.) was considered final.

4.2.6 Data conversion

Prior to the data analysis, studies that reported the same outcomes by using different units were converted to a common unit (for example, HbA1c value was presented either in % or in mmol/mol).

For continuous outcomes, the mean of the change in the outcome from baseline to end of follow-up was the measure of interest, with subsequent comparison of the difference in these means between the treatment groups. When a study did not provide these mean changes in the outcome, all other available data were extracted from the study in order to calculate or estimate these mean changes in the outcome.

4.2.7 Data analysis

The Bayesian network meta-analysis was conducted using WinBUGS software version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Dichotomous outcomes were assessed using a binomial likelihood model with a logit link function and continuous outcomes were assessed using a normal likelihood model with an identity link function as suggested by researchers at the

universities in Bristol and Leicester.[16] The default reference group for the NMAs was either metformin monotherapy or placebo plus metformin.

Effect estimates included odds ratio (OR) for dichotomous outcomes and mean difference (MD) for continuous outcomes. Point estimates and 95% credible intervals were assessed using Markov Chain Monte Carlo methods and basic parameters of the treatment effects in the model were assigned vague prior distribution, N (0, 100^2). For the random-effect model, informative priors for the between studies variance parameter were considered based on Turner et al.[17] Continuity correction was also applied before NMA to adjust for zero events reported in dichotomous outcomes by adding a fraction of the reciprocal of the size of the opposite treatment arm to the event.[18] It has been noted that the exclusion of studies with zero events in all treatment arms of the study can impact the conclusions in a meta-analysis.[249] A sensitivity analysis on this study characteristic was conducted. Both fixed-effects and random-effects NMAs were conducted. The assessment of the deviance information criterion (DIC) and the comparison of residual deviance to the number of unconstrained data points were used to evaluate the goodness of model fit, with lower DIC and residual deviance values suggesting better fit. In particular, the residual deviance value should be less than the number of uncontained data points. Model diagnostics, including trace plots and the Brooks–Gelman–Rubin statistic, were considered to assess model convergence. We utilized three chains to fit the model, each with over 10,000 iterations, with a burn-in of over 10,000 iterations.[19] The model consistency of the network was formally assessed by plotting the posterior mean of the total residual deviance derived from parameters of inconsistency models on the vertical axis (or y axis) against the deviance derived from parameters of consistency models or used in analyses on the horizontal axis (or x axis).

Consistency is assumed when points follow a diagonal trend line with closely equal x and y values.[19,20] Additional sensitivity analysis was used to assess the influence of removing inconsistent studies.

The frequentist pairwise meta-analysis was performed using RevMan when the sufficient data were not available for network meta-analysis model. A random-effects model was used in all pairwise meta-analyses using the generic inverse variance approach.

Study design characteristics are expected to be variable, and in some cases sensitivity analyses were condcuted. In particular, a wide range of the duration of the period of treatment of the included studies is expected. Sensitivity analyses were conducted on study duration; in particular, studies with duration between 3 and 12 months were considered. As well, a sensitivity analysis was conducted on background metformin therapy. That is, for the primary analysis, "low dose" background therapy with metformin was defined as below 1500 mg per day based on advice from clinical experts in diabetes. A sensitivity analysis was carried out using the World Health Organization Defined Daily Dose for metformin (2000 mg per day) (http://www.whocc.no/atc_ddd_index/).

4.2.8 Clinical significance

A result may be significant from a statistical perspective but not be clinically important. For some outcomes, clinically significant values have been identified. The reduction of HbA1c greater than 0.03 (or 0.3%) was considered clinically meaningful in lowering glucose level.[226,227]

The reductions of systolic blood pressure more than 5 mmHg and/or diastolic blood pressure more than 2 mmHg were considered clinically meaningful.[228]

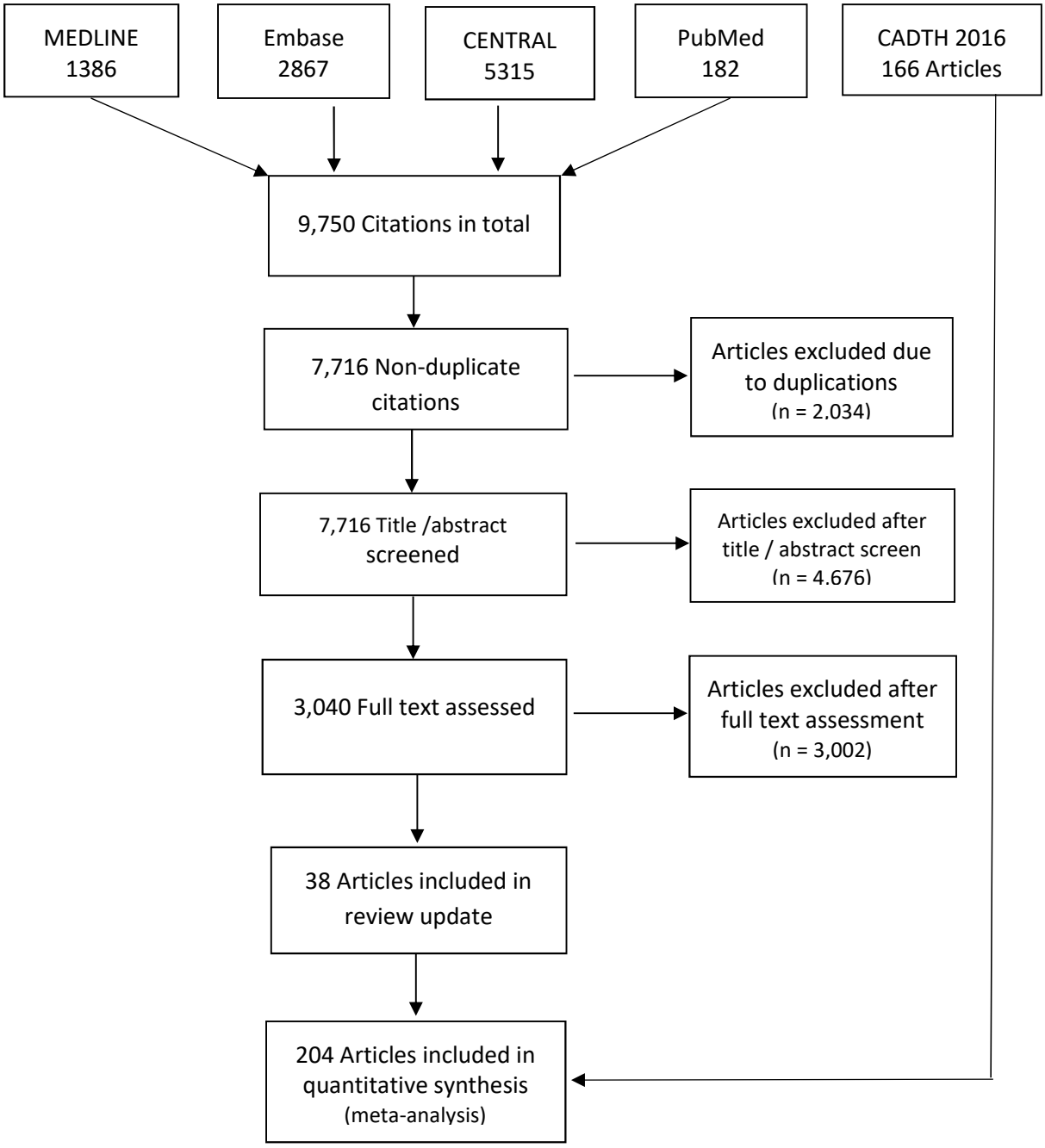
4.3 Results

4.3.1 Selection of studies

The literature search identified a total of 9,750 citations published from 2016 to October 2018. Of the 9,750 citations, 2,034 duplicates were removed, and 4,676 citations were excluded based on the selection criteria at the title and abstract stage. The full texts of the remaining 3,040 citations were reviewed, and 38 of them were eligible for inclusion based on the selection criteria at the full text article stage. These 38 studies were added to the 166 studies included in the previous 2016 review,[9] yielding a total of 204 studies[21-224] with reported outcomes of interest (Figure 4.1).

A list of all included studies (and companion publications) is available in Appendix 4B.

Figure 4.1: Flow diagram of study selection



4.3.2 Study characteristics

Studies were available for all the antihyperglycemic classes of interest added to metformin except for bolus insulins. All studies were parallel group randomized controlled trials with the exception of two crossover studies. Sixty-two studies included a metformin plus placebo group. Sample sizes ranged from 21 to 2,789. The duration of study treatment ranged from 4 to 208 weeks. The baseline HbA1c for inclusion in studies typically ranged from 7.0% to 10%; however, a small number of studies used an HbA1c as low as 6.5% and as high as 12.0%. The majority of studies (76%, 154/204) were sponsored by the pharmaceutical industry and approximately half (48%, 97/204) were multinational studies. Detailed characteristics of the included studies are provided in Table 4.3. At baseline, the average age of subjects was 56.4 years (range: 43.4 to 72.6 years), males accounted for 52.8%, the mean HbA1c was 8.0% (range; 6.4 to 9.9 %), and the mean duration of diabetes 6.4 years (range: 3.7 to 12.3 years).

Consistent with previous reviews,[9] there were some differences in study patients in the duration and dosage of metformin monotherapy prior to randomization to treatment in the RCT. The detailed treatment history prior to randomization was usually unknown. Patients taking various oral antihyperglycemic agents often underwent a run-in period with metformin monotherapy on study entry and if glucose control was insufficient at the end of the run-in period then they were considered for the RCT and randomized to add-on therapy. The studies often reported populations of insufficient glucose control with T2DM with a variety of comorbid conditions.

Table 4.3: Summary of study characteristics

Trail Characteristics	Categories	Number of included Studies N=204
Country	Multinational*	97 (47.5%)
	Single Country	96 (47.1%)
	Not Reported	11 (5.4%)
Study Design	Parallel RCTs	202 (99.0%)
	Crossover RCTs	2 (1.05)
Sponsors	Industry	154 (75.5%)
	Public Funding	12 (5.9%)
	Not Reported	38 (18.6%)
Intervention Comparison	Placebo Control	62
	Active Control	111
	Both	31
Duration of stable background therapy		Range: ≥4 to ≥12 weeks
Publication Year		Range: 1997 to 2018
Sample Size		Range: 21 to 2,789
Duration of Study Treatment		Range: 4 to 208 weeks

* 27 of the 97 (27%) multinational RCTS included countries in Asia/China, but the results were not reported separately by regions or countries.

The detailed individual study characteristics of all included studies are provided in Appendix 4C. As well, the specific inclusion criteria and criteria for insufficient glucose control for all included studies are provided in Appendix 4D.

4.3.3 Risk of bias and GRADE

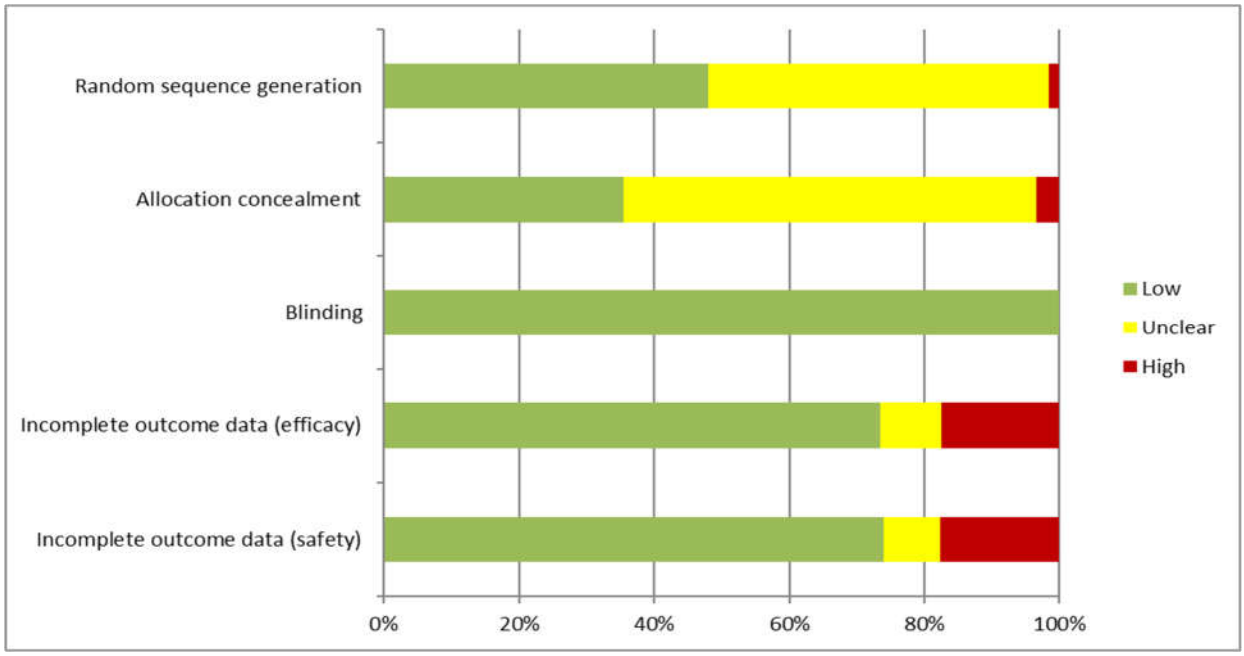
Risk of Bias (ROB) was assessed for all included studies using the Cochrane Collaboration's Risk of Bias tool.[15] A summary of the ROB results is presented in Figure 4.2. In general, studies relevant to data quality were assessed as having a moderate ROB. Often, studies did not report their methods sufficiently for random sequence generation and allocation concealment. Approximately 20% of the studies were assessed to be at high ROB for incomplete outcome reporting for efficacy and safety outcomes.

To assess the certainty of evidence according to the GRADE, we further classified a study as either "High ROB" or "Not High ROB". In total, 21% of the studies (43/204) were assessed as "High ROB".

As indicated in previous analysis,[9] studies used surrogate outcomes such as HbA1c instead of clinically meaningful measurements, had limited sample size, and duration of follow-up. Many studies did not register in a trial registry (e.g., Clinicaltrials.gov) or failed to publish a study protocol. Poor reporting was a common problem across studies. For example, studies did not report protocol definitions for intention-to-treat analysis (i.e., an analysis including all initially randomized patients), did not mention dose and/or duration of stable metformin therapy prior to randomization and did not provide definition of study outcomes (e.g., hypoglycemia).

In addition, several studies used an HbA1c threshold of 6.5% to define sufficient glucose control that differs from the threshold of 7.0% which is commonly recommended in Canada.

Figure 4.2: Summary of risk of bias assessment



Study-level risk of bias results for all included studies are available in Appendix 4E1 and, as well, Corresponding GRADE assessment of quality of evidence on overall ROB for each study are available in Appendix 4E2. Detailed funding information for all included studies available in Appendix 4F.

4.3.4 Data synthesis

Network meta-analyses were conducted for 23 of the clinical outcomes for the antihyperglycemic class comparisons. The choice of outcomes for NMA was based on clinical relevance and the sufficiency of the data available to derive robust and consistent network meta-analysis models. For eight clinical outcomes (hospitalization for unstable angina, non-fatal

stroke, non-fatal-myocardial infarction, fatal-myocardial infarction, ketoacidosis, bladder cancer, pancreatic cancer, and coronary revascularization procedures) only a descriptive analysis was possible, and for one outcome (non-fatal myocardial) both a pairwise meta-analysis and descriptive analysis were conducted. A summary of the analyses performed is presented in Table 4.4.

Table 4.4: Overview of analyses performed

Outcome	NMA[1] Model Likelihood/Link	MA[2] Only	Descriptive Analysis Only	All zero[3]	Duration[4] <3, >12m	Section
HbA1c	Normal/Identity	--	--	---	18/110	4.3.4.1
Non-severe hypoglycemia	Binomial/Logit	--	--	8/72	8/72	4.3.4.3
Severe hypoglycemia	Binomial/Logit	--	--	37/65	13/65	4.3.4.2
Body mass index	Normal/Identity	--	--	---	0/18	4.3.4.4a
Weight	Normal/Identity	--	--	---	15/90	4.3.4.4b
Systolic blood pressure	Normal/Identity	--	--	---	5/43	4.3.4.5a
Diastolic blood pressure	Normal/Identity	--	--	---	6/36	4.3.4.5b
Total cholesterol	Normal/Identity	--	--	---	4/33	4.3.4.6b
LDL cholesterol	Normal/Identity	--	--	---	3/41	4.3.4.6a
HDL cholesterol	Normal/Identity	--	--	---	3/48	4.3.4.6c
Total adverse events	Binomial/Logit	--	--	1/76	9/76	4.3.4.7a
Serious Adverse events	Binomial/Logit	--	--	10/90	15/90	4.3.4.7b
Withdrawals due to adverse events	Binomial/Logit	--	--	9/102	14/102	4.3.4.7c
Urogenital adverse events	Binomial/Logit	--	--	0/35	6/35	4.3.4.8
Renal adverse events	Binomial/Logit	--	--	4/24	9/24	4.3.4.9
Unstable angina	Binomial/Logit	--	--	0/17	5/17	4.3.4.18a
Hospitalization for unstable angina	--	--	Y	(0/1)	(0/1)	4.3.4.18b
Heart failure	Binomial/Logit	--	--	3/18	6/18	4.3.4.12
Transient ischemic attack	Binomial/Logit	--	--	2/18	7/18	4.3.4.14
Fractures	Binomial/Logit	--	--	5/20	3/20	4.3.4.10
All-cause mortality	Binomial/Logit	--	--	27/61	13/61	4.3.4.11a
Cardiovascular mortality	Binomial/Logit	--	--	21/37	8/37	4.3.4.11b

Outcome	NMA[1] Model Likelihood/Link	MA[2] Only	Descriptive Analysis Only	All zero[3]	Duration[4] <3, >12m	Section
Non-fatal stroke	--	Y	Y	(6/10)	(1/10)	4.3.4.13b
Fatal stroke	Binomial/Logit	--	--	23/30	3/30	4.3.4.13a
Non-fatal myocardial Infarction	--	--	Y	(2/10)	(5/10)	4.3.4.18c
Fatal myocardial infarction	--	--	Y	(33/46)	(7/46)	4.3.4.18d
Ketoacidosis	--	--	Y	(5/6)	(1/6)	4.3.4.17
Pancreatitis	Binomial/Logit	--	--	14/26	6/26	4.3.4.15
Bladder cancer	--	--	Y	(3/6)	(4/6)	4.3.4.16b
Pancreatic cancer	--	--	Y	(1/6)	(1/6)	4.3.4.16a
Coronary revascularization procedures	--	--	Y	(1/1)	(0/1)	4.3.4.18e

[1] NMA - network meta-analysis
[2] MA – meta-analysis
[3] All zero – all arms of the study have zero events
[4] Duration – duration of the study between 3 to 12 months

The duration of the study treatment period of the included randomized controlled trials (RCT) ranged from 4 to 208 weeks. With such a wide range in the treatment periods, sensitivity analyses were conducted to assess the effect of the treatment period on the results of the NMA for the 23 study outcomes for which a NMA was conducted. Two approaches were considered for the sensitivity analysis on treatment duration. First, the trend of the effect estimates over the duration of treatment periods was evaluated for outcomes for which there was a sufficient number of studies in the different subgroups for NMA to be possible and the models would converge. Second, since most of the 204 studies (83.2%) had treatment periods between 3 months and 12 months, a sensitivity analysis for all 23 outcomes of interest was conducted restricting studies in the analysis to those with treatment periods between 3 to 12 months. In addition, for the dichotomous outcomes, zero event counts in some studies were found and numeric adjustments for these zeros were needed in order to include the studies in the network

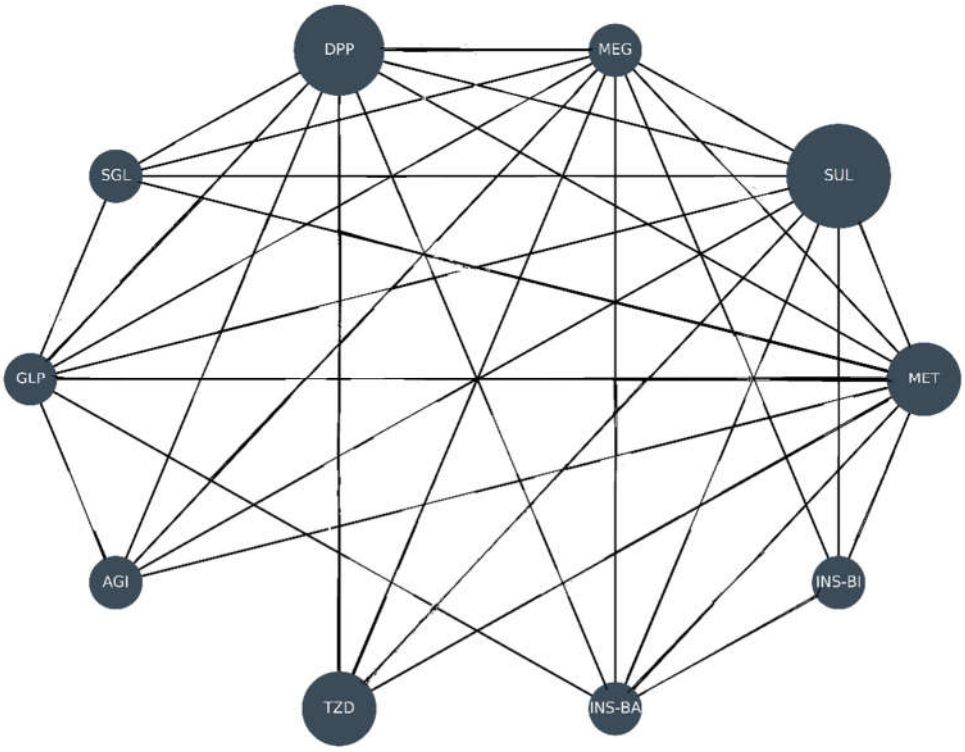
meta-analysis. Zero event counts can lead to problems in the analysis. In particular, if all treatment arms have zero events; we label this situation of all arms with zero counts as 'zero case'. A two-way sensitivity analysis was considered for all 15 dichotomous outcomes for which a network meta-analysis was conducted. First, zero case studies were removed; that is, the studies for a dichotomous outcome that had zero events for all arms were removed from the NMA. Second, as for continuous outcomes, since most of the 204 studies had treatment periods between 3 months and 12 months, a sensitivity analysis was conducted restricting studies in the analysis to those with treatment duration periods between 3 to 12 months. More specifically: restrict duration 3 to 12 months, exclude zero cases; restrict duration 3 to 12 months, include zero cases; no restriction on duration, exclude zero cases; and no restriction on duration, include zero cases (that is, the base case). In Appendix 4G, the detailed results are provided of these sensitivity analyses that were conducted in conjunction with these network meta-analyses. The general conclusion was that the sensitivity analyses confirmed that the base case results were acceptable.

For each outcome, the mean difference (MD) or odds ratio (OR) is provided comparing each antihyperglycemic class added on to metformin background therapy. The results for all class comparisons, and model diagnostics for the fixed- and random-effects models, are presented in the following sections.

4.3.4.1 Hemoglobin A1c

There were 110 studies[21-23,26,29,31,33-36,45-48,52,54,57,58,60,64,66,68,69,73-75,79,82,84-88,90,92,95,97-99,101-105,109-111,113,117,119,120,122,123,125,126,128,129,133-135,137,138,141,142,144-146,148,152,158,159,161,164,165,168-170,172-174,180,176,185,188,189-191,196,195,198-200,203,205-209,212,211,214,216,218-225] that reported on HbA1c and were included in the NMA. Data were available for all antihyperglycemic classes. The treatment network is illustrated in Figure 4.3.

Figure 4.3: Evidence network for HbA1c



Legend: MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

Note: Mr. Victor Guo, a software engineer, helped to create the network graph.

The results of the random-effects NMA model are provided in Table 4.5. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin alone, the addition of any one of the eight classes to metformin resulted in statistically significantly greater reductions in HbA1c from baseline compared to metformin alone, with varying degrees of reduction (MD -0.50, 95%Crl: -0.80, -0.21 for AGI to MD -0.92, 95%Crl: -1.35, -0.49 for biphasic insulin). When the classes were compared, GLP-1 RAs significantly decreased HbA1c compared to DPP-4 inhibitors (MD -0.27, 95%Crl:-0.40, -0.15), SGLT-2 inhibitors (MD -0.20, 95%Crl: -0.36, -0.04), and sulfonylureas (MD -0.17, 95%Crl:-0.31,-0.03), whereas there was no statistically significant difference between DPP-4 inhibitors and SGLT-2 inhibitors (MD -0.07, 95%Crl:-0.20, 0.05). In addition, TZDs (MD -0.13, 95%Crl: -0.24, -0.01), sulfonylureas (MD -0.1, 95%Crl: -0.01, -0.20) and basal insulin (MD -0.28, 95%Crl: -0.53, -0.04) significantly reduced HbA1c when compared with DPP-4 inhibitors.

In addition to statistical significance, all the reductions in HbA1c were greater than 0.03 (or 0.3%) which is considered clinically meaningful in lowering glucose level.

In a sensitivity analysis excluding those studies with metformin background treatment below the WHO defined daily doses of 2,000 mg per day, results of antihyperglycemic classes added to metformin relative to metformin monotherapy were similar with the exception of meglitinides which did not significantly reduce HbA1c relative to metformin. None of the antihyperglycemic classes significantly reduced HbA1c when compared with one another.

Table 4.5: HbA1c change from baseline - network meta-analysis: mean difference and 95% credible interval

Treatment	Reference	MD (95%Crl)	MD (95%Crl) Sensitivity *
MET+SUL	MET	**-0.68(-0.78, -0.57)**	**-0.81(-1.07, -0.56)**
MET+MEG		**-0.51(-0.77, -0.26)**	-0.51(-1.15,0.13)
MET+DPP-4		**-0.58(-0.66, -0.49)**	**-0.80(-1.06, -0.52)**
MET+SGLT-2		**-0.65(-0.76, -0.53)**	**-0.67(-0.98, -0.36)**
MET+GLP-1		**-0.85(-0.98, -0.72)**	**-0.77(-1.06, -0.49)**
MET+AGI		**-0.50(-0.80, -0.21)**	**-0.68(-1.27, -0.11)**
MET+TZD		**-0.70(-0.83, -0.58)**	**-0.95(-1.24, -0.66)**
MET+INS-BA		**-0.86(-1.10, -0.61)**	**-0.98(-1.56, -0.42)**
MET+INS-BI		**-0.92(-1.35, -0.49)**	**-1.34(-2.28, -0.41)**
MET+MEG	MET+SUL	0.16(-0.10,0.43)	0.30(-0.39,0.99)
MET+DPP-4		**0.10(0.01,0.20)**	0.02(-0.29,0.33)
MET+SGLT-2		0.03(-0.10,0.16)	0.14(-0.18,0.47)
MET+GLP-1		**-0.17(-0.31, -0.03)**	0.04(-0.32,0.40)
MET+AGI		0.18(-0.12,0.47)	0.13(-0.50,0.75)
MET+TZD		-0.03(-0.14,0.09)	-0.14(-0.42,0.14)
MET+INS-BA		-0.18(-0.43,0.08)	-0.17(-0.79,0.43)
MET+INS-BI		-0.24(-0.67,0.18)	-0.53(-1.49,0.42)
MET+DPP-4	MET+MEG	-0.06(-0.32,0.20)	-0.29(-0.98,0.41)
MET+SGLT-2		-0.13(-0.41,0.14)	-0.16(-0.87,0.55)
MET+GLP-1		-0.33(-0.62, -0.05)	-0.26(-0.97,0.44)
MET+AGI		0.01(-0.38,0.41)	-0.17(-1.05,0.67)
MET+TZD		-0.19(-0.47,0.09)	-0.44(-1.15,0.26)
MET+INS-BA		-0.34(-0.70,0.01)	-0.47(-1.33,0.37)
MET+INS-BI		-0.41(-0.91,0.09)	-0.83(-1.95,0.28)
MET+SGLT-2	MET+DPP-4	-0.07(-0.20,0.05)	0.13(-0.26,0.50)
MET+GLP-1		**-0.27(-0.40, -0.15)**	0.03(-0.36,0.40)
MET+AGI		0.08(-0.22,0.37)	0.11(-0.50,0.71)
MET+TZD		**-0.13(-0.24, -0.01)**	-0.15(-0.53,0.21)
MET+INS-BA		**-0.28(-0.53, -0.04)**	-0.19(-0.82,0.42)
MET+INS-BI		-0.35(-0.77,0.08)	-0.55(-1.53,0.40)
MET+GLP-1	MET+SGLT-2	**-0.20(-0.36, -0.04)**	-0.10(-0.52,0.31)
MET+AGI		0.15(-0.16,0.46)	-0.01(-0.66,0.63)
MET+TZD		-0.06(-0.21,0.10)	-0.28(-0.67,0.10)
MET+INS-BA		-0.21(-0.47,0.06)	-0.31(-0.96,0.33)
MET+INS-BI		-0.27(-0.71,0.16)	-0.67(-1.66,0.30)
MET+AGI	MET+GLP-1	**0.35(0.04,0.65)**	0.09(-0.50,0.67)

MET+TZD		0.14(-0.02,0.30)	-0.18(-0.57,0.22)
MET+INS-BA		-0.01(-0.24,0.23)	-0.21(-0.71,0.27)
MET+INS-BI		-0.07(-0.51,0.35)	-0.57(-1.46,0.31)
MET+TZD	MET+AGI	-0.20(-0.51,0.11)	-0.27(-0.90,0.38)
MET+INS-BA		-0.36(-0.73,0.02)	-0.30(-1.06,0.47)
MET+INS-BI		-0.42(-0.93,0.08)	-0.66(-1.72,0.39)
MET+INS-BA	MET+TZD	-0.15(-0.41,0.11)	-0.03(-0.66,0.60)
MET+INS-BI		-0.22(-0.65,0.21)	-0.39(-1.37,0.57)
MET+INS-BI	MET+INS-BA	-0.07(-0.49,0.36)	-0.36(-1.09,0.36)
Random-effect model	Residual Deviance	226.4 vs. 238 data points	69.36 vs. 74 data points
	Deviance information criteria	-256.688	-54.343

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.
* excluding those RCTs with metformin background therapy dose below the defined daily dose of 2,000 mg daily.

Model consistency of the network was assessed by plotting the posterior mean of the total residual deviance derived from parameters of inconsistency models against the deviance derived from parameters of consistency models (Figure 4.4). Since most points plotted followed the diagonal trend line with no major deviations below the line, model consistency was indicated.

Figure 4.4: Consistency plot for HbA1c

4.3.4.2 Severe hypoglycemia

There were 65 studies[21,22,24,31,46,48-50,54,56,58,66,79,82,84,85,87,99-102,105,109,110,112,113,117,122,123,125-127,135,137-139,146,148,157,158,161,168-170,172,174,176,185,190-192,194-196,199,204-206,209,219,214,211,213,220-222] that reported on severe hypoglycemia and were included in the NMA. All antihyperglycemic classes were included.

The results of the random effects NMA model are presented in Table 4.6. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin alone, sulfonylureas plus metformin significantly increased the risk of severe hypoglycemia (OR; 7.70, 95%Crl: 3.37, 15.91). When compared with sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 RAs significantly reduced the risk of severe hypoglycemia, with odds ratios ranging from 0.10 (95%Crl: 0.06, 0.17) for SGLT2 to 0.19, (95%Crl: 0.07, 0.63) for DPP-4, and the three classes showed similar impacts. Basal insulin (OR; 0.39, 95%Crl: 0.09, 2.20) and biphasic insulin (OR; 0.37, 95%Crl: 0.03, 7.17) did not significantly reduce the risk of severe hypoglycemic in comparison with sulfonylureas. No statistically significant differences either increased or decreased the risk of severe hypoglycemia when compared one another among DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs, TZDs, and insulin.

Table 4.6: Severe hypoglycemia - network meta-analysis: odds ratio and 95% credible interval

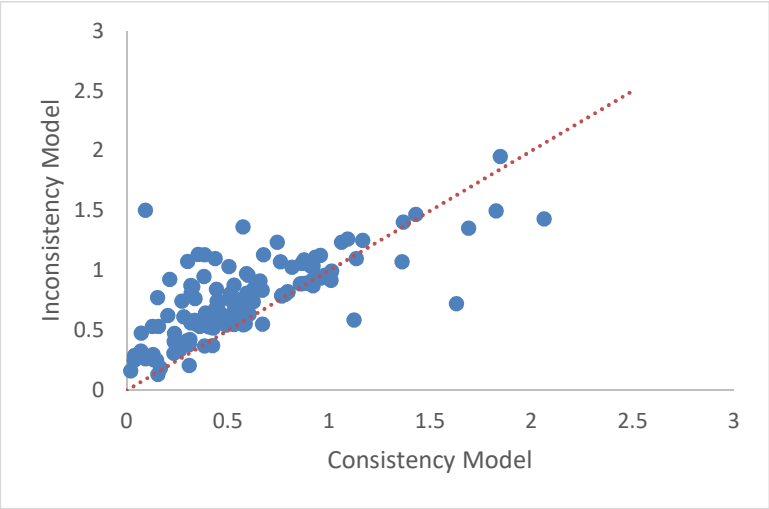
Treatment	Reference	OR (95% Crl)
MET+SUL	MET	**7.70(3.37,15.91)**
MET+DPP-4		1.01(0.44,2.13)
MET+SGLT-2		0.74(0.32,1.59)

MET+GLP-1		1.49(0.60,4.26)
MET+TZD		2.49(0.58,15.17)
MET+INS-BA		2.97(0.63,15.41)
MET+INS-BI		2.77(0.25,57.32)
MET+DPP-4	MET+SUL	**0.13(0.07,0.24)**
MET+SGLT-2		**0.10(0.06,0.17)**
MET+GLP-1		**0.19(0.07,0.63)**
MET+TZD		0.33(0.08,2.41)
MET+INS-BA		0.39(0.09,2.02)
MET+INS-BI		0.37(0.03,7.17)
MET+SGLT-2	MET+DPP-4	0.72(0.36,1.52)
MET+GLP-1		1.47(0.58,4.36)
MET+TZD		2.48(0.66,14.68)
MET+INS-BA		2.98(0.74,16.36)
MET+INS-BI		2.78(0.27,67.14)
MET+GLP-1	MET+SGLT-2	1.98(0.69,7.20)
MET+TZD		3.38(0.79,25.27)
MET+INS-BA		3.95(0.88,20.34)
MET+INS-BI		3.86(0.33,76.17)
MET+TZD	MET+GLP-1	1.75(0.32,11.05)
MET+INS-BA		2.04(0.48,10.75)
MET+INS-BI		1.88(0.19,45.04)
MET+INS-BA	MET+TZD	1.19(0.10,9.15)
MET+INS-BI		1.10(0.06,30.33)
MET+INS-BI	MET+INS-BA	0.94(0.10,11.97)
Random-effect model	Residual Deviance	79.45 vs. 136 data points
	Deviance information criteria	416.066

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.5, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.5: Consistency plot for severe hypoglycemia



4.3.4.3 Non-severe hypoglycemia

There were 72 studies[21-24,31,33,36,40,45,46,48,52,54,56-58,64,66,68,73,74,79,82,84,85,87,88,90,99,102-105,107,109,110,117,119,122,123,129,133,135,137-139,141,142,144-146,148,158,159,161,164,165,168-170,172-174,176,180,185,199,190,192,209,223,225] that reported on non-severe hypoglycemia and were included in the NMA. Data were available for all antihyperglycemic classes.

The results of the random effects NMA model are presented in Table 4.7. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin monotherapy, sulfonylurea, meglitinides, basal insulin and biphasic insulin add-on to metformin significantly increased the risk of non-severe hypoglycemia, with odds ratios ranging from 3.37 (95%Crl: 1.76, 6.41) for basal insulin to 8.75 (95%Crl: 5.96, 13.31) for sulfonylureas. When the classes were compared to one another, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 RAs significantly reduced the risk of non-severe

hypoglycemia in comparison with sulfonylureas, meglitinides, basal insulin and biphasic insulin, while the risk was not statistically difference among the three classes **(**DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 RAs)**.** Basal insulin (OR 0.38, 95%Crl: 0.21, 0.70) and TZDs (OR 0.08, 95%Crl: 0.04, 0.14) significantly decreased the risk of non-severe hypoglycemia when compared with sulfonylureas. Biphasic insulin significantly increased the risk of non-severe hypoglycemia relative to basal insulin (OR 2.21, 95%Crl: 1.20, 4.13).

Table 4.7: Non-severe hypoglycemia - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	**8.75(5.96,13.31)**
MET+MEG		**7.81(3.44,18.55)**
MET+DPP-4		0.85(0.60,1.23)
MET+SGLT-2		0.87(0.55,1.40)
MET+GLP-1		0.75(0.45,1.25)
MET+TZD		0.66(0.37,1.23)
MET+INS-BA		**3.37(1.76,6.41)**
MET+INS-BI		**7.42(3.37,16.51)**
MET+MEG	MET+SUL	0.89(0.38,2.10)
MET+DPP-4		**0.10(0.07,0.13)**
MET+SGLT-2		**0.10(0.06,0.16)**
MET+GLP-1		**0.08(0.05,0.14)**
MET+TZD		**0.08(0.04,0.14)**
MET+INS-BA		**0.38(0.21,0.70)**
MET+INS-BI		0.85(0.40,1.76)
MET+DPP-4	MET+MEG	**0.11(0.05,0.26)**
MET+SGLT-2		**0.11(0.04,0.28)**
MET+GLP-1		**0.10(0.04,0.24)**
MET+TZD		**0.09(0.03,0.23)**
MET+INS-BA		0.43(0.15,1.16)
MET+INS-BI		0.95(0.31,2.85)
MET+SGLT-2	MET+DPP-4	1.03(0.63,1.66)
MET+GLP-1		0.88(0.55,1.42)

MET+TZD		0.78(0.42,1.46)
MET+INS-BA		**3.98(2.14,7.18)**
MET+INS-BI		**8.80(4.05,18.58)**
MET+GLP-1	MET+SGLT-2	0.86(0.46,1.60)
MET+TZD		0.77(0.37,1.58)
MET+INS-BA		**3.86(1.85,7.92)**
MET+INS-BI		**8.52(3.62,20.02)**
MET+TZD	MET+GLP-1	0.89(0.43,1.84)
MET+INS-BA		**4.51(2.40,8.36)**
MET+INS-BI		**9.98(4.47,21.89)**
MET+INS-BA	MET+TZD	**5.06(2.23,11.35)**
MET+INS-BI		**11.18(4.37,28.23)**
MET+INS-BI	MET+INS-BA	**2.21(1.20,4.13)**
Random-effect model	Residual deviance	136.4 vs 151 data points
	Deviance information criteria	728.193

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS BA= basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.6, since several points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

The inconsistency in direct and indirect estimates involving the study by Charpentier[161] was investigated. In this study, patients reported any clinical symptoms of hypoglycemia including hunger, sweating, tachycardia, tremor, various sensory perceptions, headache, altered mood, deficit syndromes and disturbed vigilance. Patients then rated the severity of each symptom using a 5-point scale (0=no symptoms, 1=symptoms allowing normal activity, 2= symptoms not allowing normal activity, 3=symptoms necessitating assistance from another person and 4=loss of consciousness and /or medical intervention). In those with monotherapy, 75% of patients in the glimepiride (sulfonylureas) plus metformin group versus 89% in the metformin group

reported one or two episodes of hypoglycemia. There is a possibility that the total events of hypoglycemia were reported higher in this study relative to others. The study did not find differences between groups on severe hypoglycemia. Sensitivity analysis excluding the Charpentier 2001 study did not lead to in any substantive differences in the results (Table 4.7.1).

Figure 4.6: Consistency plot for non-severe hypoglycemia

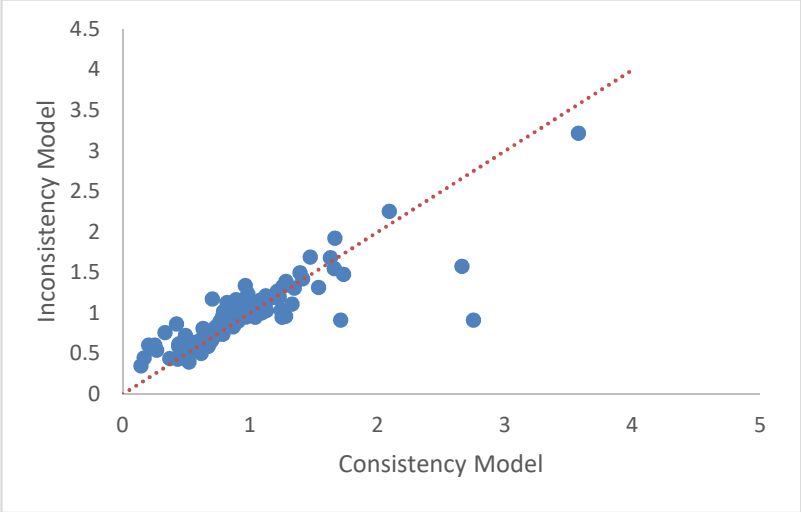


Table 4.7.1: Non-severe hypoglycemia - network meta-analysis with Charpentier study removed: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	**9.86(6.62,15.10)**
MET+MEG		**8.22(3.73,19.26)**
MET+DPP-4		0.91(0.63,1.32)
MET+SGLT-2		0.92(0.58,1.47)
MET+GLP-1		0.79(0.48,1.33)
MET+TZD		0.70(0.39,1.26)
MET+INS-BA		**3.67(1.94,7.06)**
MET+INS-BI		**8.17(3.75,17.81)**
MET+MEG	MET+SUL	0.83(0.37,1.92)
MET+DPP-4		**0.09(0.07,0.13)**

MET+SGLT-2		**0.09(0.06,0.15)**
MET+GLP-1		**0.08(0.05,0.13)**
MET+TZD		**0.07(0.04,0.13)**
MET+INS-BA		**0.37(0.20,0.67)**
MET+INS-BI		0.83(0.40,1.68)
MET+DPP-4	MET+MEG	**0.11(0.05,0.25)**
MET+SGLT-2		**0.11(0.04,0.27)**
MET+GLP-1		**0.10(0.04,0.24)**
MET+TZD		**0.08(0.03,0.22)**
MET+INS-BA		0.45(0.16,1.17)
MET+INS-BI		0.99(0.34,2.86)
MET+SGLT-2	MET+DPP-4	1.02(0.63,1.62)
MET+GLP-1		0.87(0.54,1.39)
MET+TZD		0.77(0.41,1.41)
MET+INS-BA		**4.05(2.23,7.26)**
MET+INS-BI		**9.01(4.28,18.65)**
MET+GLP-1	MET+SGLT-2	0.86(0.46,1.56)
MET+TZD		0.76(0.38,1.52)
MET+INS-BA		**3.99(1.97,8.06)**
MET+INS-BI		**8.89(3.89,20.34)**
MET+TZD	MET+GLP-1	0.89(0.43,1.80)
MET+INS-BA		**4.67(2.50,8.58)**
MET+INS-BI		**10.36(4.74,22.60)**
MET+INS-BA	MET+TZD	**5.24(2.32,11.81)**
MET+INS-BI		**11.69(4.70,29.07)**
MET+INS-BI	MET+INS-BA	**2.23(2.23,4.08)**
Random-effect model	Residual deviance	132.9 vs 149 data points
	Deviance information criteria	713.65

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS BA= basal insulin, INS-BI=biphasic insulin.

4.3.4.4 Body mass index and weight

Body mass index

There were 18 studies[29,47,60,64,225,74,75,90,92,95,146,161,164,168,200,212,218,217] that reported changes from baseline in body mass index (BMI, kg/m^2) and were included in the NMA. Data were available for all drug classes, except for SGLT-2 inhibitor and biphasic insulin.

The results of the random effects NMA model are presented in Table 4.8. The residual deviance value is similar to the number of unconstrained data points indicating model convergence. GLP-1 RAs significantly decreased the change of BMI from baseline when compared to metformin monotherapy (MD; -1.27, 95%Crl: -2.40, -0.22) and sulfonylureas (MD; -1.92, 95%Crl: -3.07, -0.86). Thiazolidinediones significantly increased BMI (MD; 2.58, 95%Crl: 1.35, 3.99) relative to GLP-1 RAs. There was no statistically significant difference in the change of BMI between GLP-1 RAs and DPP-4 inhibitors (MD; -1.02, 95%Crl: -2.30, 0.28).

Table 4.8: Body mass index from baseline - network meta-analysis: mean difference and 95% credible interval

Treatment	Reference	MD (95% Crl)
MET+SUL	MET	0.64(-0.28,1.61)
MET+DPP-4		-0.26(-1.05,0.45)
MET+GLP-1		**-1.27(-2.40,-0.22)**
MET+AGI		-0.52(-1.91,0.80)
MET+TZD		1.32(0.31,2.38)
MET+ INS-BA		0.43(-1.07,2.14)
MET+DPP-4	MET+SUL	-0.90(-2.13,0.24)
MET+GLP-1		**-1.92(-3.07,-0.86)**
MET+AGI		-1.16(-2.60,0.15)
MET+TZD		0.67(-0.32,1.71)
MET+ INS-BA		-0.22(-1.74,1.49)
MET+GLP-1	MET+DPP-4	-1.02(-2.30,0.28)
MET+AGI		-0.25(-1.74,1.19)
MET+TZD		1.58(0.40,2.90)
MET+ INS-BA		0.69(-0.92,2.57)
MET+AGI	MET+GLP-1	0.76(-0.61,2.08)
MET+TZD		**2.58(1.35,3.99)**
MET+ INS-BA		1.71(0.65,2.97)
MET+TZD	MET+AGI	1.84(0.34,3.48)
MET+ INS-BA		0.95(-0.71,2.88)
MET+ INS-BA	MET+TZD	-0.88(-2.63,0.95)
Random-effect model	Residual deviance	37.16 vs. 37 data points
	Deviance information criteria	59.432

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin.

As illustrated in Figure 4.7, since two points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

There was inconsistency in direct and indirect estimates involving the study by Fonseca et al.[164] This study assessed the effect of metformin and rosiglitazone (TZD) combination therapy. Before the study, all eligible patient discontinued antihyperglycemic medications except metformin and went through a 3-week metformin titration to 2.5 g/day. And then patients entered a 4-week weight-maintenance diet period and a weight change between screening and baseline could not be more than 10%. These may contribute to the observed lowest point. Sensitivity analysis excluding the Fonseca study[164] did not result in any substantive differences in results. Table 4.8.1.

Figure 4.7: Consistency plot for BMI

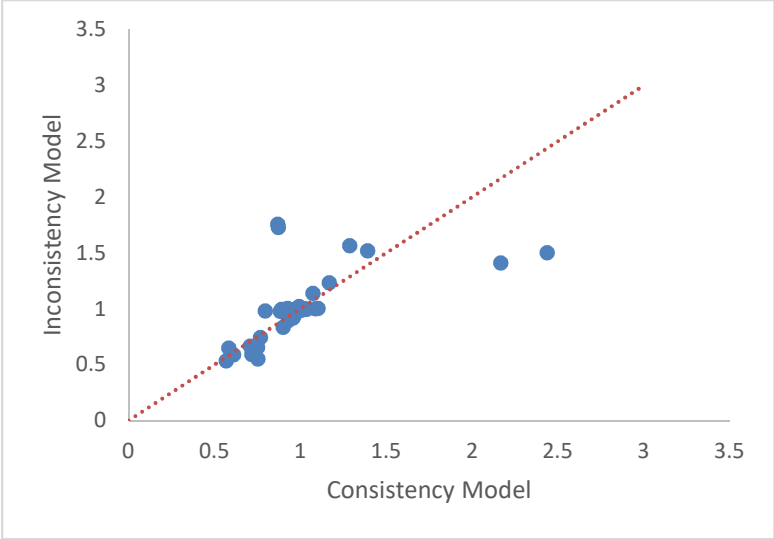


Table 4.8.1: Body mass index - network meta-analysis with Fonseca study removed: odds ratio and 95% credible interval

Treatment	Reference	MD (95%Crl)
MET+DPP-4	MET	-0.17(-0.59,0.13)
MET+GLP-1		**-1.34(-1.92, -0.85)**
MET+AGI		-0.51(-1.54,0.56)
MET+TZD		0.51(-0.18,1.17)
MET+ INS-BA		0.20(-0.64,1.10)
MET+DPP-4	MET+SUL	-0.54(-1.13,0.02)
MET+GLP-1		**-1.72(-2.26, -1.18)**
MET+AGI		-0.87(-1.90,0.18)
MET+TZD		0.14(-0.39,0.72)
MET+ INS-BA		-0.18(-0.99,0.77)
MET+GLP-1	MET+DPP-4	**-1.17(-1.79, -0.54)**
MET+AGI		-0.34(-1.32,0.73)
MET+TZD		0.68(-0.03,1.47)
MET+ INS-BA		0.37(-0.49,1.40)
MET+AGI	MET+GLP-1	0.84(-0.18,1.89)
MET+TZD		**1.85(1.13, 2.64)**
MET+ INS-BA		1.54(0.90,2.29)
MET+TZD	MET+AGI	1.02(-0.17,2.21)
MET+ INS-BA		0.71(-0.59,1.93)
MET+ INS-BA	MET+TZD	-0.31(-1.28,0.75)
Random-effects model	Residual deviance	32.27 vs 35 data points
	Deviance information criteria	48.937

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin.

Body weight

There were 90 studies[21-23,26,31,34-36,40,45,46,48,52,54-58,60,64,66,69,225,74,75,79,82,84-88,95,97,99,101,102,104,105,109-111,113,117,119,120,122,123,126,129,133-135,137,138,142,144,146,152,158,159,161,165,168,169,170,172,174,176,185,188,213,189,196,209,218,191,208,192,194,195,199,200,205-207,211,214,217,219,221] that reported changes from baseline in body weight (in kilograms) and were included in the NMA. Data were available for all antihyperglycemic classes.

The results of the random effects NMA model are presented in Table 4.9. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin monotherapy, participants allocated to SGLT-2 inhibitors and GLP-1 RAs lost significantly more weight (MD; -1.39, 95%Crl: -2.24, -0.54 for SGLT-2 inhibitors and MD; -1.73, 95%Crl: -2.40, -1.08 for GLP-1 RAs), while those allocated to sulfonylureas, TZDs, and basal insulin significantly increased body weight, with mean differences ranging from 1.90 (95%Crl: 1.22, 2.58) for sulfonylureas to 2.79 (95%Crl: 1.22, 4.39) for basal insulin. When the antihyperglycemic classes were compared, all noninsulin treatments except TZDs significantly decreased body weight when compared with sulfonylureas or with meglitinides, while meglitinides were superior to sulfonylureas in reducing body weight *(*MD*;* -1.13, 95%Crl: -1.98, -0.28). Relative to DPP-4 inhibitors, SGLT-2 inhibitors (MD; -1.48, 95%Crl: -2.23, -0.75) and GLP-1 RAs (MD; -1.14, 95%Crl: -1.99, -0.28) significantly decreased body weight, with no statistically significant differences between the two classes of SGLT-2 versus GLP-1 (MD; 0.35, 95%Crl: -0.68, 1.36).

Table 4.9: Body weight change from baseline - network meta-analysis: mean difference and 95% credible interval

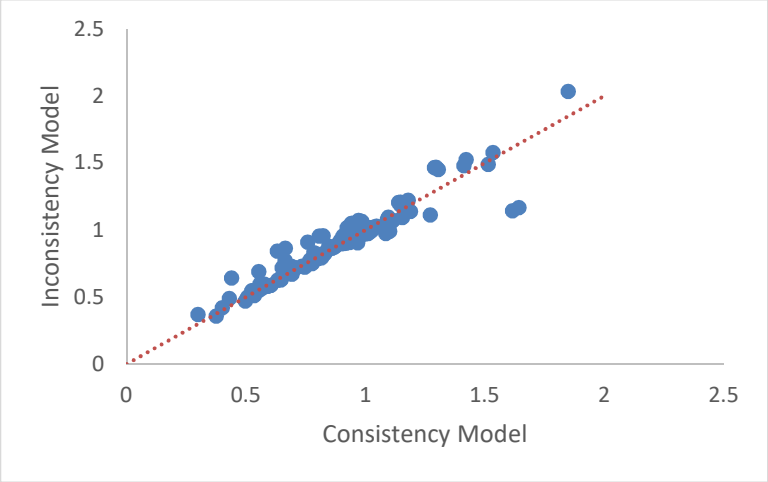
Treatment	Reference	MD (95% Crl)
MET+SUL	MET	**1.90(1.22,2.58)**
MET+MEG		**0.77(0.08,1.47)**
MET+DPP-4		-0.25(-0.76,0.26)
MET+SGLT-2		**-1.73(-2.40, -1.08)**
MET+GLP-1		**-1.39(-2.24, -0.54)**
MET+TZD		**2.72(1.95,3.50)**
MET+ INS-BA		**2.79(1.22,4.39)**
MET+ INS-BI		**3.03(0.19,5.89)**
MET+MEG	MET+SUL	**-1.13(-1.98, -0.28)**
MET+DPP-4		**-2.15(-2.73, -1.57)**

MET+SGLT-2		**-3.63(-4.50, -2.78)**
MET+GLP-1		**-3.28(-4.22, -2.36)**
MET+TZD		**0.82(0.02,1.63)**
MET+ INS-BA		0.90(-0.72,2.55)
MET+ INS-BI		1.12(-1.71,4.03)
MET+DPP-4	MET+MEG	**-1.02(-1.79,-0.27)**
MET+SGLT-2		**-2.50(-3.42, -1.60)**
MET+GLP-1		**-2.16(-3.15, -1.19)**
MET+TZD		**1.94(1.09,2.82)**
MET+ INS-BA		**2.02(0.35,3.72)**
MET+ INS-BI		2.25(-0.64,5.16)
MET+SGLT-2	MET+DPP-4	**-1.48(-2.23, -0.75)**
MET+GLP-1		**-1.14(-1.99, -0.28)**
MET+TZD		**2.97(2.21,3.74)**
MET+ INS-BA		**3.04(1.50,4.64)**
MET+ INS-BI		**3.27(0.48,6.13)**
MET+GLP-1	MET+SGLT-2	0.35(-0.68,1.36)
MET+TZD		**4.45(3.50,5.42)**
MET+ INS-BA		**4.53(2.90,6.20)**
MET+ INS-BI		**4.76(1.91,7.66)**
MET+TZD	MET+GLP-1	**4.10(3.09,5.13)**
MET+ INS-BA		**4.19(2.63,5.78)**
MET+ INS-BI		**4.40(1.62,7.26)**
MET+ INS-BA	MET+TZD	0.08(-1.59,1.80)
MET+ INS-BI		0.31(-2.57,3.25)
MET+ INS-BI	MET+ INS-BA	0.24(-2.06,2.58)
Random-effects model	Residual deviance	182.7 vs. 197 data points
	Deviance information criteria	384.955

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.8, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.8: Consistency plot for body weight



4.3.4.5 Blood pressure

Systolic blood pressure

There were 43 studies[21,22,35,40,45,46,52,54,57,60,64,84,85,87,92,97,109,110,113,116,119,144,161,168,169,172,176,185,189-191,194,196,200,209,212-214,217,219-222] that reported systolic blood pressure and were included in the NMA. Data were available for all drug classes.

The results of the random effects NMA model are presented in Table 4.10. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to either metformin alone or sulfonylureas, participants allocated to SGLT-2 inhibitors, GLP-1 RAs, DPP-4 inhibitors and thiazolidinediones had significantly reduced systolic blood pressure, with mean differences ranging from -1.41 (95%Crl: -2.58, -0.34) for DPP-4 to -4.45 (95%Crl: -5.66, -3.22) for SGLT-2. Compared with DPP-4 inhibitors, participants allocated to SGLT-2 inhibitors and GLP-1 RAs had significantly lowered systolic BP (MD; -2.48, 95%Crl: -

3.57, -1.37 for SGLT-2 and MD; -1.86, 95%Crl: -3.19, -0.52 for GLP-1 RAs), whereas there was no statistically significant difference between the two classes of SGLT-2 versus GLP-1(MD; 0.62, 95%Crl: -0.77, 2.00).

From a clinical perspective, none of these antihyperglycemic classes reduced SBP more than the threshold for clinical significance of 5 mmHg.

Table 4.10: Systolic blood pressure change from baseline - network meta-analysis: mean difference and 95% credible interval

Treatment	Reference	MD (95%Crl)
MET+SUL	MET	0.56(-0.86,1.95)
MET+DPP-4		**-1.41(-2.58, -0.34)**
MET+SGLT-2		**-3.89(-4.94, -2.89)**
MET+GLP-1		**-3.27(-4.66, -1.92)**
MET+AGI		-4.79(-11.77,2.17)
MET+TZD		**-1.80(-3.53, -0.14)**
MET+INS-BA		-0.69(-3.33,1.94)
MET+DPP-4	MET+SUL	**-1.97(-3.40, -0.57)**
MET+SGLT-2		**-4.45(-5.66, -3.22)**
MET+GLP-1		**-3.83(-5.52, -2.12)**
MET+AGI		-5.35(-12.40,1.69)
MET+TZD		**-2.36(-3.83, -0.91)**
MET+INS-BA		-1.25(-3.99,1.58)
MET+SGLT-2	MET+DPP-4	**-2.48(-3.57, -1.37)**
MET+GLP-1		**-1.86(-3.19, -0.52)**
MET+AGI		-3.39(-10.34,3.63)
MET+TZD		-0.38(-2.10,1.30)
MET+INS-BA		0.73(-1.79,3.28)
MET+GLP-1	MET+SGLT-2	0.62(-0.77,2.00)
MET+AGI		-0.90(-7.84,6.09)
MET+TZD		**2.09(0.40,3.71)**
MET+INS-BA		**3.21(0.60,5.84)**
MET+AGI	MET+GLP-1	-1.53(-8.36,5.30)
MET+TZD		1.47(-0.47,3.36)
MET+INS-BA		**2.59(0.18,5.01)**

MET+TZD	MET+AGI	3.01(-4.15,10.04)
MET+INS-BA		4.12(-3.08,11.36)
MET+INS-BA	MET+TZD	1.11(-1.76,4.08)
Random-effect model	Residual deviance	84.99 vs. 90 data points
	Deviance information criteria	295.496

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.9, since two points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

There was inconsistency in direct and indirect estimates involving Rosenstock study.[196] In this study, the endpoint of blood pressure results was generated from a longitudinal data analysis model. This is different from most of the included studies that measured blood pressure directly at the end point. Sensitivity analysis excluding the Rosenstock study did not result in any substantial differences in results, with the exception that GLP-1 RAs significantly increased diastolic BP in comparison with SGLT-2 inhibitors (MD 1.44, 95%Crl: 0.10, 2.79). (Table 4.10.1).

Figure 4.9: Consistency plot for SBP

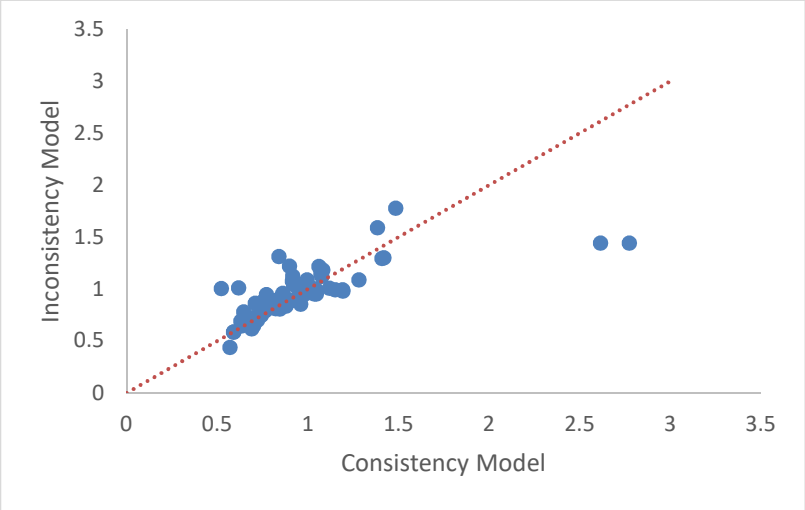


Table 4.10.1: Systolic blood pressure change from baseline - network meta-analysis Rosenstock Study removed: mean difference and 95% credible interval

Treatment	Reference	MD (95%Crl)
MET+SUL	MET	0.50(-0.80,1.77)
MET+DPP-4		**-1.30(-2.33,-0.32)**
MET+SGLT-2		**-4.07(-5.03,-3.15)**
MET+GLP-1		**-2.63(-3.94,-1.36)**
MET+AGI		-4.08(-10.75,2.61)
MET+TZD		**-1.71(-3.30,-0.15)**
MET+INS-BA		-0.22(-2.62,2.16)
MET+DPP-4	MET+SUL	**-1.80(-3.10,-0.50)**
MET+SGLT-2		**-4.58(-5.67,-3.47)**
MET+GLP-1		**-3.13(-4.71,-1.55)**
MET+AGI		-4.58(-11.31,2.19)
MET+TZD		**-2.20(-3.54,-0.89)**
MET+INS-BA		-0.72(-3.24,1.84)
MET+SGLT-2	MET+DPP-4	**-2.77(-3.77,-1.78)**
MET+GLP-1		**-1.33(-2.58,-0.09)**
MET+AGI		-2.77(-9.44,3.89)
MET+TZD		-0.41(-1.98,1.15)
MET+INS-BA		1.08(-1.20,3.38)
MET+GLP-1	MET+SGLT-2	**1.44(0.10,2.79)**
MET+AGI		0.01(-6.69,6.71)

MET+TZD		**2.37(0.82,3.87)**
MET+INS-BA		3.85(1.44,6.26)
MET+AGI	MET+GLP-1	-1.42(-8.01,5.10)
MET+TZD		0.93(-0.88,2.69)
MET+INS-BA		2.42(0.23,4.62)
MET+TZD	MET+AGI	2.38(-4.43,9.14)
MET+INS-BA		3.84(-3.06,10.85)
MET+INS-BA	MET+TZD	1.49(-1.15,4.18)
Random-effect model	Residual deviance	80.3 vs 88 data points
	Deviance information criteria	283.31

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

Diastolic blood pressure

There were 36 studies[21,22,35,45,46,52,54,57,64,81,85,87,92,97,99,109,110,113,120,134,137,144,161,169,172,185,189,191,196,200,209,212-214,219,220,222] that reported diastolic blood pressure and were included in the NMA.

The results of the random effects NMA model are presented in Table 4.11. The residual deviance value is less than the number of unconstrained data points indicating model convergence.

Relative to metformin monotherapy, there was statistically significant reduction in diastolic blood pressure from baseline for those using SGLT-2 inhibitors (MD -2.25, 95% Crl: -2.83, -1.64) and DPP-4 inhibitors (MD -0.81, 95%Crl: -1.44, -0.15). SGLT-2 inhibitors significantly reduced diastolic BP compared with DPP-4 (MD -1.44, 95%Crl: -2.13, -0.76) and sulfonylureas (MD -2.16, 95%Crl: -2.95, -1.38). GLP-1 RAs significantly increased diastolic BP in comparison with SGLT-2 inhibitors (MD 1.58, 95%Crl: 0.64, 2.56). TZDs reduced diastolic BP relative to sulfonylureas (MD -0.82, 95%Crl: -1.65, -0.02).

From a clinical perspective, SGLT-2 inhibitors reduced diastolic BP more than the clinical significance threshold of 2 mmHg in comparison with metformin monotherapy and sulfonylurea.

Table 4.11: Diastolic blood pressure change from baseline - network meta-analysis: mean difference and 95% credible interval

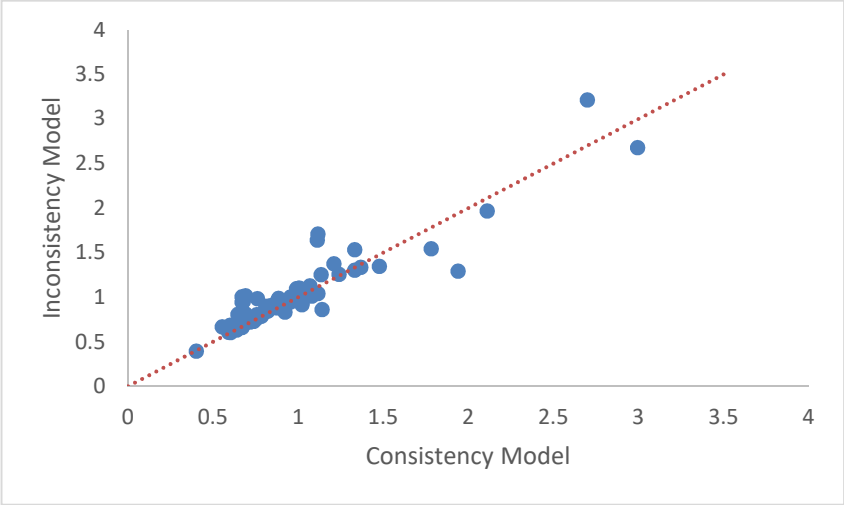
Treatment	Reference	MD (95% Crl)
MET+SUL	MET	-0.09(-0.93,0.78)
MET+DPP-4		**-0.81(-1.44, -0.15)**
MET+SGLT-2		**-2.25(-2.83, -1.64)**
MET+GLP-1		-0.68(-1.53,0.23)
MET+AGI		0.23(-3.95,4.38)
MET+TZD		-0.91(-1.95,0.15)
MET+INS-BA		-0.65(-5.90,4.56)
MET+INS-BI		-0.59(-6.03,5.05)
MET+DPP-4	MET+SUL	-0.72(-1.56,0.13)
MET+SGLT-2		**-2.16(-2.95, -1.38)**
MET+GLP-1		-0.58(-1.64,0.50)
MET+AGI		0.32(-3.93,4.51)
MET+TZD		**-0.82(-1.65, -0.02)**
MET+INS-BA		-0.55(-5.77,4.72)
MET+INS-BI		-0.50(-5.95,5.15)
MET+SGLT-2	MET+DPP-4	**-1.44(-2.13, -0.76)**
MET+GLP-1		0.13(-0.69,0.99)
MET+AGI		1.03(-3.17,5.18)
MET+TZD		-0.10(-1.11,0.90)
MET+INS-BA		0.16(-5.03,5.37)
MET+INS-BI		0.22(-5.19,5.88)
MET+GLP-1	MET+SGLT-2	**1.58(0.64,2.56)**
MET+AGI		2.48(-1.75,6.64)
MET+TZD		**1.34(0.32,2.36)**
MET+INS-BA		1.60(-3.58,6.83)
MET+INS-BI		1.66(-3.78,7.30)
MET+AGI	MET+GLP-1	0.90(-3.21,4.98)
MET+TZD		-0.24(-1.43,0.92)
MET+INS-BA		0.02(-5.10,5.20)
MET+INS-BI		0.10(-5.26,5.64)
MET+TZD	MET+AGI	-1.14(-5.36,3.16)
MET+INS-BA		-0.84(-7.66,5.80)
MET+INS-BI		-0.74(-7.74,6.07)

MET+INS-BA	MET+TZD	0.26(-5.01,5.52)
MET+INS-BI		0.32(-5.15,6.03)
MET+INS-BI	MET+INS-BA	0.09(-1.64,1.80)
Random-effect model	Residual deviance	78.63 vs. 80 data points
	Deviance information criteria	222.414

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.10, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.10: Consistency plot for DBP



4.3.4.6 Cholesterol

LDL cholesterol

There were 41 studies[21,22,40,46,54,57,60,64,79,84-86,97,109,110,113,120,123,129,134,135,141,146,152,158,159,164,165,168,169,185,189,191,192,195,200,212,214,217,219,222] that reported LDL cholesterol and were included in the NMA. Data were available for all antihyperglycemic classes.

The results of the random effects NMA model are presented in Table 4.12. The residual deviance value is not less than the number of unconstrained data points (98.57 vs 84 data points), and model convergence is a concern. Nevertheless, the residual deviance is better for the chosen random-effects model than the fixed-effects model (150.5 vs 84 data points). Thizaolidinediones added-on to metformin resulted in significantly greater increase from baseline for LDL cholesterol when compared with metformin monotherapy, sulfonylureas and DPP-4 inhibitors, with mean differences ranging from 0.24 (95%Crl: 0.13, 0.35) for DPP-4 to 0.16 (95% Crl: 0.05, 0.28) for sulfonylureas. SGLT-2 inhibitors significantly increased in LDL compared to metformin monotherapy 0.15 (95%Crl: 0.04, 0.26) and DPP-4 inhibitors 0.17 (95Crl: 0.05, 0.29). Basal insulin significantly reduced in LDL compared to TZD -0.28 (95%Crl: -0.52, -0.03). None of other antihyperglycemic classes resulted in either increase or decrease in the change of LDL cholesterol levels relative to metformin monotherapy or compared to one another.

Table 4.12: LDL cholesterol change from baseline - network meta-analysis: mean difference and 95% credible interval

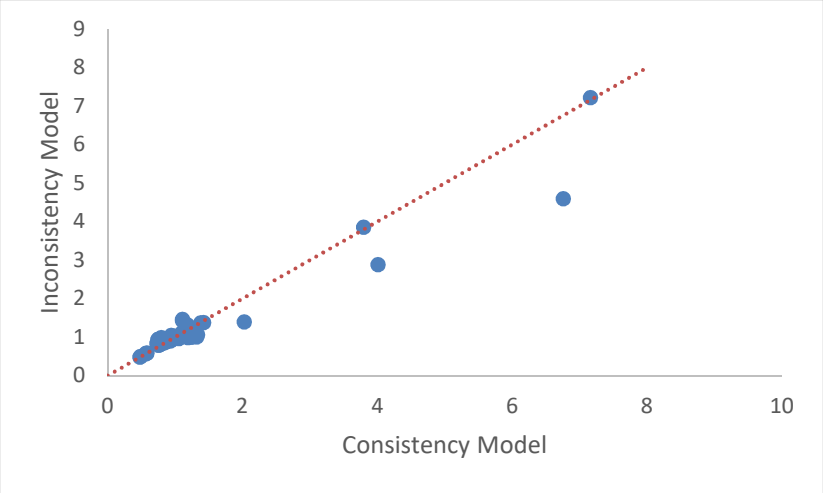
Treatment	Reference	MD (95% Crl)
MET+SUL	MET	0.06(-0.07,0.19)
MET+MEG		0.06(-0.22,0.34)

MET+DPP-4		-0.01(-0.11,0.07)
MET+SGLT-2		**0.15(0.04,0.26)**
MET+GLP-1		0.03(-0.13,0.18)
MET+AGI		-0.06(-0.61,0.47)
MET+TZD		**0.22(0.12,0.33)**
MET+INS-BA		-0.05(-0.29,0.19)
MET+MEG	MET+SUL	0.00(-0.31,0.30)
MET+DPP-4		-0.08(-0.20,0.04)
MET+SGLT-2		0.09(-0.05,0.23)
MET+GLP-1		-0.03(-0.22,0.15)
MET+AGI		-0.13(-0.68,0.42)
MET+TZD		**0.16(0.05,0.28)**
MET+INS-BA		-0.11(-0.36,0.14)
MET+DPP-4	MET+MEG	-0.08(-0.37,0.21)
MET+SGLT-2		0.09(-0.21,0.39)
MET+GLP-1		-0.03(-0.35,0.28)
MET+AGI		-0.13(-0.74,0.48)
MET+TZD		0.16(-0.13,0.46)
MET+INS-BA		-0.12(-0.47,0.25)
MET+SGLT-2	MET+DPP-4	**0.17(0.05,0.29)**
MET+GLP-1		0.04(-0.11,0.20)
MET+AGI		-0.05(-0.59,0.49)
MET+TZD		**0.24(0.13,0.35)**
MET+INS-BA		-0.04(-0.26,0.19)
MET+GLP-1	MET+SGLT-2	-0.12(-0.30,0.06)
MET+AGI		-0.21(-0.77,0.33)
MET+TZD		0.07(-0.06,0.21)
MET+INS-BA		-0.20(-0.45,0.05)
MET+AGI	MET+GLP-1	-0.09(-0.61,0.43)
MET+TZD		**0.19(0.03,0.36)**
MET+INS-BA		-0.08(-0.31,0.16)
MET+TZD	MET+AGI	0.29(-0.25,0.84)
MET+INS-BA		0.01(-0.56,0.59)
MET+INS-BA	MET+TZD	**-0.28(-0.52,-0.03)**
Random-effects model	Residual deviance	98.57 vs 84 data points
	Deviance information criteria	-51.474

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.11, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.11: Consistency plot for LDL cholesterol



Total cholesterol

There were 33 studies[22,26,35,40,54,64,189,78,79,84-86,92,97,109,113,120,123,129,134,141,146,158,159,161,165,191-195,213,212, 217, 222] that reported results for total cholesterol and were included in the NMA. Data were available for all drug classes.

The results of the random effects NMA model are presented in Table 4.13. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Thiazolidinediones (TZDs) significantly increased the change from baseline for total cholesterol

relative to metformin monotherapy, sulfonylureas, DPP-4 inhibitors, GLP-1 RAs and alpha-glucosidase inhibitors, with mean differences ranging from 0.29 (95%Crl: 0.17, 0.42) for metformin to 0.50 (95%Crl: 0.23, 0.97) for AGI. Those allocated to basal insulin had significantly decreased total cholesterol in comparison with those allocated to TZDs (MD; -0.44, 95%Crl: -0.74, -0.14). SGLT2 inhibitors significantly increased total cholesterol compared to metformin monotherapy, sulfonylureas and DPP-4 inhibitors from 0.19 (95%Crl; 0.05, 0.34) for metformin to 0.22 (95%Crl; 0.07, 0.37). None of other antihyperglycemic classes resulted in either increase or decrease in the change of total cholesterol levels relative to metformin monotherapy or compared to one another.

Table 4.13: Total cholesterol change from baseline - network meta-analysis: mean difference and 95% credible interval

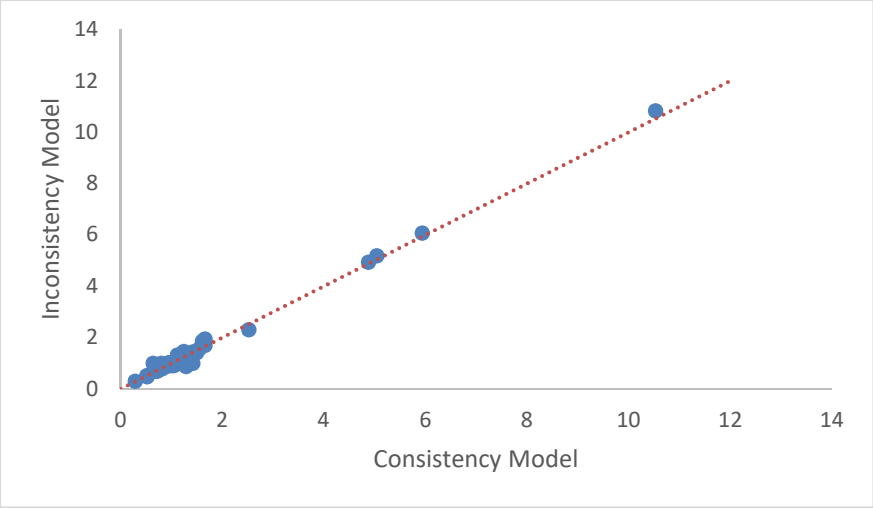
Treatment	Reference	MD (95% Crl)
MET+SUL	MET	0.00(-0.13,0.12)
MET+DPP-4		-0.03(-0.12,0.07)
MET+ SGLT-2		**0.19(0.05,0.34)**
MET+ GLP-1		-0.04(-0.21,0.11)
MET+ AGI		-0.21(-0.48,0.06)
MET+ TZD		**0.29(0.17,0.42)**
MET+ INS-BA		-0.15(-0.43,0.15)
MET+ MEG		0.00(-0.28,0.28)
MET+DPP-4	MET+SUL	-0.03(-0.15,0.10)
MET+ SGLT-2		**0.20(0.04,0.36)**
MET+ GLP-1		-0.04(-0.23,0.14)
MET+ AGI		-0.21(-0.49,0.08)
MET+ TZD		**0.30(0.17,0.42)**
MET+ INS-BA		-0.15(-0.44,0.16)
MET+ MEG		0.00(-0.30,0.31)
MET+ SGLT-2	MET+DPP-4	**0.22(0.07,0.37)**
MET+ GLP-1		-0.01(-0.18,0.13)
MET+ AGI		-0.18(-0.43,0.07)
MET+ TZD		**0.32(0.20,0.45)**
MET+ INS-BA		-0.12(-0.38,0.16)

MET+ MEG		0.03(-0.26,0.33)
MET+ GLP-1	MET+ SGLT-2	**-0.24(-0.45,-0.04)**
MET+ AGI		**-0.40(-0.70,-0.11)**
MET+ TZD		0.10(-0.07,0.28)
MET+ INS-BA		**-0.34(-0.65,-0.02)**
MET+ MEG		-0.19(-0.51,0.13)
MET+ AGI	MET+ GLP-1	-0.17(-0.45,0.12)
MET+ TZD		**0.34(0.17,0.52)**
MET+ INS-BA		-0.11(-0.40,0.22)
MET+ MEG		0.04(-0.27,0.37)
MET+ TZD	MET+ AGI	**0.50(0.23,0.79)**
MET+ INS-BA		0.06(-0.30,0.44)
MET+ MEG		0.21(-0.17,0.60)
MET+ INS-BA	MET+ TZD	**-0.44(-0.74,-0.14)**
MET+ MEG		-0.29(-0.60,0.01)
MET+ MEG	MET+ INS-BA	0.15(-0.26,0.55)
Random-effects model	Residual deviance	77 vs.97.51 data points
	Deviance information criteria	-23.122

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.12, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.12: Consistency plot for total cholesterol



HDL cholesterol

There were 48 studies[21,22,26,35,40,46,47,54,57,60,64,79,84-86,97,109,110,113,120,123,129,134,135,141,146,148,152,158,159,161,164-169,185,213,191,189,192,195,200,207,212,214,217,219,222] that reported change from baseline in HDL cholesterol and were included in the NMA. Data were available for all drug classes.

The results of the random effects NMA model are presented in Table 4.14. The residual deviance value is not less than the number of unconstrained data points (182.4 vs. 103 data points), and model convergence is a concern. Nevertheless, the residual deviance is better for the chosen random-effects model than the fixed-effects model (290.2 vs 103 data points). SGLT-2 inhibitors and TZDs significantly increased the change for HDL cholesterol relative to metformin alone, sulfonylureas, meglitinides and DPP-4 inhibitors, with mean differences ranging from 0.07 (95% Crl:0.04, 0.09) for metformin to 0.11 (95%Crl:0.08, 0.13) for DPP-4.Whereas TZDs were superior to SGLT-2 inhibitors in increasing HDL (MD 0.03, 95%Crl:

0.00, 0.07). Relative to SGLT-2 inhibitors, GLP-1 RAs (MD -0.09, 95%Crl: -0.13, -0.04) and alpha glucosidase inhibitors (MD -0.10, 95%Crl: -0.18, -0.02) significantly decreased HDL from baseline. Basal insulin significantly reduced HDL cholesterol when compared with TZDs (MD -0.09, 95%Crl: -0.16, -0.02).

Table 4.14: HDL cholesterol change from baseline - network meta-analysis: mean difference and 95% credible interval

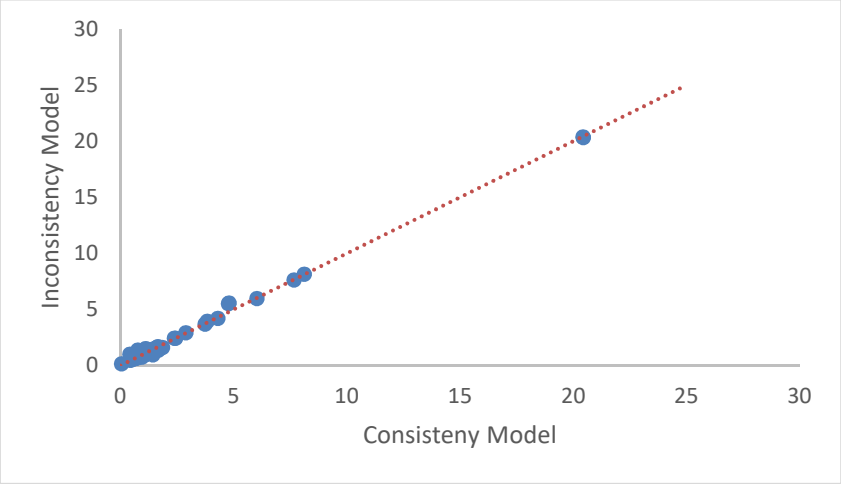
Treatment	Reference	MD (95%Crl)
MET+SUL	MET	-0.03(-0.05,0.00)
MET+MEG		0.00(-0.06,0.05)
MET+DPP-4		-0.01(-0.03,0.02)
MET+SGLT-2		**0.07(0.04,0.09)**
MET+GLP-1		-0.02(-0.06,0.02)
MET+AGI		-0.03(-0.11,0.04)
MET+TZD		**0.10(0.07,0.13)**
MET+INS-BA		0.01(-0.06,0.08)
MET+INS-BI		0.02(-0.05,0.10)
MET+MEG	MET+SUL	0.02(-0.04,0.08)
MET+DPP-4		0.02(-0.01,0.05)
MET+SGLT-2		**0.09(0.06,0.13)**
MET+GLP-1		0.01(-0.04,0.05)
MET+AGI		-0.01(-0.08,0.07)
MET+TZD		**0.13(0.10,0.15)**
MET+INS-BA		0.04(-0.03,0.11)
MET+INS-BI		0.05(-0.02,0.12)
MET+DPP-4	MET+MEG	0.00(-0.06,0.06)
MET+SGLT-2		**0.07(0.01,0.13)**
MET+GLP-1		-0.02(-0.08,0.05)
MET+AGI		-0.03(-0.12,0.06)
MET+TZD		**0.10(0.05,0.16)**
MET+INS-BA		0.01(-0.07,0.10)
MET+INS-BI		0.03(-0.07,0.12)
MET+SGLT-2	MET+DPP-4	**0.07(0.04,0.10)**
MET+GLP-1		-0.02(-0.05,0.02)
MET+AGI		-0.03(-0.10,0.04)
MET+TZD		**0.11(0.08,0.13)**
MET+INS-BA		0.01(-0.05,0.08)
MET+INS-BI		0.03(-0.05,0.11)
MET+GLP-1	MET+SGLT-2	**-0.09(-0.13,-0.04)**
MET+AGI		**-0.10(-0.18,-0.02)**

MET+TZD		**0.03(0.00,0.07)**
MET+INS-BA		-0.06(-0.13,0.01)
MET+INS-BI		-0.04(-0.13,0.04)
MET+AGI	MET+GLP-1	-0.01(-0.09,0.06)
MET+TZD		**0.12(0.08,0.16)**
MET+INS-BA		0.03(-0.04,0.10)
MET+INS-BI		0.04(-0.04,0.13)
MET+TZD	MET+AGI	**0.13(0.06,0.21)**
MET+INS-BA		0.04(-0.05,0.14)
MET+INS-BI		0.06(-0.05,0.16)
MET+INS-BA	MET+TZD	**-0.09(-0.16,-0.02)**
MET+INS-BI		-0.08(-0.15,0.00)
MET+INS-BI	MET+INS-BA	0.02(-0.09,0.12)
Random-effect model	Residual deviance	182.4 vs. 103 data points
	Deviance information criteria	-245.107

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.13, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.13: Consistency plot for HDL cholesterol



4.3.4.7 Adverse events

Total adverse events

There were 76 studies[21-23,33,36,40,45,46,48,52,57,58,60,66,73,79,82,84,85,87,88,90,101,103,104,107,110,111,113,119,122,125,126,129,133-135,137,138,141,142,144,147,148,152,158,159,161,164,169,170,172-174,176,177,189,188,190-192,208,194-196,198,205-207,209,214,217,219,220-222] that reported total adverse events and were included in the NMA. Data were available for all drug classes. The total number of adverse events was most often reported in the studies. In cases where totals were not reported, we added the number of individual events reported in a safety table to determine an overall number.

The results of the random effects NMA model are presented in Table 4.15. The residual deviance value is not less than the number of unconstrained data points (192.1 vs. 161 data points), and model convergence is a concern. Nevertheless, the residual deviance is better for the chosen random-effects model than the fixed-effects model (215.8 vs 161 data points). Relative to metformin monotherapy, GLP-1 RAs, biphasic insulin and alpha glucosidase inhibitors significantly increased the risk of total adverse events, with odds ratios ranging from 1.52 (95%CrL: 1.28, 1.81) for GLP-1 to 1.83 (95%Crl: 1.12, 3.04) for biphasic insulin. When the classes were compared, GLP-1 RAs and biphasic insulin significantly increased the risk of total adverse events relative to sulfonylureas, DPP-4 inhibitors and SGLT2 inhibitors, with odds ratios ranging from 1.39 (95%Crl: 1.15, 1.68) for sulfonylureas to 1.94 (95%Crl: 1.19 3.18) for DPP-4. When compared with DPP-4 inhibitors, GLP-1 RAs (OR 1.61, 95%Crl: 1.36, 1.92) and SGLT-2 inhibitors (OR 1.14, 95%Crl: 1.00, 1.29) significantly increased the risk of total adverse events, whereas GLP-1 RAs increased total adverse events compared to SGLT-2 inhibitors (OR 1.42, 95%Crl: 1.18, 1.73).

Table 4.15: Total adverse events - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.10(0.97,1.25)
MET+MEG		1.10(0.72,1.70)
MET+DPP-4		0.94(0.85,1.04)
MET+SGLT-2		1.07(0.95,1.21)
MET+GLP-1		**1.52(1.28,1.81)**
MET+AGI		**1.66(1.05,2.64)**
MET+TZD		0.97(0.82,1.15)
MET+INS-BA		1.51(0.99,2.24)
MET+INS-BI		**1.83(1.12,3.04)**
MET+MEG	MET+SUL	1.00(0.65,1.58)
MET+DPP-4		**0.86(0.78,0.95)**
MET+SGLT-2		0.98(0.86,1.11)
MET+GLP-1		**1.39(1.15,1.68)**
MET+AGI		1.51(0.96,2.41)
MET+TZD		0.88(0.76,1.04)
MET+INS-BA		1.38(0.90,2.05)
MET+INS-BI		**1.67(1.03,2.73)**
MET+DPP-4	MET+MEG	0.86(0.55,1.32)
MET+SGLT-2		0.98(0.62,1.51)
MET+GLP-1		1.38(0.86,2.18)
MET+AGI		1.51(0.81,2.82)
MET+TZD		0.88(0.55,1.38)
MET+INS-BA		1.38(0.75,2.45)
MET+INS-BI		1.67(0.86,3.22)
MET+SGLT-2	MET+DPP-4	**1.14(1.00,1.29)**
MET+GLP-1		**1.61(1.36,1.92)**
MET+AGI		**1.76(1.12,2.77)**
MET+TZD		1.02(0.88,1.20)
MET+INS-BA		**1.60(1.06,2.35)**
MET+INS-BI		**1.94(1.19,3.18)**
MET+GLP-1	MET+SGLT-2	**1.42(1.18,1.73)**
MET+AGI		1.55(0.97,2.48)
MET+TZD		0.90(0.75,1.08)
MET+INS-BA		1.41(0.92,2.11)
MET+INS-BI		**1.71(1.04,2.81)**
MET+AGI	MET+GLP-1	1.09(0.68,1.77)
MET+TZD		**0.64(0.51,0.79)**
MET+INS-BA		0.99(0.63,1.51)

MET+INS-BI		1.20(0.72,2.03)
MET+TZD	MET+AGI	**0.58(0.36,0.94)**
MET+INS-BA		0.91(0.49,1.63)
MET+INS-BI		1.11(0.57,2.20)
MET+INS-BA	MET+TZD	**1.57(1.00,2.36)**
MET+INS-BI		**1.90(1.13,3.14)**
MET+INS-BI	MET+INS-BA	1.22(0.78,1.91)
Random-effect model	Residual deviance	192.1 vs. 161 data points
	Deviance information criteria	1152.78

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.14, since two points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

There was inconsistency in direct and indirect estimates involving the Yin study.[217] This is a study about insulin glargine (basal insulin) and exenatide add-on to metformin monotherapy. In this study, there was insufficient information of the total adverse events reported on the basal insulin. Sensitivity analysis excluding the Yin 2018 study did not result in any substantial differences in results, with the exception of basal insulin increasing the risk of total adverse events compared to metformin alone and other (Table 4.15.1).

Figure 4.14: Consistency plot for total adverse events

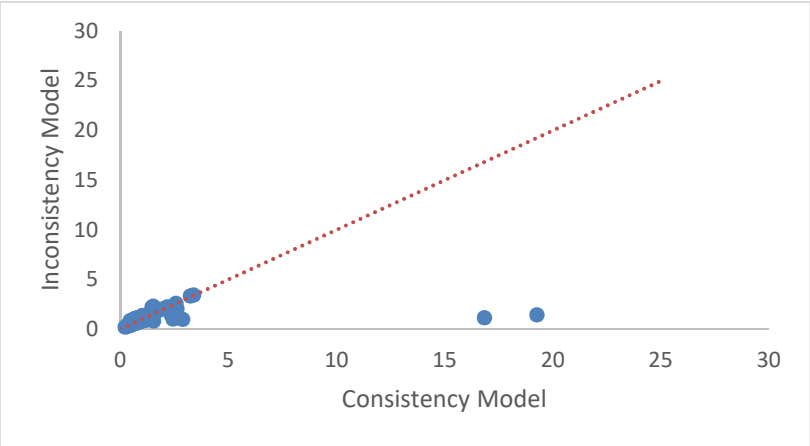


Table 4.15.1: Total adverse events - network meta-analysis Yin Study removed: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.11(0.99,1.26)
MET+MEG		1.11(0.74,1.67)
MET+DPP-4		0.96(0.87,1.06)
MET+SGLT-2		1.08(0.96,1.21)
MET+GLP-1		**1.45(1.23,1.71)**
MET+AGI		**1.69(1.09,2.65)**
MET+TZD		0.97(0.84,1.14)
MET+INS-BA		**2.16(1.46,3.23)**
MET+INS-BI		**2.24(1.39,3.64)**
MET+MEG	MET+SUL	0.99(0.65,1.53)
MET+DPP-4		**0.86(0.78,0.95)**
MET+SGLT-2		0.97(0.86,1.09)
MET+GLP-1		**1.31(1.09,1.57)**
MET+AGI		1.52(0.98,2.39)
MET+TZD		0.87(0.76,1.02)
MET+INS-BA		**1.94(1.31,2.87)**
MET+INS-BI		**2.01(1.26,3.25)**
MET+DPP-4	MET+MEG	0.87(0.57,1.31)
MET+SGLT-2		0.97(0.63,1.49)
MET+GLP-1		1.31(0.84,2.02)
MET+AGI		1.53(0.83,2.81)
MET+TZD		0.88(0.57,1.35)

MET+INS-BA		**1.95(1.10,3.45)**
MET+INS-BI		**2.03(1.08,3.83)**
MET+SGLT-2	MET+DPP-4	**1.13(1.00,1.26)**
MET+GLP-1		**1.52(1.28,1.79)**
MET+AGI		**1.76(1.15,2.73)**
MET+TZD		1.01(0.88,1.17)
MET+INS-BA		**2.26(1.53,3.31)**
MET+INS-BI		**2.34(1.47,3.78)**
MET+GLP-1	MET+SGLT-2	**1.35(1.12,1.61)**
MET+AGI		1.57(1.00,2.47)
MET+TZD		0.90(0.77,1.07)
MET+INS-BA		**2.01(1.34,3.00)**
MET+INS-BI		**2.08(1.28,3.40)**
MET+AGI	MET+GLP-1	1.16(0.73,1.87)
MET+TZD		**0.67(0.55,0.83)**
MET+INS-BA		1.49(0.98,2.26)
MET+INS-BI		1.55(0.94,2.56)
MET+TZD	MET+AGI	**0.57(0.36,0.91)**
MET+INS-BA		1.28(0.71,2.28)
MET+INS-BI		1.33(0.70,2.53)
MET+INS-BA	MET+TZD	**2.23(1.47,3.35)**
MET+INS-BI		**2.30(1.42,3.77)**
MET+INS-BI	MET+INS-BA	**1.04(0.67,1.62)**
Random-effect model	Residual deviance	157.9 vs 159 data points
	Deviance information criteria	1108.62

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

Serious adverse events

There were 90 studies[21-23,31,33,36,40,45,46,48,52,57,58,60,66,73,79,82,84-88,90,97,99,101,103-105,107,109-111,113,117,119,120,122,123,125,126,129,133-135,137-139,141,142,144-146,152,159,161,164,165,169,170,172,173,176,177,185,188-191,198,192,194-196,199,204-209,211,213,214,217,219-222] that reported data on serious adverse events and were included in the NMA. The definition for "serious adverse events" in RCT includes any untoward medical event resulting in life-threatening, hospitalization and/or fatality. For our outcome, we did not consider "severe adverse events" to be "serious".

The results of the random effects NMA model are presented in Table 4.16. The residual deviance value is less than the number of unconstrained data points indicating model convergence. TZDs significantly increased the risk of serious adverse events relative to Sulfonylurea (OR 1.22, 95%Crl: 1.00, 1.57) and DPP-4 inhibitors (OR 1.26, 95% Crl: 1.03, 1.61). There were no significantly differences between the rest antihyperglycemic classes.

Table 4.16: Serious adverse events - network meta-analysis: odds ratio and 95% credible interval

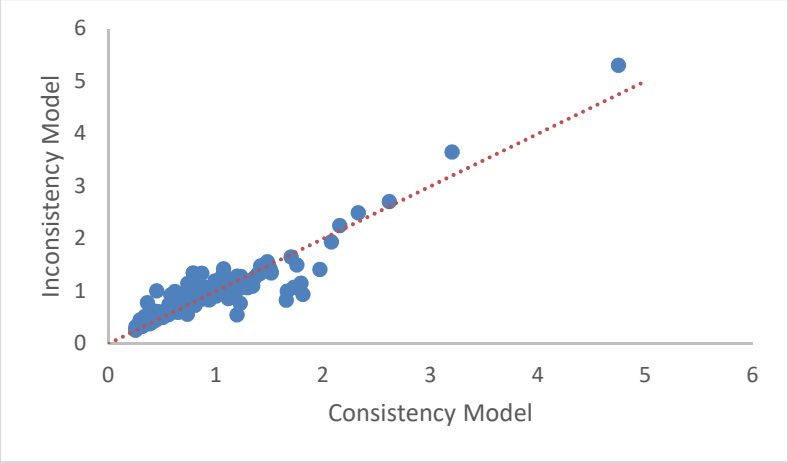
Treatment	Reference	OR (95% Crl)
MET+SUL	MET	0.88(0.71,1.10)
MET+DPP-4		0.86(0.69,1.06)
MET+SGLT-2		1.00(0.79,1.27)
MET+GLP-1		1.02(0.74,1.42)
MET+AGI		0.32(0.03,1.83)
MET+TZD		1.08(0.85,1.43)
MET+INS-BA		1.42(0.64,3.19)
MET+INS-BI		1.47(0.39,7.41)
MET+DPP-4	MET+SUL	0.97(0.85,1.12)
MET+SGLT-2		1.13(0.95,1.36)
MET+GLP-1		1.15(0.82,1.64)
MET+AGI		0.36(0.03,2.04)
MET+TZD		**1.22(1.00,1.57)**
MET+INS-BA		1.60(0.74,3.60)
MET+INS-BI		1.66(0.44,7.97)
MET+SGLT-2	MET+DPP-4	1.17(0.95,1.43)
MET+GLP-1		1.19(0.86,1.66)
MET+AGI		0.38(0.03,2.05)
MET+TZD		**1.26(1.03,1.61)**
MET+INS-BA		1.65(0.77,3.64)
MET+INS-BI		1.71(0.46,8.28)
MET+GLP-1	MET+SGLT-2	1.01(0.71,1.46)
MET+AGI		0.32(0.03,1.81)
MET+TZD		1.08(0.84,1.44)
MET+INS-BA		1.41(0.65,3.20)
MET+INS-BI		1.47(0.39,7.08)

MET+AGI	MET+GLP-1	0.32(0.03,1.81)
MET+TZD		1.07(0.74,1.56)
MET+INS-BA		1.39(0.62,3.23)
MET+INS-BI		1.44(0.39,7.25)
MET+TZD	MET+AGI	3.37(0.59,40.45)
MET+INS-BA		4.44(0.71,58.74)
MET+INS-BI		4.75(0.55,60.84)
MET+INS-BA	MET+TZD	1.31(0.58,3.02)
MET+INS-BI		1.35(0.35,6.70)
MET+INS-BI	MET+INS-BA	1.05(0.34,3.81)
Random-effect model	Residual Deviance	169.4 vs 186 data points
	Deviance Information Criteria	919.422

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thiazolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.15, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.15: Consistency plot for serious adverse events



Withdrawals due to adverse events

There were 102 studies[21-23,29,31,33,34,36,40,45,46,48,52,54,57,58,60,64,66,73,74,79,82,84-88,90,92,95,97,99,101-105,107,109-111,113,119,120,122,123,125,126,129,133-135,137-139,141,142,144-146,148,152,158,159,161,164,168-170,172-174,176,180,177,185,188-192,194-199,204-209,211,213,214,219-222,225] that reported data on withdrawals due to adverse events and were included in the NMA. Data pertaining to this outcome were commonly reported in RCTs as per CONSORT guidelines. Data were available for all antihyperglycemic classes.

The results of the random effects NMA model are presented in Table 4.17. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin alone, GLP-1 RAs significantly increased the risk of withdrawals due to adverse events (OR 1.68, 95%Crl; 1.14, 2.50). When the classes were compared to one another, GLP-1 RAs significantly increased the risk of withdrawals due to adverse events in comparison with sulfonylureas, DPP-4 inhibitors or SGLT-2 inhibitors, with odds ratios ranging from 1.78 (95%Crl; 1.12, 2.89) for SGLT-2 to 2.28 (95%Crl; 1.50, 3.48) for sulfonylureas, whereas there was no statistically significant difference between SGLT-2 and DPP-4. When compared with GLP-1 RAs, TZDs (OR 0.56, 95%Crl: 0.35, 0.92) and basal insulin (OR 0.21, 95%Crl: 0.05, 0.78) significantly decreased the risk of withdrawals due to adverse events.

Table 4.17: Withdrawals due to adverse events - network meta-analysis: odds ratio and 95% credible interval

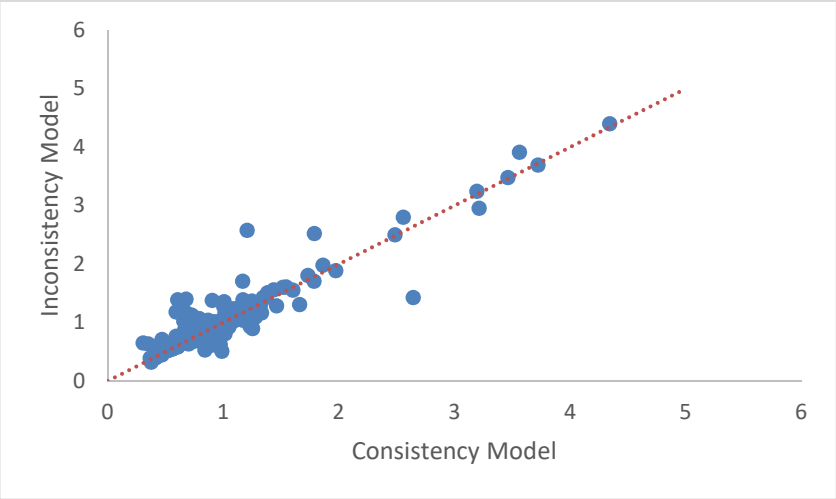
Treatment	Reference	OR (95% CrL)
MET+SUL	MET	0.74(0.54,1.02)
MET+MEG		0.75(0.24,2.43)
MET+DPP-4		0.77(0.58,1.02)
MET+SGLT-2		0.95(0.67,1.35)
MET+GLP-1		**1.68(1.14,2.50)**
MET+AGI		0.38(0.03,3.50)

MET+TZD		0.95(0.65,1.41)
MET+INS-BA		0.36(0.08,1.32)
MET+INS-BI		1.88(0.30,15.98)
MET+MEG	MET+SUL	1.03(0.31,3.32)
MET+DPP-4		1.04(0.80,1.35)
MET+SGLT-2		1.28(0.91,1.81)
MET+GLP-1		**2.28(1.50,3.48)**
MET+AGI		0.52(0.04,4.82)
MET+TZD		1.28(0.92,1.82)
MET+INS-BA		0.49(0.11,1.79)
MET+INS-BI		2.54(0.42,21.09)
MET+DPP-4	MET+MEG	1.01(0.31,3.30)
MET+SGLT-2		1.25(0.38,4.19)
MET+GLP-1		2.23(0.66,7.57)
MET+AGI		0.50(0.03,6.46)
MET+TZD		1.25(0.37,4.20)
MET+INS-BA		0.47(0.08,2.71)
MET+INS-BI		2.54(0.28,28.28)
MET+SGLT-2	MET+DPP-4	1.24(0.86,1.76)
MET+GLP-1		**2.20(1.46,3.26)**
MET+AGI		0.50(0.04,4.57)
MET+TZD		1.23(0.88,1.76)
MET+INS-BA		0.47(0.11,1.69)
MET+INS-BI		2.45(0.40,20.49)
MET+GLP-1	MET+SGLT-2	**1.78(1.12,2.83)**
MET+AGI		0.40(0.03,3.78)
MET+TZD		1.00(0.64,1.56)
MET+INS-BA		0.38(0.09,1.43)
MET+INS-BI		1.99(0.31,16.55)
MET+AGI	MET+GLP-1	0.23(0.02,2.13)
MET+TZD		**0.56(0.35,0.92)**
MET+INS-BA		**0.21(0.05,0.78)**
MET+INS-BI		1.12(0.18,9.56)
MET+TZD	MET+AGI	2.48(0.26,35.08)
MET+INS-BA		0.94(0.07,17.29)
MET+INS-BI		5.11(0.28,168.10)
MET+INS-BA	MET+TZD	0.38(0.09,1.41)
MET+INS-BI		1.99(0.31,16.79)
MET+INS-BI	MET+INS-BA	5.37(0.99,42.86)
Random-effect model	residual Deviance	211.1 vs. 219 data points
	Deviance information criteria	1067.56

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, MEG=meglitinides, AGI=alpha-glucosidase inhibitor, INS-BA=basal insulin, INS-BI=biphasic insulin.

As illustrated in Figure 4.16, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.16: Consistency plot for withdrawals due to adverse events



4.3.4.8 Urogenital adverse events

There were 35 studies[21-23,52,54,57,73,79,82,88,90,103,104,109,110,119,123,133,137,138,141,189-192,194,196,198,199,208,206,214,219,221,222] that reported urogenital adverse events and were included in the NMA. For this outcome, two types of urogenital adverse events were included: urinary tract infections and genital (mycotic) infections. Data were available for all drug classes, with the exception of alpha-glucosidase inhibitors, meglitinides and biphasic insulin.

The results of the random effects NMA model are presented in Table 4.18. The residual deviance value is less than the number of unconstrained data points indicating model convergence. SGLT-2 inhibitors significantly increased the risk of urogenital adverse events when compared with metformin monotherapy (OR 1.67, 95%Crl: 1.17, 2.46), sulfonylureas (OR 1.88, 95%Crl: 1.41, 2.55) and DPP-4 inhibitors (OR 1.59, 95%Crl: 1.11, 2.27). GLP-1 RAs (OR 0.55, 95%Crl: 0.23, 0.94) and TZDs (OR 0.32, 95%Crl: 0.09, 0.94) significantly reduced the risk relative to SGLT-2 inhibitors.

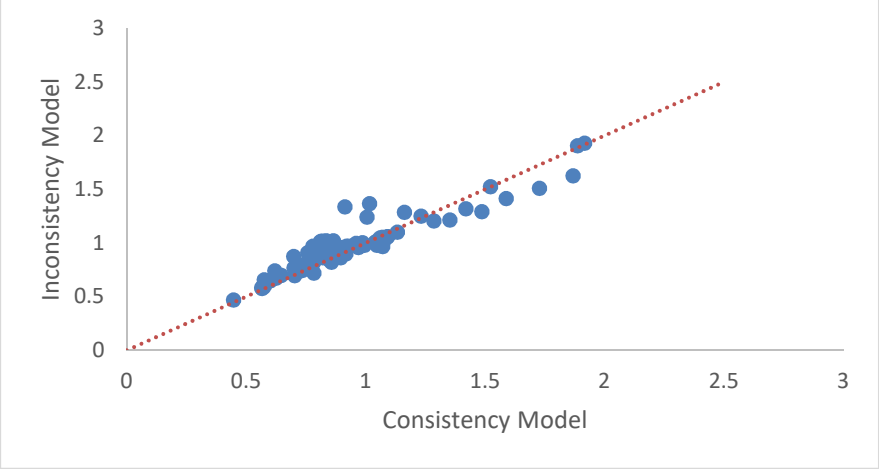
Table 4.18: Urogenital adverse Eevents - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	0.89(0.60,1.31)
MET+DPP-4		1.05(0.76,1.48)
MET+SGLT-2		**1.67(1.17,2.46)**
MET+GLP-1		0.92(0.55,1.58)
MET+TZD		0.53(0.16,1.58)
MET+INS-BA		0.63(0.05,5.03)
MET+DPP-4	MET+SUL	1.19(0.86,1.66)
MET+SGLT-2		**1.88(1.41,2.55)**
MET+GLP-1		1.04(0.59,1.83)
MET+TZD		0.59(0.18,1.77)
MET+INS-BA		0.71(0.06,5.63)
MET+SGLT-2	MET+DPP-4	**1.59(1.11,2.27)**
MET+GLP-1		0.87(0.51,1.49)
MET+TZD		0.50(0.15,1.45)
MET+INS-BA		0.60(0.05,4.78)
MET+GLP-1	MET+SGLT-2	**0.55(0.32,0.94)**
MET+TZD		**0.32(0.09,0.94)**
MET+INS-BA		0.38(0.03,2.97)
MET+TZD	MET+GLP-1	0.57(0.17,1.70)
MET+INS-BA		0.69(0.06,4.98)
MET+INS-BA	MET+TZD	1.19(0.09,12.63)
Random-effects model	Residual deviance	70.22 vs. 74 data points
	Deviance information criteria	410.453

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, INS-BA=basal insulin.

As illustrated in Figure 4.17, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.17: Consistency plot for urogenital adverse events



4.3.4.9 Renal adverse events

There were 24 studies[40,45,48,52,54,79,84,86,87,97,103-105,109,110,120,176,185,190,194,198,195,209,222] that reported renal adverse events and were included in the NMA. For this outcome, the renal adverse events included: cancer (carcinoma, stage I), non-cancerous tumors (adenoma, oncocytoma), inflammation of renal tissue (pyelonephritis), nephrolithiasis (renal, urinary, and bladder calculi), renal dysfunction/worsening renal function (renal failure, impairment, colic, cysts, embolism, and neoplasm), urinary events related to renal dysfunction (hematuria, azotaemia, ketonuria, proteinurea, and urinary retention, and urinary tract obstruction). Data were available for all

antihyperglycemic classes, with the expectation of insulin, meglitinides and alpha-glucosidase inhibitors.

The results of the random effects NMA model are presented in Table 4.19. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased the risk of renal adverse events.

Table 4.19: Renal adverse events - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	1.16(0.52,2.64)
MET+DPP-4		1.27(0.56,2.93)
MET+SGLT-2		0.97(0.49,1.99)
MET+GLP-1		1.70(0.61,5.20)
MET+TDZ		0.63(0.23,1.79)
MET+DPP-4	MET+SUL	1.09(0.57,2.06)
MET+SGLT-2		0.83(0.45,1.55)
MET+GLP-1		1.48(0.40,5.26)
MET+TDZ		0.54(0.29,1.10)
MET+SGLT-2	MET+DPP-4	0.77(0.34,1.67)
MET+GLP-1		1.34(0.41,4.70)
MET+TDZ		0.49(0.21,1.23)
MET+GLP-1	MET+SGLT-2	1.75(0.55,6.03)
MET+TDZ		0.64(0.27,1.66)
MET+TDZ	MET+GLP-1	0.37(0.09,1.54)
Random-effect model	Residual deviance	39.24 vs.54 data points
	Deviance information criteria	205.869

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones.

As illustrated in Figure 4.18, since a few points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

There was inconsistency in direct and indirect estimates involving Ahren study.[54] This study had a long-term (104 weeks) follow-up, while most included studies had relatively short study periods. Sensitivity analysis excluding the Ahren study did not result in any substantial differences in results (Table 4.19.1).

Figure 4.18: Consistency plot for renal adverse events

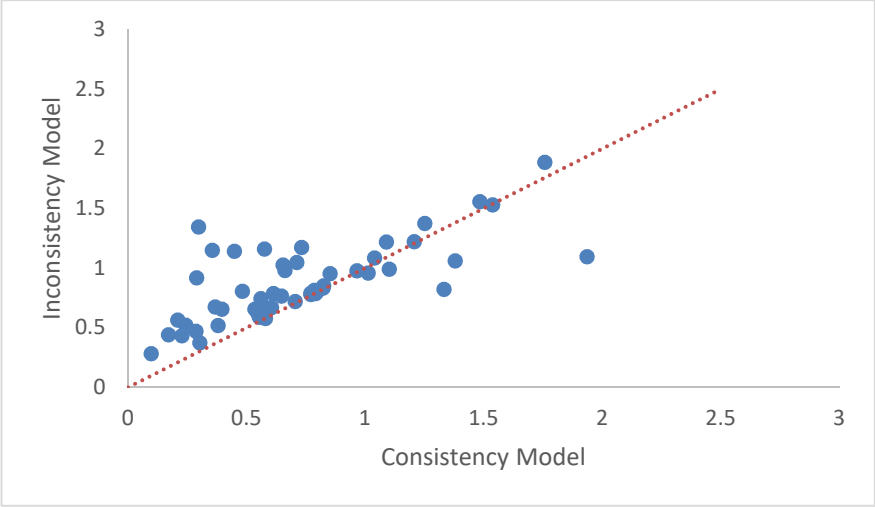


Table 4.19.1: Renal adverse events - network meta-analysis with Ahren study removed: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	1.47(0.63,3.46)
MET+DPP-4		1.54(0.62,3.66)
MET+SGLT-2		1.11(0.53,2.48)
MET+GLP-1		1.90(0.63,7.07)
MET+TDZ		0.77(0.29,2.21)
MET+DPP-4	MET+SUL	1.04(0.54,1.96)
MET+SGLT-2		0.76(0.41,1.45)
MET+GLP-1		1.29(0.38,4.86)
MET+TDZ		0.52(0.28,1.08)
MET+SGLT-2	MET+DPP-4	0.73(0.34,1.65)
MET+GLP-1		1.21(0.37,4.66)
MET+TDZ		0.50(0.22,1.30)
MET+GLP-1	MET+SGLT-2	1.69(0.53,6.46)
MET+TDZ		0.69(0.30,1.73)
MET+TDZ	MET+GLP-1	0.41(0.10,1.60)
Random-effect model	Residual deviance	35.3 vs 51 data points
	Deviance information criteria	193.39

4.3.4.10 Fractures

There were 20 studies[23,31,45,52,60,82,86,87,90,110,117,133,176,180,185,195,214,221,219,222] that reported data on fractures and were included in the NMA. Data were not available for GLP-1 RAs, alpha-glucosidase inhibitors, meglitinides and insulin classes.

The results of the random effects NMA model are presented in Table 4.20. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased the odds of fractures.

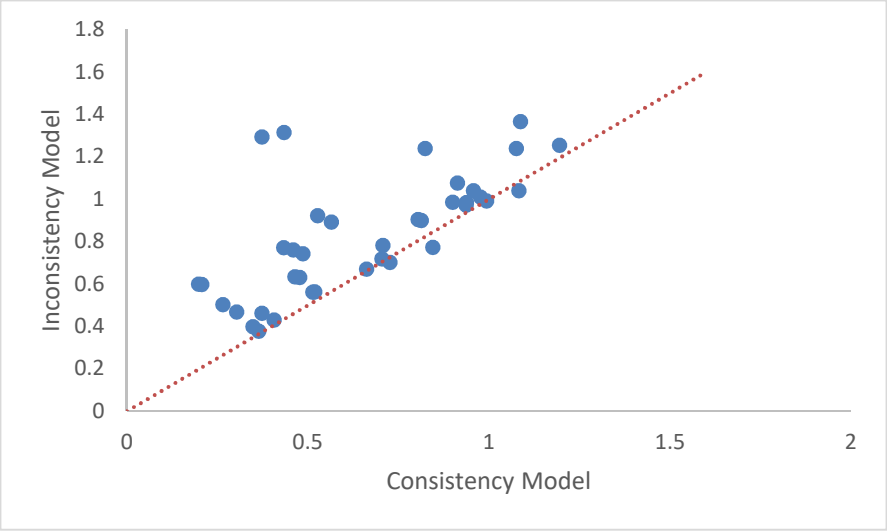
Table 4.20: Fractures - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	0.76(0.25,3.12)
MET+DPP-4		1.07(0.36,4.21)
MET+SGLT-2		0.77(0.24,3.58)
MET+TZD		1.38(0.39,6.32)
MET+DPP-4	MET+SUL	1.42(0.71,2.88)
MET+SGLT-2		1.02(0.56,1.93)
MET+TZD		1.85(0.85,3.88)
MET+SGLT-2	MET+DPP-4	0.72(0.30,1.79)
MET+TZD		1.29(0.48,3.47)
MET+TZD	MET+SGLT-2	1.81(0.67,4.51)
Random-effect model	Residual deviance	24.85 vs.38 data points
	Deviance information criteria	141.273

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, TZD=thizaolidinediones.

As illustrated in Figure 4.19, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models generally followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.19: Consistency plot for fractures



4.3.4.11 Mortality

All-Cause mortality

There were 61 studies[21-23,31,33,40,45,46,48,52,54,57,58,66,79,86,87,90,101,105,107,109-111,113,117,119,122,126,127,133-135,137-139,143,144,145,152,164,169,170,176,185,188,190,191,198,208,195,199,194,205,206,211,214,219,221-223] that reported all-cause mortality. Data were available for all drug classes, except for meglitinides, insulin, and alpha-glucosidase inhibitors.

The results of the random effects NMA model are presented in table 4.21. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes, none of the classes significantly increased or decreased the odds of all-cause mortality.

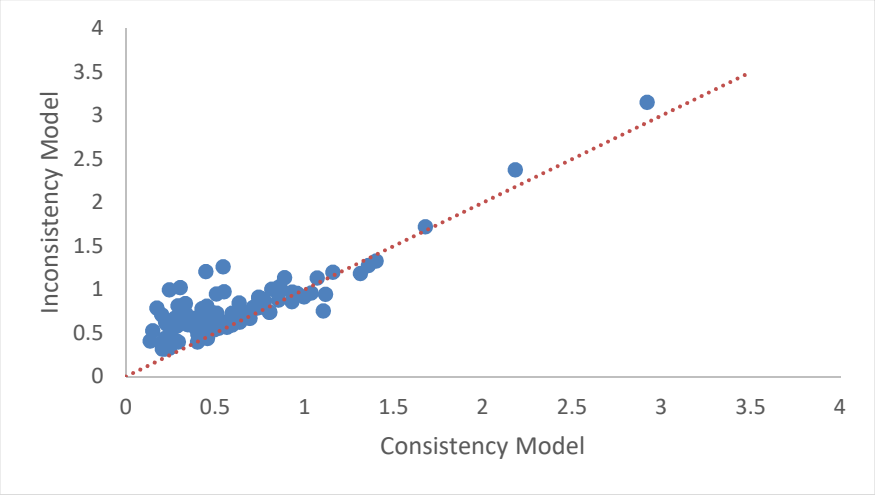
Table 4.21: All-Cause mortality - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.35(0.72,2.61)
MET+DPP-4		1.01(0.52,1.99)
MET+SGLT-2		1.13(0.57,2.47)
MET+GLP-1		0.81(0.29,2.08)
MET+TZD		1.17(0.62,2.25)
MET+DPP-4	MET+SUL	0.75(0.44,1.17)
MET+SGLT-2		0.85(0.47,1.52)
MET+GLP-1		0.60(0.18,1.62)
MET+TZD		0.87(0.56,1.36)
MET+SGLT-2	MET+DPP-4	1.15(0.59,2.36)
MET+GLP-1		0.80(0.27,2.25)
MET+TZD		1.16(0.66,2.19)
MET+GLP-1	MET+SGLT-2	0.71(0.20,1.94)
MET+TZD		1.01(0.53,2.03)
MET+TZD	MET+GLP-1	1.44(0.52,4.83)
Random-effects model	Residual deviance	72.5 vs.127 data points
	Deviance information criteria	400.082

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon- like peptide-1 receptor agonist, TZD=thizaolidinediones.

As illustrated in Figure 4.20, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.20: Consistency plot for all-cause mortality



Cardiovascular mortality

There were 37 studies[21,22,31,33,40,45,46,48,57,66,79,82,86,90,101,105,107,109,110,113,119,122,127,133-135,137-139,144,145,164,170,176,206,198,222] that reported cardiovascular mortality outcomes. Data were available for all antihyperglycemic classes, except for meglitinides, insulin, and alpha-glucosidase inhibitors.

The results of the random effects NMA model are presented in Table 4.22. The residual deviance value is less than the number of unconstrained data points indicating model convergence.

Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased the odds of cardiovascular mortality.

Table 4.22: Cardiovascular mortality - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.04(0.34,3.06)
MET+DPP-4		0.66(0.27,1.72)
MET+SGLT-2		1.16(0.29,4.86)
MET+GLP-1		0.51(0.12,1.87)
MET+TZD		1.09(0.21,5.16)
MET+DPP-4	MET+SUL	0.64(0.27,1.48)
MET+SGLT-2		1.18(0.22,6.21)
MET+GLP-1		0.48(0.13,1.75)
MET+TZD		1.04(0.24,4.71)
MET+SGLT-2	MET+DPP-4	1.82(0.36,8.22)
MET+GLP-1		0.79(0.20,2.43)
MET+TZD		1.62(0.39,7.92)
MET+GLP-1	MET+SGLT-2	0.43(0.05,3.16)
MET+TZD		0.94(0.12,6.55)
MET+TZD	MET+GLP-1	2.23(0.38,14.27)
Random-effect model	residual Deviance	40.89 vs. 75 data points
	Deviance information criteria	220.929

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones.

As illustrated in Figure 4.21, since several points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models fell well below the diagonal trend line, model inconsistency was indicated.

There was inconsistency in direct and indirect estimates involving Pratley study[113]. The study assessed liraglutide versus sitagliptin effect and safety on a 26-week open-label trial. Analyses

were done on full dataset with missing values imputed. Sensitivity analysis excluding the Pratley 2010 study did not result in any substantial differences in results (Table 4.22.1).

Figure 4.21: Consistency plot for cardiovascular mortality

Table 4.22.1: Cardiovascular mortality- network meta-analysis with Pratley study removed: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.03(0.33,3.13)
MET+DPP-4		0.60(0.21,1.53)
MET+SGLT-2		1.14(0.29,5.24)
MET+GLP-1		0.68(0.18,2.55)
MET+TZD		1.08(0.32,4.28)
MET+DPP-4	MET+SUL	0.58(0.25,1.34)
MET+SGLT-2		1.12(0.22,5.74)
MET+GLP-1		0.66(0.19,2.23)
MET+TZD		1.12(0.27,4.46)
MET+SGLT-2	MET+DPP-4	1.91(0.45,9.89)
MET+GLP-1		1.14(0.31,3.92)
MET+TZD		1.94(0.43,6.99)
MET+GLP-1	MET+SGLT-2	0.60(0.10,3.65)
MET+TZD		0.99(0.14,6.19)
MET+TZD	MET+GLP-1	1.70(0.34,7.60)
Random-effect model	Residual Deviance	37.44 vs 73 data points
	Deviance information criteria	211.564

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones.

4.3.4.12 Heart failure

There were 18 studies[23,45,54,79,85,86,97,105,117,125,126,134,145,152,173,221,219,222] that reported heart failure outcomes. Data were available for all antihyperglycemic classes, except for meglitinides, insulin, alpha-glucosidase inhibitors and GLP-1 RAs.

The results of the random effects NMA model are presented in Table 4.23. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Relative to metformin monotherapy, thiazolidinediones (TZDs) significantly increased the risk of heart failure (OR 3.31 95%Crl: 1.44, 9.02). When the classes were compared one another, TZDs significantly increased the risk of heart failure in comparison with sulfonylureas (OR 2.82, 95%Crl: 1.10, 9.19) and DPP-4 inhibitors (OR 4.30, 95%Crl: 1.55, 14.14) respectively, whereas no difference was observed between the two classes.

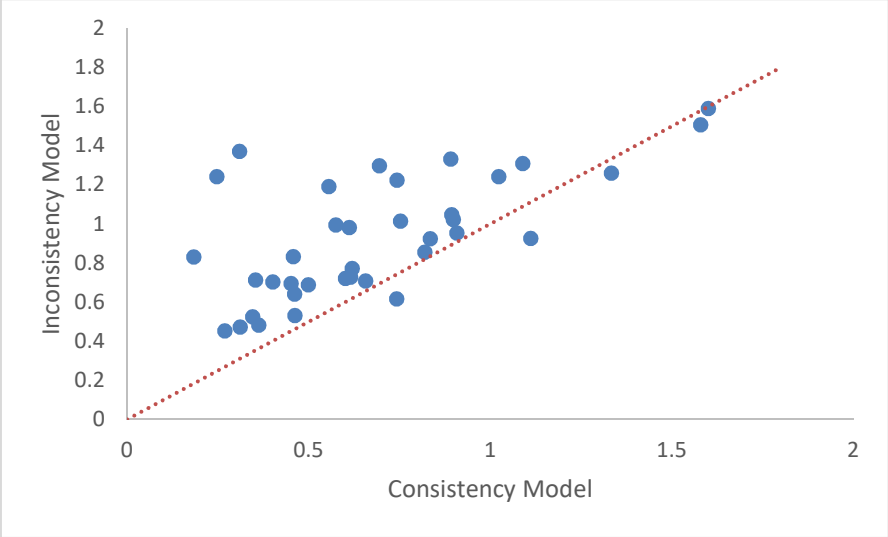
Table 4.23: Heart failure - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	1.14(0.36,4.05)
MET+DPP-4		0.74(0.24,2.55)
MET+SGLT-2		0.99(0.18,5.16)
MET+TZD		**3.31(1.44,9.02)**
MET+DPP-4	MET+SUL	0.65(0.28,1.44)
MET+SGLT-2		0.84(0.20,3.56)
MET+TZD		**2.82(1.10,9.19)**
MET+SGLT-2	MET+DPP-4	1.29(0.29,6.33)
MET+TZD		**4.30(1.55,14.14)**
MET+TZD	MET+SGLT-2	3.41(0.63,17.97)
Random-effect model	Residual deviance	25.25 vs.37 data points
	Deviance information criteria	132.088

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, TZD=thizaolidinediones.

As illustrated in Figure 4.22, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models generally followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.22: Consistency plot for heart failure



4.3.4.13 Stroke

Fatal stroke

There were 30 studies [21,22,28,31,40,45,46,57,66,82,86,90,101,105,109,122,127,133-135,137-139,144,145,170,176,194,219, 222] that reported on fatal stroke outcomes. Data were available for all classes, except for alpha-glucosidase inhibitors, meglitinides and insulin.

The results of the random effects NMA model are presented in Table 4.24. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classed with one another, none of the classes significantly increased or decreased the odds of fatal stroke.

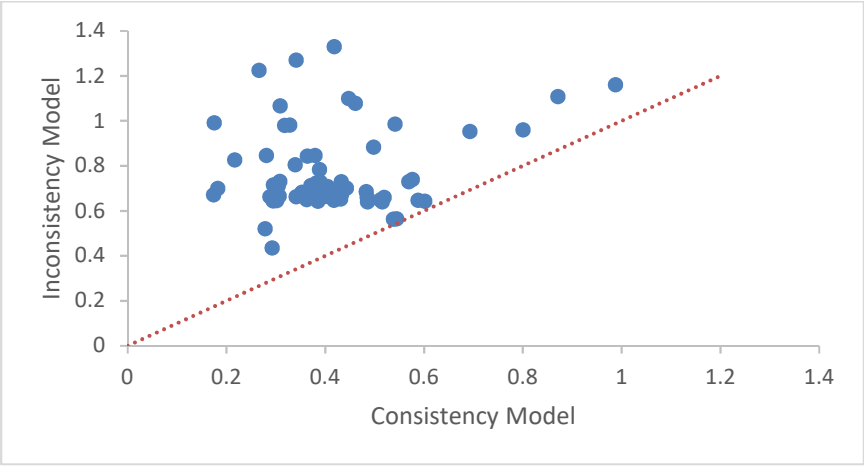
Table 4.24: Fetal stroke - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	0.64(0.13,4.06)
MET+DPP-4		0.63(0.23,1.85)
MET+SGLT-2		1.00(0.26,4.69)
MET+GLP-1		0.72(0.11,3.38)
MET+TZD		0.88(0.12,6.65)
MET+DPP-4	MET+SUL	0.97(0.21,4.61)
MET+SGLT-2		1.61(0.21,9.22)
MET+GLP-1		1.15(0.11,8.31)
MET+TZD		1.29(0.16,11.14)
MET+SGLT-2	MET+DPP-4	1.60(0.37,6.59)
MET+GLP-1		1.12(0.18,5.54)
MET+TZD		1.33(0.21,10.47)
MET+TZD	MET+SGLT-2	0.72(0.09,4.29)
MET+GLP-1		0.90(0.08,8.81)
MET+TZD	MET+GLP	1.26(0.12,14.77)
Random-effect model	Residual deviance	25.6 vs. 61 data points
	Deviance information criteria	164.934

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones.

As illustrated in Figure 4.23, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models generally followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.23: Consistency plot for fatal stroke



Non-fatal stroke

Ten studies[78,79,82,86,101,105,109,135,137,229] reported non-fatal stroke outcomes (N=7,821). The results from the NMA model for non-fatal stroke were not robust because of a large number of zero events in the data set (e.g., six studies reported zero events in one study arm). All studies included the class of DPP-4 inhibitors, but no studies reported the classes of insulins, SGLT-2 inhibitors or GLP-1 RAs add-on to metformin monotherapy.

Four studies[78,82,86,137] compared metformin monotherapy to a DPP-4 inhibitor. In these studies, non-fatal strokes follows in the metformin arm vs DPP-4 inhibitor arm were reported as: 1 vs 0 (n=129)[86]; 0 vs 0 (n=395)[78]; 0 vs 0 (n=438)[82]; and 0 vs 1 (n=544)[137].

4.3.4.14 Transient ischemic attack

There were 18 studies[23,36,40,48,52,54,79,87,99,105,110,120,123,135,137,185,221,222] that reported transient ischemic attack outcomes. Data were available for all classes, except for alpha-glucosidase inhibitors, meglitinides, GLP-1 RAs and insulin.

The results of the random effects NMA model are presented in Table 4.25. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased in the odds of transient ischemic attack.

Table 4.25: Transient ischemic Aatack - network meta-analysis: odds ratio and 95% credible interval

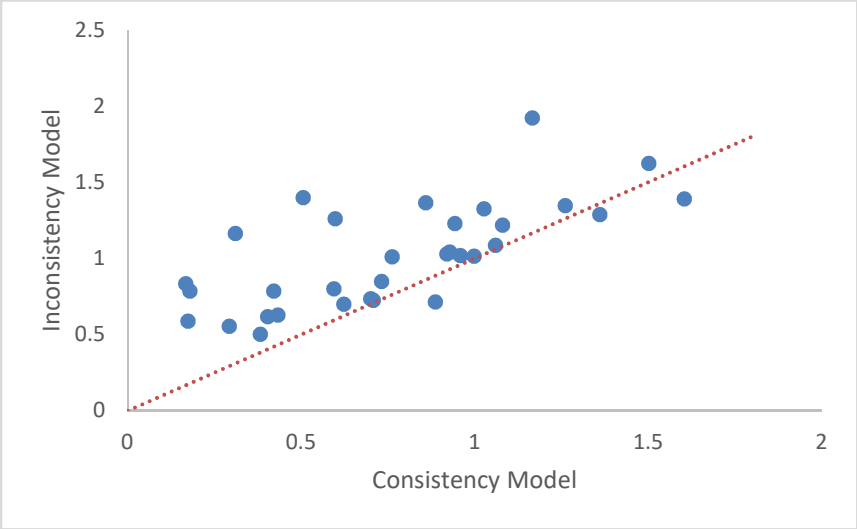
Treatment	Reference	OR (95%Crl)
MET+SUL	MET	0.78(0.16,4.39)
MET+DPP-4		0.54(0.12,2.81)
MET+SGLT-2		0.55(0.11,2.95)
MET+TZD		0.66(0.10,4.97)
MET+DPP-4	MET+SUL	0.71(0.25,1.90)
MET+SGLT-2		0.70(0.25,2.08)
MET+TZD		0.86(0.31,2.35)
MET+SGLT-2	MET+DPP-4	1.01(0.28,3.47)
MET+TZD		1.21(0.31,4.83)
MET+TZD	MET+SGLT-2	1.21(0.28,5.19)
Random-effect model	Residual deviance	24.54 vs.32 data points
	Deviance information criteria	115.993

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones.

As illustrated in Figure 4.24, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models generally

followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.24: Consistency plot for transient ischemic attack



4.3.4.15 Pancreatitis

A total of 26 studies[23,31,40,48,54,58,66,79,86,102,109,113,123,170,180,198,192,194,195,205,199,206,209,214,219,222] reported on pancreatitis as an adverse event while on treatment. Data were available for all classes, except for alpha-glucosidase inhibitors and meglitinides.

The results of the random effects NMA model are presented in Table 4.26. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased in the odds of pancreatitis.

Table 4.26: Pancreatitis - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95% Crl)
MET+SUL	MET	0.80(0.16,5.82)
MET+DPP-4		0.75(0.23,4.08)
MET+SGLT-2		0.83(0.10,5.71)
MET+GLP-1		1.20(0.37,4.56)
MET+TZD		1.35(0.21,8.62)
MET+INS-BA		0.49(0.00,43.24)
MET+DPP-4	MET+SUL	0.92(0.28,3.07)
MET+SGLT-2		1.02(0.17,5.02)
MET+GLP-1		1.50(0.30,6.46)
MET+TZD		1.59(0.30,11.48)
MET+INS-BA		0.59(0.00,41.40)
MET+SGLT-2	MET+DPP-4	1.06(0.18,6.37)
MET+GLP-1		1.57(0.45,5.01)
MET+TZD		1.70(0.36,10.64)
MET+INS-BA		0.63(0.00,43.31)
MET+GLP-1	MET+SGLT-2	1.41(0.26,11.48)
MET+TZD		1.54(0.19,17.85)
MET+INS-BA		0.55(0.00,68.50)
MET+TZD	MET+GLP-1	1.08(0.19,7.32)
MET+INS-BA		0.40(0.00,20.29)
MET+INS-BA	MET+TZD	0.36(0.00,23.32)
Random-effect model	Residual deviance	29.57 vs. 60 data points
	Deviance information criteria	172.469

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, GLP-1= glucagon-like peptide-1 receptor agonist, TZD=thizaolidinediones, INS-BA=basal insulin.

As illustrated in Figure 4.25, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models generally followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.25: Consistency plot for pancreatitis

4.3.4.16 Cancer

Pancreatic cancer

A total of six studies[23,45,45,79,101,113] reported pancreatic cancer as an adverse event while on treatment (N = 3,961).

The NMA model for pancreatic cancer was not robust due to the frequent number of zero events in the data set. Pairwise meta-analysis was also not possible. Included studies compared sulfonylureas (1 event), GLP-1 RAs (1 event), SGLT-2 (zero events) and DPP-4 inhibitors (3 events) added to a metformin background therapy. Only one study compared an intervention to metformin monotherapy (zero events).

Bladder cancer

Six studies[23,45,48,54,105,110] that reported on bladder cancer events while on treatment (N = 4,605). The NMA model for bladder cancer was not robust due to the frequent number of zero events in the data set; all studies reported zero events in one or all study arms. Pairwise meta-analysis was also not possible. All three studies[23,48,105] that reported bladder cancer events compared sulfonylurea to a DPP-4 inhibitor. All events were singular and occurred in the DPP-4 inhibitor study arms. One study [54] comparing metformin monotherapy to sulfonylurea and DPP-4 inhibitors reported zero events in all study arms. Two studies[45,110] comparing metformin monotherapy to SGLT-2 inhibitors also reported zero events in all study arms.

4.3.4.17 Ketoacidosis

There were six studies[48,185,196,214,219,222] that reported events of ketoacidosis. The NMA model for ketoacidosis was not robust due to the frequent number of zero events in the data set; all studies reported zero events in one or all study arms. For example, one study[50] comparing sulfonylurea to DPP-4 inhibitors, a single event was reported in the DPP-4 inhibitor arm (n = 1,747). In another study,[224] there were zero ketoacidosis events in the three study arms (metformin, DPP-4 and SGLT-2 inhibitors). Pairwise meta-analysis was also not possible.

4.3.4.18 Other: Cardiovascular health

Unstable angina

A total of 17 studies[23,48,52,79,84,86,105,109,110,120,125,129,133,137,145,185,221] reported unstable angina as an outcome and were included in the NMA. Data were available for all classes, except for alpha-glucosidase inhibitors, meglitinides, insulin and GLP-1 RAs.

The results of the random effects NMA model are presented in Table 4.27. The residual deviance value is less than the number of unconstrained data points indicating model convergence. Compared with metformin monotherapy and selected classes with one another, none of the classes significantly increased or decreased in the odds of unstable angina.

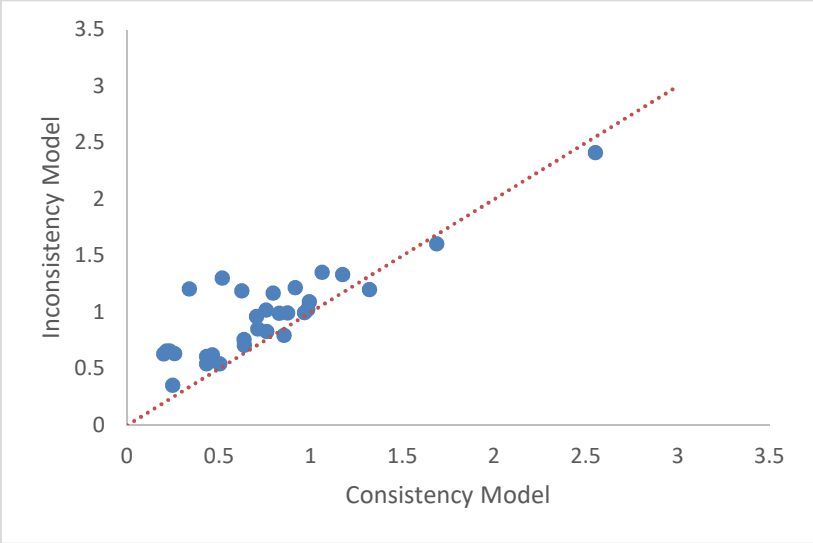
Table 4.27: Unstable angina - network meta-analysis: odds ratio and 95% credible interval

Treatment	Reference	OR (95%Crl)
MET+SUL	MET	0.90(0.25,3.93)
MET+DPP-4		1.05(0.33,3.50)
MET+SGLT-2		0.86(0.20,3.74)
EMT+TZD		0.71(0.15,3.55)
MET+DPP-4	MET+SUL	1.14(0.46,2.90)
MET+SGLT-2		0.93(0.29,3.24)
MET+TZD		0.77(0.33,1.81)
MET+SGLT-2	MET+DPP-4	0.81(0.21,3.16)
MET+TZD		0.68(0.19,2.15)
MET+TZD	MET+SGLT-2	0.82(0.19,3.48)
Random-effect model	Residual deviance	23.65 vs.31 data points
	Deviance information criteria	112.765

MET=metformin, SUL=sulfonylurea, DPP-4=dipeptidyl peptidase 4 inhibitor, SGLT-2=Sodium-glucose co-transporter 2, TZD = thizaolidinediones.

As illustrated in Figure 4.26, since the points representing the posterior means of the total residual deviance for inconsistency models against the deviance of consistency models followed the diagonal trend line with no major deviations below the trend line, model consistency was indicated.

Figure 4.26: Consistency plot for unstable angina



Hospitalization for unstable angina

A single study[83] of a sulfonylurea compared to a DPP-4 inhibitor add-on to metformin background reported hospitalization for unstable angina. In this study, 3 participants in each treatment group were admitted to hospital for unstable angina (SUL: n = 775; DPP-4 n = 776).

Non-fatal myocardial infarction

Eleven studies[31,48,79,85,103,105,138,142,145,151,152] reported on non-fatal myocardial infarction (MI) as an outcome (N = 8,010). Data were not available for any of the insulins. The NMA model for non-fatal MI was not robust due to the frequent number of zero events in the data set; 9 of the 11 studies reported zero events in one (7 studies) or all study arms (2 studies). Eight of the studies included DPP-4 inhibitors. No studies reported on insulin.

A pairwise meta-analysis comparing DPP-4 inhibitors to sulfonylurea found no difference in the odds of nonfatal MI (OR 1.35, 95% CI 0.63, 2.92). No other direct estimates could be estimated. Two studies[151,103] reported zero events during the study period. In total, thirty-one non-fatal MI events were reported among the other studies, including 12 events in the DPP-4 inhibitor arms of 4 studies[31,48,79,105] (n = 2156); 17 events in the sulfonylurea arms of 4 studies[48,79,138,142,145] (n =2329); one event in the SGLT-2 inhibitor arm of one study[85] (n = 179); one event in the GLP-1 inhibitor arm of one study[142] (n = 36); and no events were reported in participants taking metformin monotherapy.

Fatal myocardial infarction

Forty-six studies[21-23,28,30-32,40,42,43,45,46,51,56,57,66,67,69,70,79,82,90,105-107,109,110,118,122,124,127,131-133,135,137-139,144,145,148,153,156,162,164,170,176] reported either fatal myocardial infarction or zero deaths (inferred as zero fatal myocardial infarctions). In total, 2 participants experienced a fatal myocardial infarction (0.06%). The NMA model for fatal myocardial infarction was not robust due to the frequent number of zero events in the data set; all studies reported zero events in at least one (n=12 studies) or all study arms (n=34 studies). Pairwise meta-analysis was also not possible.

Data were available for all drug classes, including basal and biphasic insulin (2 studies), one comparing GLP-1RAs added to metformin with basal insulin as an add-on to metformin[56] (zero events, N=319) and another[148] comparing sulfonylurea plus metformin with biphasic insulin added to metformin (one event, N=222).

Coronary revascularization

Only one study[31] reported a single coronary revascularization procedure in a comparison of metformin monotherapy to a DPP-4 inhibitor (saxagliptin) add-on to metformin. The event was described as "*a 100% right coronary artery ostial occlusion with collateralization was noted, and the 80%–90% proximal left circumflex artery lesion was treated with percutaneous transluminal coronary angioplasty and a stent*". The patient after the procedure begun carrying on the medication of DPP-4 inhibitor and completed the trial.

4.4 Discussion

This systematic review and network meta-analysis comprehensively assessed and compared medically important benefit-harm outcomes of eight antihyperglycemic classes combined with metformin, namely: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, insulin, DPP-4 inhibitors, GLP-1 RAs, and SGLT-2 inhibitors. These classes differ in their physiological mechanisms of glucose-lowering action, risk or side effects and some ancillary cardiovascular benefits that may be translated into clinical practice.

Regarding treatment efficacy, all eight of the antihyperglycemic classes in comparison with metformin monotherapy significantly reduced HbA1c levels to varying degrees. Among combination therapies (metformin plus one class), GLP-1 RAs add-on to metformin decreased HbA1c more than DPP-4 inhibitors, which is consistent with the previous review.[9] In addition, the updated NMA showed that GLP-1 RAs were more efficacious than SGLT-2 inhibitors and sulfonylureas in reduction of HbA1c. Two recent NMA studies[11,12] also found GLP-1 RAs

superior to SGLT-2 inhibitors in lowering HbA1c. Another NMA[230] showed that SGLT-2 inhibitors were superior to sulfonylureas in lowering HbA1c two years after drug initiation. From a clinical perspective, the magnitude of treatment effect is associated with a clinically important change of 0.3% decrease in HbA1c (or 3 mmol/mol) as recommended by the US Food and Drug Administration[227] and the European Medicines Agency.[226] In our updated NMA results, all the selected antihyperglycemic classes reduced HbA1c statistically and clinically relative to metformin monotherapy. When the classes were compared to one another, some were superior to others in reduction of HbA1c, however, these differences were no longer observed after taking metformin background doses into account (or excluding those studies with metformin background therapy doses below 2,000mg daily). An important next step in this investigation of efficacy is long-term efficacy, including observational studies of large clinical populations in a more real-world setting.

Given that recent literature has suggested that preventing even mild hypoglycemia is as important for diabetes management as tight glycemic control, because hypoglycemia was associated with increased risks of mortality and retinopathy,[231,232] a therapy's HbA1c-lowering efficacy must be weighed against its potential to cause hypoglycemia. Effect estimates from the NMA show a significant increase in non-severe hypoglycemia with sulfonylureas, meglitinides, basal insulin and biphasic insulin in comparison with metformin monotherapy. These differences were maintained when all antihyperglycemic classes were compared to one another in the NMA, albeit basal insulin showed significantly less hypoglycemia when directly compared with sulfonylureas. In addition, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 RAs significantly

reduced the risk of non-severe hypoglycemia and no differences were reported among the three classes.

Most patients with T2DM meet the criteria for overweight or obesity, which is a predictor for diabetes-associated mortality.[233,234] Our study showed that GLP-1 RAs and SGLT-2 inhibitors significantly decreased body weight when compared with metformin monotherapy and other antihyperglycemic classes (range: -1.39 to -3.63 kg). Although there are no clear cut-off value for clinically significant weight loss, some studies suggested 2.3 kg (five pounds) reductions in body weight associated with better improvement of lipids and blood pressure.[235,236] Furthermore, the NMA results showed that GLP-1 RAs significantly reduced BMI relative to metformin alone, sulfonylureas and TZDs (range: -1.27 to -2.58 kg/m^2). A large observational study found that one unit increment in BMI was associated with 4% higher risk of ischemic stroke and 6% higher risk of hemorrhagic stroke.[237] In our study, both GLP-1 RAs and SGLT-2 inhibitors demonstrated the capacity to reduce body weight but no significant difference between the two antihyperglycemic classes was found. Physiologically, they reduce body weight through different mechanisms, with GLP-1 RAs influence on appetite and gastric emptying,[238,239] while SGLT-2 inhibitors increase urinal glucose excretion and consequent caloric loss.[240] Further studies on these two classes are warranted to compare their long-term effects on weight and BMI loss and clinical implications.

As expected, our effect estimates showed increased weight was associated with use of insulin, sulfonylureas, meglitinides and TZDs (range: 1.90 kg to 2.79 kg). Observational studies found a 10-kg greater body weight was associated with a 12% greater risk of coronary heart disease and 24% greater risk of stroke.[241] Thus, prescriptions of these antihyperglycemic classes for patients

that are overweight, and especially with underlying cardiovascular conditions, require careful consideration of all these factors.

Guidelines[5,6] recommend good blood pressure control for patients with type 2 diabetes in order to reduce the risk of cardiovascular disease. Reductions in systolic blood pressure were seen with SGLT-2 inhibitors, GLP-1 RAs, DPP-4 inhibitors and TZDs when compared with metformin monotherapy and sulfonylureas (range; -1.41 to -4.45 mmHg). SGLT-2 inhibitors and GLP-1 RAs were superior to DPP-4 inhibitors in lowering systolic BP (range; -1.86 to -2.48 mmHg), and no significant difference between these two classes was found. Although changes smaller than 5 mmHg are not enough for the Federal Drug Administration to license a drug for treatment of blood pressure, they might still be clinically significant on a population level.[228] In terms of diastolic blood pressure, SGLT-2 inhibitors significantly reduced diastolic BP when compared with metformin monotherapy or sulfonylureas (range; -2.16 to -2.26 mmHg), which are clinically important benefits in lowering diastolic BP more than 2 mmHg.[228] Although not approved as antihypertensive agents, the updated NMA further supports previous results[9] that some of the antihyperglycemic classes studied may have the capacity to lower blood pressure.

Diabetes-associated dyslipidemia is a contributor to the cardiovascular risk for patients with diabetes, which is mainly characterized by low HDL cholesterol and high triglycerides.[242] Our NMA results showed that SGLT-2 inhibitors were associated with a significant increase in HDL cholesterol, which is consistent with other similar NMA analyses.[10,243] Studies further supported that dapagliflozin, a SGLT-1 inhibitor, can reduce fat mass for patients with diabetes over a 104-week treatment period.[87,244] On the other hand, some studies present the argument that SGLT-2

inhibitors reduce body fluid content or weight loss associated with lean mass, not fat mass,[245]and did not increase the HDL levels.[246] Notably, another complexity of antihyhyperglycemic class on HDL may be the differences by ethinicity.[247] Nevertheless, the overall clinical implications of these findings remain unclear, and need to investigate further on how these changes may translate into cardiovascular protection.

The NMA found that GLP-1 RAs, insulin and alpha-glucosidase inhibitors increased the risk of total adverse events when compared with metformin alone. Effect estimates of withdrawals due to adverse events showed no significant differences among the antihyperglycemic classes, except for GLP-1 RAs. This review analyzed total numbers of adverse events, and we did not analyze the type of individual adverse events commonly reported in the studies. It is well documented that gastrointestinal adverse events are commonly reported with the GLP-1 RAs and alpha-glucosidase inhibitors, and hypoglycemia is common with the insulins. In addition, GLP-1 RAs and insulins are known for irritation, redness and itchiness at the injection site. This update extended our previous results[9] and showed that thiazolidinediones significantly increased the risk of heart failure when compared to metformin monotherapy and the other antihyperglycemic classes. This finding is also consistent with other NMA studies.[248]

As a novel antihyperglycemic class, SGLT-2 inhibitors lower glucose levels by excreting glucose into the urine, which increases the risk of genital infections. In our previous analysis,[9] data were available only for sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors compared with metformin monotherapy and the NMA did not show a statistically significant difference in the risk. The updated NMA added more recent studies that clearly demonstrated that SGLT-2

inhibitors were significantly associated with increased risk of urogenital adverse events when compared with either metformin monotherapy or other classes (OR: 1.59 to 1.88). This finding extends our previous results and supports guidelines being recommended for this patient population by Diabetes Canada.[6]

Although this review included significantly more studies, compared with metformin monotherapy and with one another, none of the eight antihyperglycemic classes for which data were available, significantly increased or decreased the risk of renal adverse events, fractures, all-cause mortality, cardiovascular mortality, fatal stroke, transient ischemic attack, unstable angina, pancreatitis, ketoacidosis, bladder cancer, pancreatic cancer, and coronary revascularization procedure. One explanation is low number of events or zero events commonly reported in these outcomes.

The current systematic review and NMA comprehensively assessed risk-benefit for eight antihyperglycemic classes combined with metformin, including 23 outcomes. It provides evidence to help physicians and patients compare efficacy and safe profiles between these treatment options.

Strengths and Limitations

A key strength in the updated NMA is that the protocol was specified in advance before any study selection and data extraction, using systematic and standard approaches for identification of evidence, data extraction, quality assessment and analysis. Second, the majority of "High ROB" studies came from RCTs with incomplete outcomes reporting for efficacy and safety,

which mainly related to treatment duration. That is, the longer the duration of a trial then the more likely a lower than 80% complete rate (cut-value for high risk of bias in our study) will be. We conducted sensitivity analyses for the effect of treatment duration and confirmed that the results were not substantively different from the overall results. Thus, the certain of evidence is at least moderate. In addition, the NMA incorporates both direct and indirect estimates of the treatment comparisons, which can be informative to patients, practitioners and policy makers; in particular, when there is a paucity of head-to-head treatment comparisons. There are some limitations in this review: First, the cardiovascular outcome trials could not be included in this meta-analysis because participants were on varied and unspecified antihyperglycemic agents as background or baseline treatment, and thus these studies did not allow comparison of metformin plus study drug versus metformin alone. These studies, including EMPA-REG,[250] LEADER[251] and CREDENCE,[252] reported clinically important outcomes but did not qualify for this systematic review. Second, the NMA is based some key assumptions, including homogeneity, transitivity and consistency. In general, the NMA analyses of current results were assessed to be valid, however, we were unable to statistically assess the consistency assumption for some outcomes due to the limited number of studies informing the evidence network. In addition, this review excluded studies where the language of full-text publications was not English. Results may not capture potential differences between various races, in particular those published in other languages, rather than English. Finally, some important sensitivity analyses could not be done due to unavailability of data. Only a few trials (27 RCTs) involved Asians, and even for these studies results were not provided by race/ethnicity. As well, the sensitivity analysis by sex/gender could not be done given that the subgroup data by sex were not provided. These

demographic characteristics are important in T2DM and neeed to be considered in the design and reporting of future RCTs.

Conclusions

When considering an adjunct agent added-on to metformin, all eight antihyperglycemic classes can lower HbA1c but to varying degrees. They also present with varying effects on hypoglycemia, body weight, BMI, blood pressure, HDL, LDL, total cholesterol, total adverse events, withdrawals due to adverse events, urogenital adverse events and heart failure.

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Chapter 5 Development of a patient decision aid for adults in China with type 2 diabetes mellitus considering add-on agents for good glucose control after failure with metformin treatment alone

5.1 Introduction

Shared decision making is a collaborative approach by which patients and practitioners work together to share evidence-based information about treatments, and patient values and preferences in order to identify reasonable treatment options addressing the unique situation of patients.[1] The principle of shared decision making is to promote patient informed decision-making, respectful of and responsive to individual patient preferences, needs, and values.[2,3] As a means of implementing shared decision making, patient decision aids (PDA) can be used to facilitate shared decision making by providing information on the treatment options and outcomes, helping patients clarify and communicate their personal values and preferences about options, and coaching or guidance in the steps of decision-making and communicating with others.[4,5] A Cochrane Collaboration systematic review of 105 randomized controlled trials (RCT) of PDAs showed that these interventions improved patient knowledge of their disease, helped them set more realistic expectations of the treatment, reduced decisional conflict, and reduced cost in some contexts in the healthcare system, when compared to usual care.[6] Evidence continues to build that PDAs increase patient trust[7] and reduce the likelihood and cost of litigation.[8] Although the concept of shared decision making is promising, it is not always implemented in clinical practice. Currently, research in this field occur mostly in developed

countries.[9,10] Some developed countries have made efforts to promote shared decision making and PDAs, including Canada,[11] the United States,[12,13] and the United Kingdom.[14]

Shared decision making is consistent with patient-centered care, which aligns with the healthcare priorities in developing countries as well. For example, the 2018 diabetes guidelines in China introduced a patient-centered approach to the management of hyperglycemia for the first time.[15] However, research in shared decision making and patient decision aids is still in its infancy in developing countries, including China.[16-18] For example, Huang[18] conducted a broad literature search on shared decision making in Chinese populations and fourteen relevant studies were found. However, all the studies were based on patients who immigrated to developed counties, or who lived in Hong Kong or Taiwan. More recently, a study in China interviewed 200 clinicians from two hospitals and no one knew what shared decision making meant or had experience of applying shared decision making in clinical practice.[19]

Although there is a growing interest in the development of patient decision aids, it may lead to poor decisions if a PDA is not designed and developed following rigorous standards.[20] The International Patient Decision Aid Standards (IPDAS)[20-22] provides a guide to systematically develop high quality PDAs that should include evidence-based information on treatment options and culturally relevant patient values and preferences specific to the medical condition of interest. The evolution of a PDA involves a complex process of designing and developing a PDA prototype, followed by alpha and beta testing of the PDA with all the stakeholders.[47] The alpha testing is described as "direct feedback from "typical" users sought during the development

process. This may include members of the steering group and others involved in the development process". Beta testing is described as "testing with patients (and occasionally providers) in real world settings to assess feasibility" (http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf).

The objective was to systematically develop an evidence-based, culturally appropriate and theory-driven PDA prototype for patients with type 2 diabetes mellitus (T2DM) who consider add-on antihyperglycemic agents after metformin monotherapy failure to achieve adequate glucose control in China.

5.2 Methods

5.2.1 The Ottawa decision support framework

The Ottawa Decision Support Framework (ODSF)[23-25] is a framework that consists of theories and concepts being derived from multi-disciplnary fields (e.g., psychology and methodology) to fundamentally support a decision model development to various audiences (e.g., patients, practitioners, and researchers). The ODSF is one of the most common shared decision making frameworks to support the development of shared decision making interventions. The ODSF covers three key principal components: decision needs, decision quality and decision support. Given the fact that there is no such needs assessment found for this population with type 2 diabetes in China, we followed this Framework to assess patient decisional needs at Fu Wai Hospital, Beijing, China. Specifically, we followed the steps, including 1) define the objective of

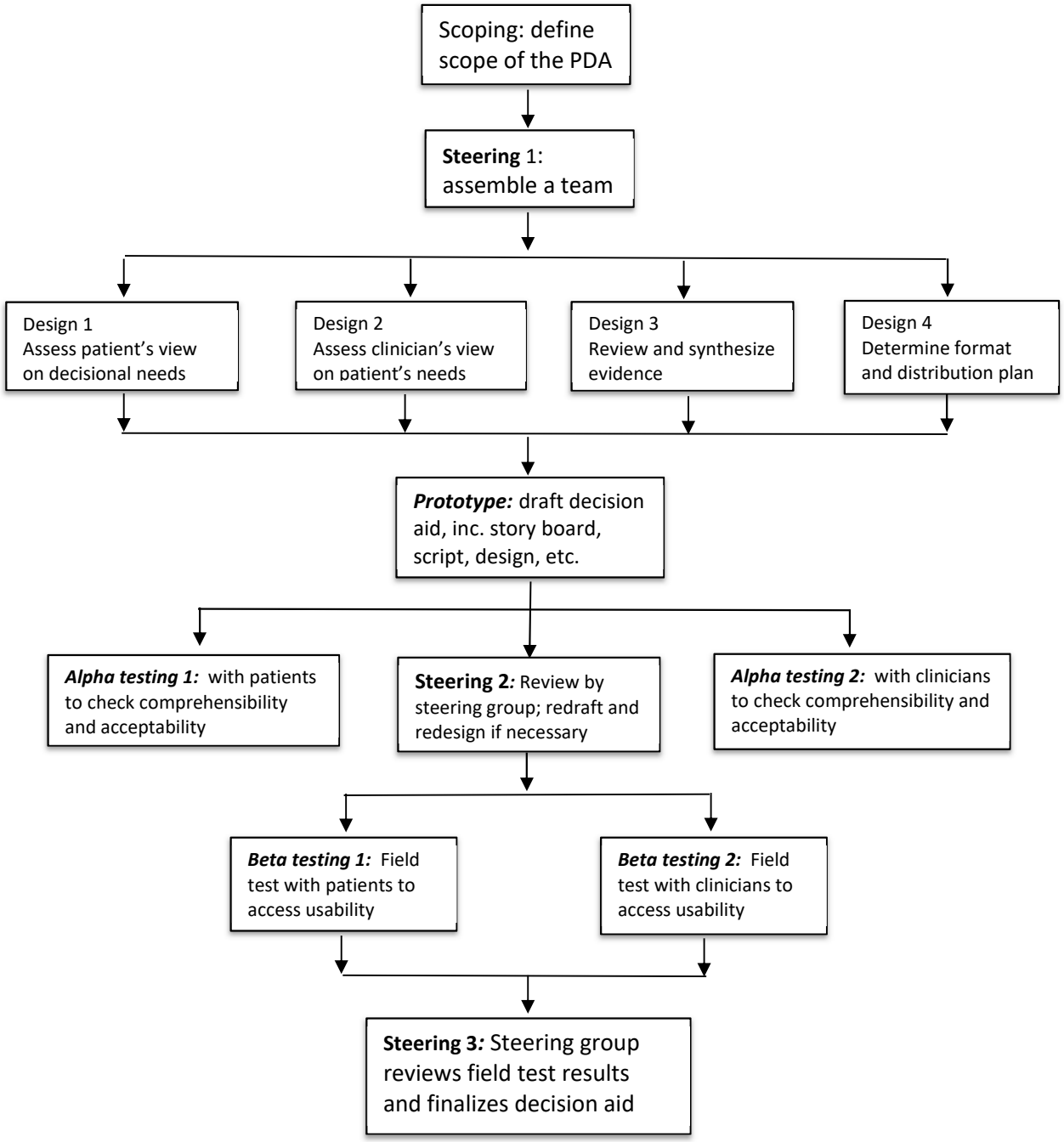
the needs assessment; 2) identify the participants; 3) identify the rationale or purpose of the needs assessment; 4) identify the information to be collected; 5) select the methods for collecting the information; 6) develop data collection tools; 7) select the sample, sample size and sampling procedure; 8) develop a schedule; 9) conduct the needs assessment and analyses; and 10) summarize and present the information, as guided by the Decisional Needs Assessment in Population developed at the Ottawa Hospital Research Institute.[11,26,27]

5.2.2 Systematic development process for PDA

In 2003, the International Patient Decision Aids Standards (IPDAS) collaboration was established, led by Drs. Glyn Elwyn of the United Kingdom and Dawn Stacey of Canada.[20-22] The main goal of IPDAS is to standardize the development and evaluation of PDAs by providing rigorous methods and criteria.

A systematic development process for patient decision aids following the IPDAS principles[28] is illustrated in Figure 5.1. We elaborate on each of the steps below.

Figure 5.1: A systematic development process for patient decision aid *



*Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

5.2.2.1 Assembling the research team and defining the scope of the PDA

Assembling the research team and defining scope of the PDA*		
Element	Definition	Method
Scoping	Describe health condition or problem; state the decision that needs to be considered; specify target audience	Developer advised by multi-disciplinary steering group, ideally involving topic experts, clinicians, and patients
Steering group	A team of stakeholders who advise on the development, evaluation, and implementation of the patient decision aid (PDA)	Steering group members will have relevant expertise in decision-making for the specific topic: patient representatives; clinicians, patient educators, shared decision-making expertise, policy makers

*Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

Following the developmental steps as outlined in the above table, a multi-disciplinary team was assembled for the purpose of developing this PDA. It included researchers with experience in shared decision making and PDA development, qualitative and quantitative research, economics and physicians and nurses who provide clinical care to patients with diabetes. Team members were from both China and Canada. It was also important to include patient partners with T2DM and patient family members from China to help ensure that the developed PDA would be relevant to this population, given the fact that they all involve in making a decision as indicated in our patient needs assessment (Chapter 3). The committee was responsible for guiding, developing, revising and approving the PDA.

Discussions among team members and a scoping review of PDAs for type 2 diabetes in China helped determine the scope of the PDA. Members of the research team were motivated to

develop a PDA for patients with T2DM in China who had insufficient glucose control on metformin monotherapy and considered add-on medications.

5.2.2.2 Views on patient decisional needs

Views on patient decisional needs*		
Element	Definition	Methods**
Design 1 Assess patients' views on decisional needs	Elicit patients' and clinicians' views on patient's information and decision support needs	**Focus groups** **Stakeholder interviews** Survey Systematic literature review (including qualitative and quantitative studies) Direct observation
Design 2 Assess clinicians' views on patients' needs		

*Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

** Methods in bold have been used in this project

In order to elicit patients' and practitioners' perspectives on patient decisional needs when adding an antihyperglycemic agent for the treatment of a patient with T2DM in China, we conducted individual patient interviews and practitioner focus groups at the Fu Wai Hospital, Beijing, China. Guided by the Decisional Needs Assessment in Population from the Ottawa Hospital Research Institute,[26,27] we developed interview guides for patients and practitioners respectively, and modified them for use in the Chinese context. The details of these methods and results are described in Chapter 3 of this thesis.

5.2.2.3 Review and synthesize evidence

Review and synthesize evidence*		
Element	Definition	Methods
Design 3 Review and synthesize evidence	Summary of clinical evidence relevant to the decisional and options	**Comprehensive literature search with emphasis on systematic reviews (when available)** The evidence may include empirical studies of patients' experience and/or preferences. Use quality criteria to assess clinical practice guidelines when these are used as evidence source It may be more efficient to develop patient decision aids alongside clinical practice guidelines, since they draw on the same evidence base.

*Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

** Methods in bold have been used in this project

With the considerable increase in the number of antihyperglycemic agents/classes available, patients who failed to control their blood glucose level (blood sugar level) or HbA1c (average blood sugar level over a period of weeks/months) with metformin monotherapy have many treatment options to add on to metformin. However, there is a paucity of summary information regarding comparative efficacy and safety of current antihyperglycemic agents/classes combined with metformin treatment. We conducted a systematic review of the randomized controlled trials where metformin was used as background treatment in combination with other antihyperglycemic medications. Bayesian network meta-analyses were conducted to assess differences between the medications for a wide range of efficacy and safety outcomes. The details of the methods and results of the systematic review and network meta-analysis are described in Chapter 4.

5.2.2.4 Determine format of the PDA and distribution plan

Determine format of the PDA and distribution plan*		
Element	Definition	Methods
Design 4 Determine format and distribution plan	Includes choices of media and format of decision aid, setting, timing of introduction into patient pathway, how and when decision aid will be distributed to patients and/or clinicians	Formats may include print media, audio recordings, DVDs, videos, websites, computer programs, decision boards, face-to-face discussions, group education, and any combination of these Distribution methods include handing out in clinic, mailing, telephone coaching, or direct-to-patient via websites or other means Settings include primary care, secondary care, health coaches, and community.
Prototype development	Draft decision aid, including storyboard, script, graphics, web design, video, etc.	Ranges from basic to highly sophisticated

* Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

Patient decision aids from various websites including the Ottawa Hospital Research Institute (https://decisionaid.ohri.ca/AZlist.html) were reviewed for format, script and graphics by the research team. This assessment suggested a need for a values-clarification exercise in the PDA, as well as, the need for evidence-based information on various antihyperglycemic medications that can be used as add-on to metformin. Accordingly, the key results from the previous phases of the research on patient values and preferences (Chapter 3) and the review and analysis of the efficacy and safety of adding on other antihyperglycemic medications to metformin (Chapter 4) were incorporated into the PDA in a manner that would be understandable to the patient.

Given that this is the first PDA for this specific population with T2DM in China, patients and practitioners suggested that a simple medium and distribution of the PDA be the best approach.

Depending on the acceptance level and results of this version of the PDA, more sophisticated formats of the PDA using audio and video recordings and direct-to-patient distribution methods using websites will be investigated.

5.2.2.5 Feedback from users (alpha testing)

Feedback from users (alpha testing) *		
Element	Definition	Methods
Alpha testing	Direct feedback from "typical" users sought during the development process. This may include members of the steering group and others involved in the development process.	Review by key stakeholders (patients, clinicians) via focus groups, cognitive interviews, direct observation, usability, and acceptability testing. Feedback may be sought at various stages in an iterative process.

* Citation: Coulter A, Kryworuchko J, Mullen P, Ng CJ, Stilwell D, van der Weijden T. (2012). Using a systematic development process. In Volk R & Llewellyn-Thomas H (editors). 2012 Updated of the International Patient Decision Aids Standards (IPDAS) Collaboration's Background Document[28, 29]. Chapter A. http://ipdas.ohri.ca/IPDAS-Chapter-A.pdf

During the development of the PDA, direct feedback and observation from "future users" of the PDA were sought and continuously incorporated throughout the different stages of development of the PDA. They included Chinese patients with T2DM who had been taking metformin alone and failed to achieve adequate glucose control to consider add-on medications, patients' family members, and nurses and physicians who provide clinical care to patients with T2DM at Fu Wai Hospital in China.

The PDA underwent several iterations by the multi-disciplinary team members during this first phase of the alpha-testing.

5.2.3 IPDAS quality assessment of the patient decision aid

The International Patient Decision Aid Standards collaboration was formed to establish a set of criteria to determine the quality of PDAs. These criteria were designed to be helpful to a wide variety of individuals and organizations that use and/or develop PDAs, including: patients, practitioners, developers, researchers and policy makers or payers. The original checklist of IPDAS criteria included 74 items.[20] Subsequently, the International Patient Decision Aid Standards Instrument (IPDASi) was made more practical and reduced to 47 items for assessing the quality of decision support technologies.[22] (Appendix 5A) A later version identified a minimum set of 44 items, with the aim to set minimum standards for certifying PDAs.[30]

The PDA prototype developed for patients with T2DM when considering an add-on antihyperglycemic agent after metformin monotherapy failed to achieve adequate glucose control, was assessed using the IPDASi. The 47 criteria of this instrument are categorized into 10 dimensions (Appendix 5A).[22] The purpose of the assessment was to highlight which IPDASi criteria were met, and to identify the steps that will be required for future development and testing. It is important to keep in mind that since the PDA prototype will not have undergone the full evaluation, not all IPDASi criteria will be met. This is a preliminary assessment to see which criteria need to be considered for possible improvements of the PDA in the future.

5.3 Results

5.3.1 Research team and scope of the patient decision aid

The multi-disciplinary steering committee included experts in the field of shared decision making and patient decision aid research (KTA), qualitative and quantitative research (GW), economic research (DC), epidemiology (YC) and endocrinology (physicians: GWL, YA, SH, RS, as well as nurses: XW, F Z) who provide care to patients with diabetes in China and Canada. Members of this international research team came from the University of Ottawa and the University of Calgary, Canada, and Fu Wai Hospital, China. It also included patients with T2DM (WY, JN) and patient family members (JM, GL) in China.

The PDA was designed to help patients with T2DM in China in making a well-informed decision when metformin monotherapy had been insufficient to achieve good glucose control and they were therefore considering add-on agents. There were several reasons for this scope for the PDA. 1) A PDA becomes a useful tool to facilitate shared decision making when several treatment options arise.[31] Current diabetes guidelines in China recommend that eight antihyperglycemic classes plus traditional Chinese medicine could be considered add-on to metformin after the monotherapy failure to achieving good glycemic control.[15] 2) No PDAs could be identified for this population with T2DM in China. A recent survey in China also showed that few practitioners were aware of shared decision making and had no experience of using PDAs.[19] 3) Our patient decisional needs assessment in China indicated that patients with T2DM wanted consistent information of treatment options and wished more engagement in making a decision,

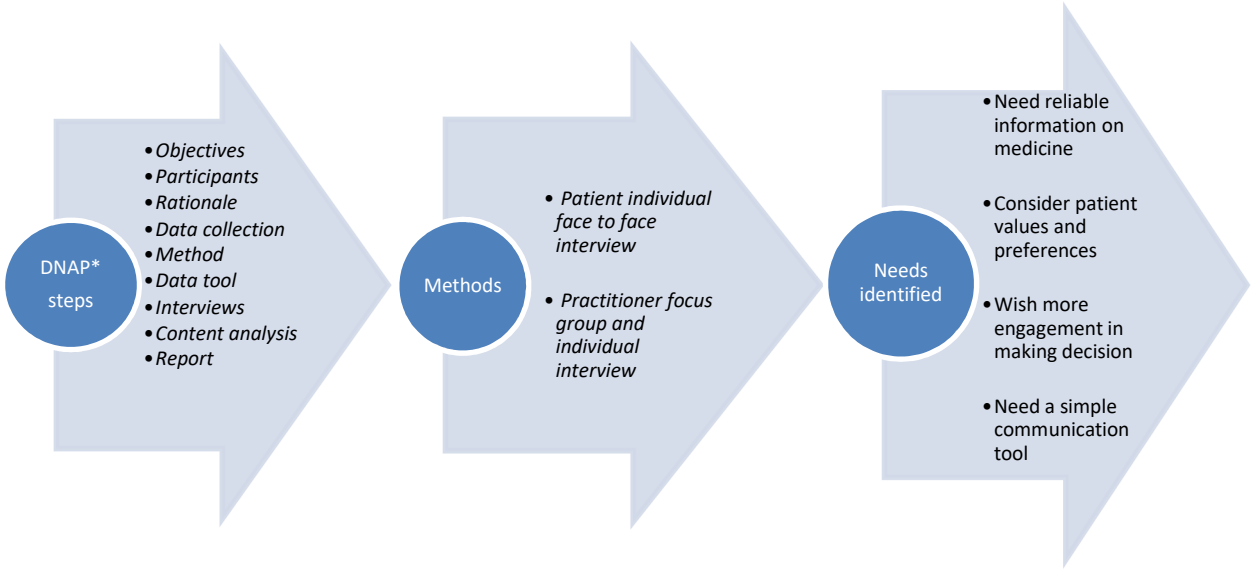
while practitioners needed some tools in supporting their communication with patients (Chapter 3).

It was decided that evidence-based medicine regarding all available eight antihyperglycemic classes would be presented to patients in the PDA. Although Traditional Chinese Medicine (TCM) was recommended for the first time in the 2019 Chinese diabetes guidelines,[15] TCM was not included in the current version of the PDA mainly because synthesizing the evidence is more challenging due to inconsistent methods being used in TCM studies and the consistently low quality of the published studies.[32]

5.3.2 Patient decisional needs

A need is "a gap between what is and what should be". Figure 5.2 highlights the key process steps and findings from the patient decisional needs assessment that was conducted in China (Chapter 3). Briefly, patients with T2DM wanted to be more engaged in decision-making when adding on medications. They need reliable information on antihyperglycemic medications, and their values and preferences need to be considered when adding medications. During the assessment, a need was also identified to improve the communication in terms of the safety and efficacy of antihypeglycemic medications between practitioners and patients.

Figure 5.2: Patient decisional needs assessment at FuWai Hospital, China



* DNAP: Decisional Needs Assessment in Population

The detailed results of the needs assessment for individual patient interviews and practitioner focus groups and individual interviews are described in Chapter 3. Key specific aspects identified as important for patient values and preferences are identified in Box 5.1. This constitutes Step 1 in the PDA on *"**Which reasons matter most to you in making a decision?**"*

Box 5.1: Which reasons matter most to you in making a decision?

How important to you is it …	**Scale from 0 (not important) to 5 (very important)**					
	0 (Not important)	1	2	3	4	5 (Very important)
to have a quick reduction in your blood sugar level						
to take a pill and not a shot						
to avoid taking medications many times during the day						
to have the medication covered by medical insurance						

to avoid weight gain						
to avoid Hypoglycemia						
to avoid medication related side effects on liver or kidney						
to control blood sugar for long-term benefits, such as eyes (avoid blindness) and kidneys (avoid kidney failure with need for dialysis).						

5.3.3 Review and synthesis of evidence

The systematic literature search initially identified a total of 9,750 citations published from 2016 to October 2018. Of the 9750 citations, 2034 duplications were removed, and 4676 citations were excluded based on the selection process at the title and abstract stage. The full texts of 3040 articles were reviewed, with 38 of them eligible for inclusion based on the selection process at the full text article stage. These 38 studies were added to the 166 studies included in the previous 2016 review,[33] yielding a total of 204 eligible studies with reported outcome of interest. Network meta-analyses were conducted for 23 of the clinical outcomes for the antihyperglycemic class comparisons. The choice of outcomes for NMA was based on clinical relevance and the sufficiency of the data available to derive robust and consistent network meta-analysis models. Effect estimates included the odds ratio for dichotomous outcomes and the mean difference for continuous outcomes. Point estimates and 95% credible intervals were assessed using Markov Chain Monte Carlo methods and basic parameters of the treatment effects in the model were assigned vague prior distribution, N (0, 100^2). Selected results were presented in the PDA as evidence-based medicine treatment options. Equally important, the PDA communicates estimated probabilities about different treatment options in T2DM in a neutral and balanced fashion using numerical and visual prompts.

The detailed results of the systematic review and network meta-analysis are described in Chapter 4. Eight types of medications were identified as available in China to be considered as an addition to metformin. The key aspects of the medications considered as important for patients were identified for each treatment as part of the background and summary of the characteristics of the studies in the systematic review. These aspects included the frequency of taking the medication, cost, medical coverage, route of administration and frequency of blood sugar checks, and are summarized in Box 5.2. This constitutes the first part of Step 2 in the PDA on *"**What medications are available to you as a patient with type 2 diabetes in China?**"*

Box 5.2: Characteristics related to: What medications are available to you as a patient with type 2 diabetes in China?

Types of Medications	Times per day	Cost	Covered by medical insurance	Shot or pill	Frequent blood checks (e.g., testing finger blood)
Metformin	2-3	$	✓	pill	No
Sulfonylureas	1-2	$	✓	pill	Yes
Meglitinides	3	$$	✓	pill	Yes
DPP-4 inhibitors	1	$$$	?	pill	No
Thiazolidinedioznes	1-2	$$	✓	pill	Yes
GLP-1 receptor agonists	1-2	$$$$	?	shot	No
SGLT-2 inhibitors	1	$$$	?	pill	No
Alpha-glucosidase inhibitors	3	$$	✓	pill	No
Basal insulin	2 or more	From $ to $$$$	✓	shot	Yes
Biphasic insulin	2 or more	From $ to $$$$	✓	shot	Yes

✓ Medications are covered by medical insurance.

? Consult your practitioners whether these medications are actually covered by medical insurance or need co-payments in your jurisdiction.

The second part constituting Step 2 of the PDA is concerned with the probability of the efficacy and safety associated with the different types of medications when combined with metformin. The efficacy and safety were based on the network meta-analysis of the evidence identified in the systematic review in Chapter 4. There were 23 clinical outcomes available in the network meta-analysis results. After consultation with physicians in China on the research team, as well as reviewing the values and preferences of the patients (Chapter 3), five outcomes were identified to be directly included in the PDA prototype as indicated in Box 5.3. Note, that outcomes may be added or removed when the PDA is beta-tested in subsequent steps in PDA development.

The calculation of the probability for these outcomes was primarily based on the network meta-analysis in Chapter 4. For the dichotomous outcomes, the probability of an outcome for patients on metformin monotherapy (p_m) was derived directly in the NMA, namely: non-severe hypoglycemia (0.01538), and urogenital adverse event (0.02752). For the comparison of each antihyperglycemic medication plus metformin to metformin alone, the OR was determined in the NMA: non-severe hypoglycemia (Chapter 4, Table 4.7), and urogenital adverse event (Chapter 4, Table 4.18). Then the probability of an outcome for patients on an antihyperglycemic medication plus metformin was derived using the formula: $(p_m\ OR)/\ (1 + p_m(OR-1))$. For the continuous outcomes, a minimal important difference (MID) was identified based on the literature and consensus among members of the research team, namely HbA1c (MID: reduction > 0.3%), body weight (MID: reduction > 2.3kg) and systolic blood pressure (MID: reduction > 5 mmHg). For the comparison of each antihyperglycemic medication plus metformin to metformin alone, the MD and 95%CrI was determined in the NMA: HbA1c (Chapter 4, Table 4.5), body weight

(Chapter 4, Table 4.9) and systolic blood pressure (Chapter 4, Table 4.10). An approximate standard deviation (SD) of the MD was determined from the 95%CrI, and the probability of reaching the MID determined from a normal distribution with this MD and SD. If a NMA could not be conducted for a particular medication and outcome, since evidence from RCTs was not available, the probability was based on information from observational studies and, failing this, expert opinion (Appendix 5B).

The probability of these outcomes is summarized in Box 5.3. As noted, this constitutes the second part of Step 2 in the PDA on *"**What medications are available to you as a patient with type 2 diabetes in China**?"*

Box 5.3: Probability of efficacy and safety outcomes*: What medications are available to you as a patient with type 2 diabetes in China?

Compared to metformin for metformin plus	HbA1c chance >0.3%	Hypoglycemia occurrence	Body weight chance >2.3kg	Urinary tract infections and genital infections occurrence	Blood pressure chance** >5 mmHg
Sulfonylureas	↓ 100%	↑ 10.50%	↑ 11.97%	↓ -0.30%	↔ 0%
Meglitinides	↓ 95.02%	↑ 9.35%	↔ 0%	↓ -0.30%	↔ 0%
DPP-4 inhibitors	↓ 100%	↔ -0.23%	↔ 0%	↔ 0.13%	↔ 0.10%
Thiazolidinedione	↓ 100%	↔ -0.52%	↑ 86.08%	↓ -1.27%	↓ 3.80%
GLP-1 agonists	↓ 100%	↔ -0.38%	↓1.61%	↔ -0.21%	↓ 9.90%
SGLT-2 inhibitors	↓ 100%	↔ -0.20%	↓ 4.21%	↑ 1.76%	↓ 13.80%
Alpha-glucosidase inhibitors	↓ 91.24%	↔	↓	↔	↓ 48.50%
Basal insulin	↓ 100%	↑ 3.47%	↑ 73.18%	↓-1.00%	↓ 6.20%
Biphasic insulin	↓ 99.80%	↑ 8.86%	↑ 69.58%	↓ -1.00%	↓ 6.20%

* ↑ arrow indicates an increase probability; ↓ arrow indicates a decrease probability; and ↔ arrow indicates little or no change in the probability of the efficacy or safety when patients are on an antihyperglycemic medication plus metformin compared to metformin alone

** In the table 4.10 NMA (Chapter 4), three antihyperglycemic classes of sulfonylureas, alpha-glucosidase inhibitors, and insulin were not statistically significant differences in comparison with metformin alone. We only consider those statistically significant classes in the table in the PDA.

5.3.4 Determine format of the patient decision aid and distribution plan

The Ottawa Personal Decision Guide[6,10,11,24] provides the content and format that are consistent with what patients and practitioners need in a PDA. Following the guide, the PDA provides information about type 2 diabetes to allow patients to understand the condition and its management, including an introduction to T2DM, and facts that are important to know about diabetes treatment and hyperglycemia. Since deciding on the desired level of HbA1c would influence treatment decision, the PDA introduces HbA1c levels setting and related factors to be considered. Also, the PDA clarifies current research and knowledge gaps in setting HbA1c levels, especially associated with macrovascular complications. In addition, the PDA provides a description of the decision at hand, and the goal of the PDA: 1) a target HbA1c level; and 2) an adjunct agent to metformin. Then, four steps are provided as a step-by-step way to guide patients in their decision-making process. Step 1 asks for clarifications of patient values and preferences in making decisions using a scale from 0 (not important) to 5 (very important). In this step, the PDA translates patient values and preferences into simple scale tables when they consider to choose a medication add-on to metformin. Step 2 provides evidence-based information on medication in type 2 diabetes. In this step, the PDA introduces information about antihyperglycemic classes and overall considerations in each class. Furthermore, the PDA presents probability of outcomes with relative benefits and harms among various treatment options based on the network meta-analysis results. Step 3 lists a few pertinent questions for patients to consider regarding whether or not this PDA helps in making an informed decision. Finally, Step 4 is concerned about making decisions. Patients hopefully will make sound decisions, understanding an appropriate glucose level setting (HbA1c) as well as choosing an adjunct medication add-on to metformin based on an individual need.

Comparative benefits and harms of treatment outcomes were translated into lay language, by using arrow signs, dollar signs, and graphics. The benefits and harms associated with each treatment option were presented in a balanced manner without favoring any particular treatment. Furthermore, the format of graphics and illustrations is consistent with the same font size and details between different treatment options to avoid potential bias due to framing effects as recommended in the development of PDA.[28,34]

Accordingly, the PDA would be printed on paper and handed out in clinic to outpatients when they arrived in the clinic. Patients and physicians would have face-to-face discussions using the PDA to help patients participate in a shared decision making process.

5.3.5 Feedback from users

During the development of the PDA, feedback was received from future users of this PDA who were part of the research team in China. These users included two patients with T2DM and two family members as well as three physicians and two nurses who directly provide medical care to patients with diabetes at Fu Wai Hospital, China. Overall, they liked the PDA and indicated that it would help patients make an informed decision. In particular, patients and practitioners felt the information on the risk of high blood glucose was presented in a simple and clear fashion in the introduction section of the PDA. Regarding HbA1c, patients and practitioners were in agreement on the way that simple target levels were summarized from the latest guidelines in China. Both patients and practitioners believed that it is important for patients to understand the factors that influence a target glucose level setting (HbA1c level), and how a specific HbA1c level would be

chosen. Regarding the four steps in the patient decision aid, the patients suggested to move the values and preferences from its initial placement in the PDA as Step 2 to Step 1 so that it would appear before the information on medications. By doing so, patients can pay more attention to those medications that are relevant to their most important concerns. When the treatment options are presented, both patients and practitioners suggested to provide simple visual signs and less text to help make the information more understandable to patients. The degree of detail in antihyperglycemic classes was one of the key components on which feedback and suggestions were made. In Step 3, practitioners suggested to simply add a check box "yes" or "no" corresponding to each question to save time for patients and practitioners in a clinic visit.

5.3.6 IPDAS checklist – patient decision aid prototype

This PDA prototype was evaluated according to the IPDASi criteria. The IPDASi criteria cover 10 dimensions, including information, probability, values, decision guidance, development, evidence, disclosure, plain language, evaluation and test. The test was related to screening or laboratory diagnosis and was not applicable for our PDA. The draft patient decision aid was initially examined by alpha testing or feedback from "future users" in the team. Overall, the PDA met the IPDASi criteria in relevant dimensions and items. It is important to keep in mind that since the current PDA prototype has not undergone the full evaluation process, in particular final alpha testing and beta testing, not all IPDAS criteria will be met. Detailed results are summarized in Table 5.1.

Table 5.1: Assessment of the alpha version PDA according to the IPDASi (v3.0) checklist

IPDAS Dimension	IPDASi Item	PDA Prototype	Note
Information	1. Describes the health conditions or problem (intervention, procedure or investigation) for which the index decision is required.	met	
	2. Describes the decision that needs to be considered (the index decision).	met	
	3. Describes the options available for the index decision.	met	
	4. Describes the natural course of the health condition or problem, if no action is taken.	met	
	5. Describes the positive features (benefits or advantages) of each options.	met	
	6. Describes the negative features (harms, side effects or disadvantages) of each option.	met	
	7. Makes it possible to compare the positive and negative features of the available options.	met	
	8. Shows the negative and positive features of options with equal details (e.g., using similar fonts, order, and display of statistical information).	met	
Probability	1. Provides information about outcome probabilities associated with the options (e.g., the likely consequences of decisions).	met	
	2. Specifies the defined group of patients for which the outcome probabilities apply.	met	
	3. Specifies the event rates for the outcome probabilities (in natural frequencies).	met	
	4. Specifies the period over which the outcome probabilities apply.	met	
	5. Allows the user to compare outcome probabilities across options using the same denominator and period.	met	
	6. Provides information about the levels of uncertainty around event or outcome probabilities (e.g., by giving a range or by using phrases such as "our best estimate is …"	met	
	7. Provides more than one way of viewing the probabilities (e.g., words, numbers, diagrams).	met	
	8. Provides balanced information about event or outcome probabilities to limit framing biases.	met	
Values	1. Describes the features of options to help patients imagine what it is like to experience the physical effects.	met	
	2. Describes the features of options to help patients imagine what it is like to experience the psychological effects.	met	
	3. Describes the features of options to help patients imagine what it is like to experience the social effects.	met	
	4. Asks patients to think about which positive and negative features of the options matter most to them.	met	
Decision guidance	1. Provides a step-by-step way to make a decision.	met	
	2. Includes tools like worksheets or lists of questions to use when discussing options with a practitioner.	met	
Development	1. Includes finding out what clients or patients need to prepare them to discuss a specific decision.	met	
	2. Includes finding out what health professionals need to prepare them to discuss a specific decision with patients.	met	
	3. Includes expert review by clients/patients not involved in producing the decision support technology.		Further alpha and subsequent beta-testing
	4. Includes expert review by health professionals not involved in producing the decision support technology.		Further alpha and subsequent beta-testing
	5. The decision support technology (or patient decision aid) was field tested with patients who were facing the decision.		Subsequent beta testing
	6. The decision support technology (or patient decision aid) was field tested with practitioner who counsel patients who face the decision.		Subsequent beta testing
Evidence	1. Provides citations to the studies selected.	met	
	2. Describes how research evidence was selected or synthesized.	met	
	3. Provides a production or publication date.	met	
	4. Provides information about the proposed update policy.	met	
	5. Describes the quality of the research evidence used.	met	
Disclosure	1. Provides information about the funding used for development.	met	

	2. Includes author/developer credentials or qualifications.	met	
Plain language	1. Reports readability levels (using one or more of the available scales).		Further alpha testing
DST Evaluation	1. Evidence that the DST improves the match between the features that matter most to the informed patient and the option chosen.		Subsequent beta testing
	2. Evidence that the DST helps patients improve their knowledge about options' features.		Subsequent beta testing

For the full list of items, please view IPDASi v3 forty-seven dimensions and items[22]: Assessing the quality of decision support technologies using the International Patient Decision Aid Standards instrument (IPDASi)

5.3.7 Patient decision aid prototype

Based on the results of the various process and procedures outlined in the previous result sections, the prototype of the PDA was assembled and is provided in Appendix 5C.

5.4 Discussion

The objective of this study was to develop an evidence-based, culturally appropriate and theory-driven prototype of a patient decision aid. The development of this PDA was done following the Ottawa Decision Support Framework, the systematic development process outlined by Coulter and colleagues[28] and the International Patient Decision Aids Standards. The target audience of this PDA is patients with T2DM in China considering add-on antihyperglycemic agents after metformin monotherapy failure to achieve adequate glycemic control. To our knowledge, this is the first PDA available for this population with type 2 diabetes in China.

Our wish to develop such a PDA in China was further inspired by a patient decisional needs assessment suggesting that patients with T2DM in China want to be more engaged in making a decision when adding on antihyperglycemic medications, and they need evidence-based information on treatment options (Chapter 3). This was consistent with the results of other

studies in which patients with diabetes ask for more information in comparison with patients with other non-communicable diseases such as cardiovascular disease, respiratory disease and cancer.[35-37] Patients with T2DM face challenges on how to choose among many treatment options with varying benefits and risks, especially after metformin monotherapy failure. Clinicians often cannot decide for patients since choices will depend on patients' individual values and preferences. Guidelines, including the latest guidelines in China, recommend[15,38-40] a patient-centered approach in clinical management of hyperglycemia. One way to facilitate this approach is to use a PDA, which can help patients make informed decisions about treatment options and take into account personal values and preferences.[24] PDAs are being implemented in type 2 diabetes in developed countries, including the Mayo Clinic[13] in the United States and the National Institute for Health and Care Excellence[41] in the United Kingdom. Some commercially supported PDA[42] are available as well. Although these PDAs are informative, they are not suitable for this specific population with T2DM in China for two prime reasons.

First, currently all available patient decision aids for type 2 diabetes simply describe the efficacy and safety of each antihyperglycemic class without being compared with metformin. To meet this challenge, we conducted a systematic review of RCTs and a Bayesian network-meta analysis was used to synthesize evidence of comparisons of clinically important benefits and harms among various outcomes to provide evidence-based treatment options in the PDA. Interestingly, a recent study suggested that developers of PDAs are expected to use the best available evidence from systematic reviews and randomised controlled trials if possible.[46]

Second, the specific patient values and preferences for this population are rooted in Chinese culture. Currently, most patient decision aids[13,31,41,42] for type 2 diabetes have been developed in the West and those PDAs are based on underlying cultural beliefs and values.[9,10] We performed a culturally relevant needs assessment in this population with T2DM in China, based on the Ottawa Decision Support Framework, from both the patient and practitioner perspectives. We followed the Ottawa Decision Support Framework and the International Patient Decision Aids Standards systematic development process and ensured the PDA met high quality standards. The development process incorporated input from experts in shared decision making and PDA studies, qualitative and quantitative research, economic research, epidemiology, and physicians and nurses who take care of patients with diabetes. In addition, patients with T2DM and family members and physicians and nurses in China as the future users of the PDA provided direct observation and feedback throughout all stages of the development.

Emerging evidence in research supports that high quality PDAs facilitate shared decision making between patients and practitioners, increases patients' trust and helps patients make a sound decision.[7,43] Stacey et al recently conducted a Cochrane database of systematic reviews on PDAs for people facing health treatment or screening decisions and concluded that PDAs improve patients' knowledge of risks and benefits of options, clarifying patient values and making patients feeling informed.[4] Studies showed that PDA for patients with T2DM have a longer-term benefits, including an increase of medication initiation compared to usual care.[44,45]

Our PDA prototype may have several positive implications. For patients with T2DM in China, the PDA provides evidence-based information to assist in making value-sensitive decisions in a

transparent, personalized and systematic way. This may lead to better knowledge, more engagement in decision-making and better decisions that are consistent with patients' values and preferences and result in potential improvement in health outcomes for this large and increasing patient population with T2DM. This in turn may lead to increased patient trust,[67] improved treatment adherence, and greater productivity of this population in the workforce.

For practitioners, the PDA will inform them about key aspects associated with patient values and preferences, knowledge and expectations when considering therapies for glycemic control. If the PDA is given prior to the consultation, it will help prepare patients to discuss their therapeutic options with their practitioners. This will help practitioners to explain and discuss these options with their patients during the limited clinical visit time, which has been identified as a gap in our patient needs assessment. The direct effect of this may be that prescriptions made will likely be better followed and will result in better health outcomes for the patients.

For policy makers, an informed patient population will make possible better acceptance of cost-effective program choices for patients with T2DM. Some studies showed that PDA could save costs in some contexts in the healthcare system[6] and may reduce the probability and cost of litigation.[8] The current PDA may provide an example to this effort through providing consistent information across different levels of hospitals.

In addition, this research will enrich the International Patient Decision Aids Standards in terms of best practice for PDAs in developing countries. There are lacking in research and practice

(e.g., PDAs) in supporting shared decision making in these countries, although guidelines recommend a patient-centered approach in clinical management of hyperglycemia in type 2 diabetes.

Next steps

There are several 'next steps' in the development of our PDA. First, we developed a PDA prototype and only conducted initial alpha testing. Although the overall feedback was encouraging and positive, the PDA will need further alpha testing to ensure acceptability and to develop the final PDA. It will then have to undergo beta testing with patients and practitioners in "real-world" settings to assess feasibility (such as a pilot RCT followed by a definitive trial). Second, at this stage, only a paper version of the PDA has been developed. Third, the current treatment options in the PDA do not include traditional Chinese medicine. As more high-quality studies become available, we will incorporate them into the evidence network and network meta-analyses. Finally, China is a large country with a complex healthcare system in place, including tier-1, tier-2 and tier-3 level hospitals across the country. This PDA prototype will be further alpha and beta-tested in subsequent research endeavours (Chapter 6). To evaluate the PDA clinically after beta testing and refinement, a large scale prospective RCT will be conducted to evaluate the use of the PDA on patient outcomes in comparison with usual care across three levels of hospitals in China. As well, as part of the next level of assessment, the acceptability and comprehensibility of the PDA will be evaluated using a validated assessment rating form that has been edited to focus on diabetes (Appendix 5D).

Conclusion

The development of this PDA prototype for diabetes is in alignment with IPDAS and matches the needs of patients with T2DM in China in accordance with the patient needs assessment. It also underwent initial alpha testing among stakeholders on the research team. This showed promising results in terms of acceptability and the PDA will undergo further testing to ensure the final version of the PDA will help patients with T2DM and practitioners to make better decisions that are informed by the evidence and are based on patient's values and preferences. Hopefully, this PDA may lead to better treatment adherence and better health outcomes for a disease that affects so many adults in China.

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Chapter 6 Discussion

6.1 Summary of thesis

Patients with type 2 diabetes mellitus (T2DM), in whom metformin monotherapy was found to be insufficient in achieving good glycemic control, face challenges when choosing among the options available for the add-on medication to metformin. These options can differ significantly in efficacy and safety, and choices among these options depend on what matters most to an individual patient. In this regard, patients should participate in and contribute to the discussion with physicians to choose the options that better fit with their individual needs.[1] This requires that the decision on the management of hyperglycemia takes into consideration patient values and preferences, includes a synthesis of the efficacy and safety of the treatment options and communicates this information in a culturally sensitive manner.

There were three main objectives of the thesis formulated to meet these requirements. First, we conducted a patient decisional needs assessment at Fu Wai Hospital, China to get insight into the values and preferences of patients with T2DM in China in making this treatment decision. Patient values refer to how individuals assess the attributes of a decision depending on their cultural context and experiences. Preferences are a tangible consequence of values in which patients face a decision.[2] In China, there is a gap in our understanding of the values and preferences of patients with T2DM when making a decision of adding medications.[3] We conducted patient interviews and practitioner focus group and individual interviews at Fu Wai Hospital using culturally relevant methods to collect information on patient decisional needs.

The interview guides were developed according to the Ottawa Decision Support Framework[4,5,6] developed at the Ottawa Hospital Research Institute, Canada. They were also culturally adapted to ensure the appropriateness of the interview guides and the relevance of the collected information. Content analyses[7] were performed to summarize patient decisional needs in this specific population with T2DM in China. Patient values and preferences when adding antihyperglycemic medications were identified, along with other six themes, including patient experience in using the health care system, patient knowledge of medications, decisional conflict, and factors related to decision conflict, role in decision-making and what patients need to make a better decision. In particular, patients need reliable information about the choice of medications and want to be more engaged in the decision-making.

Second, we performed a systematic review and network meta-analysis of the comparative efficacy and safety of medications from eight antihyperglycemic classes combined with metformin therapies in T2DM. Evidence is a fundamental building block for choosing among treatment options. With the rapidly growing number of antihyperglycemic options available, an appraisal of the evidence of the competing interventions between various antihyperglycemic classes is required. This involved a two-step process: first, a systematic review of the available evidence; and second, a comprehensive comparison of the evidence using meta-analytic methods. Regarding the latter, there is a paucity of direct evidence to compare these treatment options, and it is important to include indirect evidence to obtain accurate effect estimates for the different efficacy and safety outcomes for available treatments. In order to meet this need, a Bayesian network meta-analysis was performed to obtain the effect estimates for antihyperglycemic class comparisons on the outcomes of interest. Currently, guidelines

recommend eight antihyperglycemic classes that can be combined with metformin.[12] We included all eight classes of add-on medications to metformin in the network meta-analysis, namely: sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZDs), basal and biphasic insulin, dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitors), glucagon-like-peptide-1 receptor agonists (GLP-1 RAs), and sodium-glucose co-transport 2 inhibitors (SGLT-2 inhibitors). All of the eight classes significantly reduced HbA1c to varying degrees. The eight classes varied in their effects on hypoglycemia, body weight, BMI, systolic and diastolic blood pressure, high and low density lipoprotein cholesterol. They also varied in their safety profiles on total adverse events, urogenital adverse events, and heart failure.

Third, we encapsulated the results of the first two objectives in developing a prototype of a patient decision aid (PDA) for individuals with T2DM considering the addition of an agent after metformin monotherapy failure to achieve sufficient blood glycose control. A PDA can facilitate the shared decision making (SDM) process and promotes well-informed decisions.[8] The demand for a PDA was identified in the patient needs assessment in China in which patients clearly wanted to be more engaged in making a decision. Goal-setting and decision-making were identified for patients in making a decision when considering an add-on agent to metformin: first, understanding the importance of choosing a glycose level (HbA1c) setting; and second, choosing an adjunct agent to metformin. The design and development of the PDA followed a systematic development process, guided by the IPDAS,[9,10] in order to present a high quality and current information to patients in a comprehensible and transparent fashion. Across all the development steps, the PDA prototype was improved based on received feedback and direct observations from the future users on the team, including Chinese patients with T2DM and

family members, as well as Chinese physicians and nurses who provide care to patients with diabetes (intial alpha-testing). Overall, they perceived this PDA prototype to be useful and acceptable. In summary, there was encouraging feedback from the future users. With further assessment and refinement, the PDA hopefully will meet the needs for patients with T2DM in China: give reliable and consistent evidence that patients and practitioners could discuss while taking into account patients' values and preferences.

6.2 Contribution of thesis

6.2.1 Patient decision aids for diabetes in developed countries

Several developed countries have implemented PDAs to facilitate SDM for various health conditions where there is no universally accepted gold standard for treatment or diagnosis. These PDAs use various mediums (e.g., paper print, videos or web-based tools) and have different structures and formats, such as PDAs developed by the Ottawa Hospital Research Institute in Canada,[19] the Mayo Clinic in the US,[20] and the United Kingdom.[21]

For patients with diabetes, PDAs developed in Western countries are available, including in the United States,[22-25] Denmark,[26] the Netherlands,[27, 28] and the United Kingdom.[21] Some of the PDAs presented pharmacological treatment as a possible option to patients. For example, a PDA for consultation about diabetes medications[29] using decision cards was developed by the Mayo Clinic. The aid was further evaluated in a large scale study in primary care and found a positive impact on patients in the decision-making process.[30] More recently, a PDA[31,32] provided treatment options for patients who failed on metformin monotherapy. This PDA, evaluated in a

large clinical setting, can facilitate shared decision making for patients with T2DM in terms of improvement of knowledge, decisional conflict and decisional self-efficacy. However, the pharmacological treatments that were presented in these PDAs were based on assessments of the medications from existing fact sheets for each individual class, and none of them formally incorporated the results of an analysis that compared the efficacy and safety outcomes between eight classes combined with metformin.

The efficacy and safety of the treatment options in a PDA should be critically appraised and based on an up-to-date synthesis of the scientific evidence.[33] In this regard, the evidence synthesized for our PDA requires having treatment recommendations with relative efficacy and safety for the eight antihyperglycemic classes combined with metformin. To meet this benchmark, we conducted a systematic review and network meta-analysis using metformin as a background therapy. To the best of our knowledge, this is the first PDA for patients with T2DM that synthesized evidence-based treatment options through conducting a systematic review of RCTs and synthesized using network meta-analysis with all eight classes included. A recent article suggested that a PDA should base its comparative statistics on systematic reviews and analysis, in order to be more effective.[37]

6.2.2 Patient decision aids for diabetes in developing countries

Research on PDAs is still in an early stage in developing countries. In China, a recent study recruited physicians from two hospitals and none of them heard the concept of SDM or used PDAs in clinical practice.[34] In other Asian countries, few PDAs in diabetes are available but they are all relevant to monitoring skills and health behaviour.[35,36] Up to date, no PDAs have been

found for patients with T2DM in whom metformin monotherapy is insufficient to achieve good glycemic control.

6.3 Next steps

6.3.1 Expanding the evidence network for network meta-analysis

Network meta-analysis and living systematic review

Regarding pharmacological treatment for type 2 diabetes, there is a continual and rapid increase of various agents and classes on the global market, but there continues to be a paucity of direct head-to-head comparisons of efficacy and safety between competing interventions. The use of network meta-analysis can be highly informative in providing relative efficacy and safety outcomes between different treatments in supporting evidence-based treatment options. In this regard, the procedures and process of living systematic review procedures should be put in place and followed.

Traditional Chinese medicine

Traditional Chinese Medicine (TCM), has recently been recommended in the latest diabetes guidelines in China for treatment of type 2 diabetes.[12] Our patient needs assessment identified that most patients with T2DM were taking TCM to improve body function holistically, but not for lowering hyperglycemia. Currently, most studies on TCM are lacking methodologic rigour in comparison with western medicine, which commonly uses RCTs in assessing efficacy and safety. To synthesize the evidence and compare results across TCM is challenging.[13,14] Recognizing the limitations, it is encouraging to know that more researchers of TCM are starting to conduct better-designed observational studies and RCTs.[13] In the future, it may be worthwhile

to synthesize evidence stemming from traditional Chinese medicine studies as additional treatment options for the patients with T2DM in China.

Inclusion of observational studies

The current systematic review and network meta-analysis only focused on integrating sources of evidence from RCTs, given the fact that they meet both scientific standards and regulatory criteria. However, results from these RCTs may not reflect what happens in the real world given, for example, restrictions on patient eligibility for a RCT and regimented treatment schedule of a RCT that may not be followed in everyday practice[15,16] and this discrepancy should be taken into account when interpreting the evidence. Well designed and internally valid observational studies more closely aligned with the real world may be worthwhile to consider.[17] In particular, observational longitudinal studies with a long follow-up time period, which is not feasible for most RCTs, could be integrated into the evidence network and analysis.

Modification and addition of treatments

In alignment with expanding the evidence network, the network meta-analysis will continue to be updated with newly completed trials and possible inclusion of traditional Chinese medicine. The addition of new treatment arms, either from new pharmacological treatments and/or traditional Chinese medicine, may be included as additional treatment options in the PDA. The frequencies of updates to the NMA depend on the research activity level on treatment options and others (e.g., every 3 years). Moving forward, it is important that the PDA can be easily modified and adjusted as new appropriate treatment options become available.

6.3.2 Testing, refinement and future development of the PDA

As noted by developers of PDAs, the evolution of a PDA involves a complex and dynamic process of designing, developing and alpha testing and beta testing the PDA.

Following the initial alpha-testing, further alpha-testing of the PDA will be conducted to test the acceptability. A validated PDA assessment form has been modified (Appendix 5D), and will be used to evaluate the current PDA prototype and revisions will be made accordingly.

According to IPDAS, the next step is testing the PDA in 'real life' situations, known as beta testing, and if needed finalizing the suitability and understandability of this PDA. For this next step, beta-testing will be conducted among patients in whom metformin monotherapy was insufficient to achieve good glycemic control, and are considering an add-on glycemic agent, as well as practitioners who provide care to patients with T2DM in China. During this phase, patients and practitioners involved in the development of the alpha version of the PDA will not be included. A pilot RCT of the PDA will be conducted to test the feasibility of a full RCT.
To determine whether the PDA is superior to standard care, a large-scale multicentre RCT across the three levels of hospitals in China will be designed and conducted comparing the two approaches. Patients in the intervention arm of the trial will be randomized to receive the PDA, while patients in the control arm will receive standard care. This trial will assess and compare the impact of the PDA on the improvement of several themes that we have previously identified through the patient and practitioner interviews in China (Chapter 3), including: patient knowledge and expectations; decisional conflict; and decisional support and influence using

health care resources (e.g. the frequency of visiting different hospitals and seeing different doctors).

6.3.3 Knowledge translation and the patient decision aid

Knowledge translation (KT) is defined[38] as "*a dynamic and iterative process that includes the synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the healthcare system."* This Canadian Institutes of Health Research KT definition has been adapted worldwide.[38] In the context of the next phase of our PDA, a knowledge translation plan will be formulated that includes education, knowledge dissemination, knowledge management and technology transfer within multi-stakeholder groups in China.

One of the important considerations is to be thoughtful about the PDA message and who the target audience is for the message, as well as how to reach out the audience more efficiently and effectively. The current PDA is paper based, mainly because the patients and practitioners at Fu Wai Hospital suggested using the paper format at this formative stage of the development of this PDA. Interestingly, Denig et al[27] conducted a RCT in a primary care setting to test a PDA for prioritizing treatment goals for diabetes in the Netherlands. The study found that a printed PDA was more effective than a non-interactive computer screen version of the PDA. Also, practitioners reported that patients more often needed assistance when using the computer screen version. Nevertheless, a recent study in China found a positive outlook on patient compliance when using online communication between patients and physicians.[18] Moving forward, our final PDA will be converted to an online interactive applications if there is a demand from the "future users" of patients with T2DM in China. For example, a new medium in China provides an

innovative technology for dissemination of health-related information. WeChat, similar to Facebook, is a popular networking platform in China. Today, the active monthly WeChat users number over 700 million and 61% of them open WeChat more than 10 times per day.[39] A recent study that interviewed 1,636 WeChat users across 32 provinces in China found that most people (63%) considered WeChat as the primary means of obtaining health information, but only few (12%) believed the information useful mainly because most information was repeatedly circulated and not read friendly.[40] Thus, WeChat emerging in China provides opportunities and challenges as a media access to public health information.

Conclusions

Patients with type 2 diabetes in whom metformin monotherapy is insufficient to achieve good glycemic control face challenges in choosing among the several treatment options when considering treatment intensification. The objective of this thesis was to develop a patient decision aid prototype for these patients with T2DM in supporting them to make an informed decision. First, we conducted a patient decisional needs assessment at Fu Wai Hospital, China to gain insight into the values and preferences of patients in China in making this treatment decision. Second, we performed a systematic review and network meta-analysis of the comparative efficacy and safety of all eight antihyperglycemic classes combined with metformin therapies in T2DM. Third, we integrated the results of the first two objectives into developing a PDA prototype, following the IPDAS development process and IPDASi criteria, for patients with T2DM considering the addition of an agent after metformin monotherapy failure in achieving sufficient glucose control.

This project is an important stepping-stone towards introducing the concept of shared decision making into clinical practice in China, which is currently lacking evidence on how such as a PDA can be developed to facilitate shared decision making as part of patient care. Thus, it is critical to maintain the quality and validity of this PDA by engaging patients and practitioners through the process, by updating the evidence network and incorporating traditional Chinese medicine and by revising as needed the PDA and the format in which it is delivered. Finally, the refinement of the PDA should be ongoing so that patients can continue to rely on the information being presented and assist them in making informed decisions to meet their health care needs.

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Appendix 3A: Patients interview guide

QUESTIONNAIRE

1. After diagnosed as diabetes mellitus, what do you think are the most important matters to do? Probe role,
    - see a doctor
    - look for a specific medicine,
    - diet and exercise

2. Let's focus on one particular decision.
    - What problem or problems, if any, have you encountered when you are asked to take additional medicines to achieve better blood sugar control?

3. Let's talk about the difficulty you have making this decision about adding therapies for intensive glycemic control. How do you feel when making this decision? Probe role,
    - Constantly thinking about the decision
    - Delaying the decision
    - None of these; I do not feel distressed

4. What things make the decision difficult for you? Probe role,
    - Worried about weight gain
    - daily frequency, or convenience of dose administration and blood glucose monitor
    - Lacking information about options, benefits, risks

5. If you have to make a decision on medication today, could you select three items from the question 4 above that concern you most?

6. Thinking about this decision, what are the options that you have?

7. Who else may be involved in making this decision? Do they usually:
    - Make the decision for you
    - Share the decision with you
    - Provide support or advice for you to make the decision on their own

8. How do you usually go about making such a decision? Probe role
    - Get information on options
    - Get information on the chances of benefits and risks
    - Consider the personal importance of the benefits and risks

9. What would help you to make this decision?

10. What will hinder you (get in the way of) making this decision?

11. Is there anything else that would help overcome these barriers to decision making?

12. I will list possible ways to help some people with a decision, which ones do you think might be useful to you?

Counseling from a health practitioner	If YES, specific what types
Discuss groups of patients facing the same decision	If YES, specify what type of organization or group
Information materials	If YES, specify content. probe role, ○ General information on diabetes ○ Product monography ○ Help considering the personal importance of benefits versus risk
	If YES, specify format. probe role, ○ Booklet, pamphlets ○ Internet ○ WeChat
	If YES, who do you think should prepare information about the decision, probe role, ○ Pharmacies ○ Expert medical and health practitioners ○ Health societies for specific condition (e.g. Diabetes Society)

13. Is there anything else that would help you to do a better job supporting you in decision making?

14. When you visit a clinic, what does your doctor tell you if he or she wants to add medicines for blood sugar control?

15. What additional information you really need or want besides what your doctor told you as described above?

16. Are you taking medicines regularly as your doctors prescribed? Yes or No.

17. If answer is “No”, how often you miss taking your medicines?

18. What do you see as the main advantages/benefits, disadvantages, and risks of the anti-diabetic medications you are taking now?

CHARACTERISTICS OF PRACTITIONER

19. Age Category
    - Twenties
    - Thirties
    - Forties
    - Fifties
    - Sixties or more

20. Sex
    - Male
    - Female

21. Income(salary) per month/year

22. Occupation

23. Duration of experience with health problem

24. What is the highest grade or level of education you completed?
    - Primary school or less
    - High school diploma
    - College diploma/degree
    - University undergraduate degree
    - University graduate degree (Master or PhD)

25. Professional degree. Probe role
    - M.D.
    - Engineer
    - Statistician
    - Others

THANK RESPONDENT

Appendix 3B: Practitioner interview guide

QUESTIONNAIRE

1. What decisions do patients with type 2 diabetes have to make in your practice?

2. Let us focus on one particular decision:
    - What do patients consider most when adding anti-hyperglycemic therapies to them for glycemic control? Why?

3. Let's talk about the difficulty patients have in making this decision. How do patients feel when making this decision? Probe role,
    - Constantly thinking about the decision
    - Delaying the decision
    - Feeling physically stressed, tense muscles, difficulty sleeping

4. What factors make the decision difficult for patients? Probe role,
    - Worry about weight gain
    - Lacking information about options, benefits, risks
    - Worry about hypoglycemia

5. What do you see as the main options patients have?

6. What do you see as the main advantages/benefits, disadvantages, and risks of the options?

7. What is your usual role in making this decision? (Probe role) Do you usually:
    - Make the decision for the patients
    - Share the decision with the patients
    - Provide support or advice for patients to make the decision on their own

8. What factors make it difficult for you to support your patients' decision making?

9. What factors make it easier for you to support your patients' decision making?

10. Who else besides yourself and the patient is usually involved in making this decision? Probe role,
    - Spouse
    - Family members
    - Friends

11. What is their usual role in making this decision (e.g. the person mentioned above)? (Probe role), Do you usually:
    - Make the decision for the patients

- Share the decision with the patients
- Provide support or advice for patients to make the decision on their own

12. How do patients usually go about making such a decision?

Probe role

- Consider the personal importance of the benefits and risks
- Get information on how others go about deciding
- Get support from others

13. What would help patients to make this decision?

14. What will hinder patients (get in the way of) making this decision?

15. Is there anything else that would help overcome barriers to decision making?

16. I will list possible ways to help some people with a decision, which ones do you think might be useful to your patients?

Counseling from a health practitioner	If YES, specific what types
Discuss groups of people facing the same decision	If YES, specify what type of organization or group
Information materials	If YES, specify content. probe role, o General information on diabetes o Product Monograph o Help considering the personal importance of benefits versus risk
	If YES, specify format. Probe role, o Booklet, pamphlets o Internet o WeChat
	If YES, who do you think should prepare information about the decision? Probe role, o Pharmacies o Experts in medicine o Health societies for specific condition (e.g. Diabetes Society)

17. Is there anything else that would help you to do a better job supporting your patients' decision making?

18. Whether patients also discuss or ask other diabetes related risk?

19. How many outpatients you see per day in a clinic?

20. On average, how much time do you spend with each patient in a clinic?

21. In a clinic, what you explain to a patient when adding medicines for intensive glycaemic control?

22. What you think the patient really need or want to know when you add the medicines?

23. Do you think most of your patients take anti-hyperglycemic medicines regularly as prescribed? Yes or No.

24. If answer is “No”, how often patients miss taking their medications?

CHARACTERISTICS OF PRACTITIONER

25. Age Category
    - Twenties
    - Thirties
    - Forties
    - Fifties
    - Sixties or more

26. Sex
    - Male
    - Female

27. Practice discipline, specify

28. Practice Specialty, specify
    - Nurse
    - Resident physician
    - Attending physician

29. Practice Location, specify

THANK RESPONDENT

Appendix 3C: Letter of information - patient

Letter of information

You are invited to participate in an interview to help us better understand the needs of patients such as yourself in making choices of the medicines used for controlling blood sugar.

Background

About 60% of patients with diabetes in China that take medicines for controlling their blood sugar do not have good control of their blood sugar, and they keep changing medicines.

If we better understand what is important to patients about choosing these medicines, we will be able to tell the physicians what to say and do when they see the patient. The physician can then help the patient understand what benefits are possible from taking the medicine.

Purpose

The purpose of this interview is to understand your needs when deciding on the medicine for your blood sugar control. The results will help identify common needs of patients such as you when deciding on this medicine.

Your participation

You are invited to participate in an interview, but you do not have to participate.

If you do not participate, this will not affect your medical care in any way.

If you are interested in the interview, you can contact the Research Assistant (RA) through the contact information provided below,

During the interview, you will be asked questions about your diabetes. It will take about 40 minutes and will take place in a private office nearby the clinic waiting room.

No matter what you decide, your consideration is appreciated.

Sincerely,

XXX, Research Assistant
Fu Wai Hospital, Beijing, China
Tel: xxxx
Email: xx

Appendix 3D: Patient consent form

Patient consent form

You are invited to participate in a study aiming to identify patient decision-making needs when adding medicines for adequate blood sugar control for patients with type 2 diabetes. This study is being conducted by Hui Zheng of the University of Ottawa, Department of Epidemiology and Community Medicine and is being done as part of a PhD thesis. This research is being conducted under the direction and supervision of Dr. George A. Wells, Director at the Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Canada.

Purpose of this study

Today, China accounts for the largest number of individuals with diabetes and has become the epicenter of diabetes worldwide. To our knowledge, this is the first study to investigate the needs of patients with type 2 diabetes in China in making decisions about their therapies. The results of the study will assist patients in making more informed choices among the therapeutic options available that best fit with their needs.

The purpose of this study is to understand the needs of a patient when deciding on the medicine for their blood sugar control. The results will help identify common needs of patients when deciding on this medicine.

Questions will be posed related to domains such as personal values and preferences, decisional conflict, knowledge and expectations of the treatment of diabetes. These have been adapted from the University of Ottawa's Decision Need Assessment in Population workbook, with added items and questions based on a review of the literature on diabetes decision making, as well as from discussions with endocrinologists in China.

Your participation

You will be invited to participate in a one-time face-to-face interview of approximately 40 minutes during working hours. The interview will be conducted at a private office nearby the clinic waiting room. Hui Zheng will conduct the interview and two intervewers (H.Z, and a research team member at Fu Wai Hospital) will record in writing the responses to questions about patient decision making needs in choosing medicines for blood sugar control.

Risk

The questions are not challenging. However, if you experience some distress or anxiety about some questions then you will be provided with the contact number in the department of endocrinology at Fu Wai Hospital who will direct you to the appropriate resources to address your concerns.

Benefit

There is no direct benefit to you or family members by participate in the interview.

Your participation in the study will help us to better understand patient decision making needs when adding medicines for diabetes.

Confidentiality and anonymity

All individual response will be kept strictly confidential.

The only personal information collected is the age group and sex of the patient. This information is not specific enough to identify a particular patient and will only be reported in aggregate statistical form.

For the written responses to the questions, the recordings of their responses will only be used in the coding process. The codes/themes identified will be the result of a highly intensive, coded process across the patients, and there will not be specific enough information to identify particular patients.

Conservation of data

In China, during the study, all written records will be kept in locked cabinet drawer of the research office in Fu Wai Hospital and the electronic data will be encrypted and stored on a password protected computer in the research office.

In Canada, during the study and the 5-year conservation period after the completion of the study, all written records will be kept in a locked cabinet of the research office at the University of Ottawa and the electronic data will be encrypted and stored on a password protected computer during the study in the research office and on a password protected usb key in the same locked cabinet during the conservation period.

Compensation

There will be no compensation for your participation in this study.

Voluntary participation

You are under no obligation to participate in the interview. You may withdraw at any time or refuse to answer any questions, without suffering any negative consequences. Your choice in participating or not in this study will not affect your medical care.

This study has been approved by the Research Ethics Board approval at University of Ottawa, Canada and Fu Wai Hospital, Beijing, China.

Acceptance

There are two copies of the consent form, one of which is yours to keep.

Participant's signature (*Signature*) Date (*Date*)

Principal Investigator's signature (*Signature*) Date (*Date*)

Appendix 3E: Letter of information - practitioner

Letter of information-practitioner

You are invited to participate in a focus group aiming to identify patient decision-making needs when adding medicines for adequate blood sugar control.

Background

Approximately, 60% of patients with antihyperglycemic medicines in China have failed to achieve adequate glycemic control, and they constantly change medicines for their diabetes.

If physicians understand the common needs of the patients about making a decision on choosing a medicine, they can better inform the patient during the clinic visit using the "patient's language". Through this approach, physicians will help patients to set realistic expectations of the treatment outcomes and reduce later decisional conflict. This study will contribute to this end goal.

Purpose of this study

The purpose of this study is to explore practitioners' view of patient decision making needs in choosing medicines for blood sugar control.

Your participation

You are invited to participate in a focus group with 3-5 other practitioners. Your participation is completely voluntary, and you are under no obligation to participate.

If you do not participate, this will not affect your workplace environment.

If you participate, you will be asked questions about your patients with type 2 diabetes. It will take about one hour and will take place in a conference in the hospital. Since the discussions/opinions of the other practitioners in your focus group will be known to you, as part of the responsibility of your participation, you will be requested to keep confidential all discussion/opinions of the members of your focus group.

No matter what you decide, your consideration of taking part in this focus group is appreciated.

Sincerely,

xxx, Research Assistant
Fu Wai Hospital, Beijing, China
Tel: xxx
Email: xxx

Appendix 3F: Practitioner consent form

Practitioner consent form

You are invited to participate in a study to identify patient decision-making needs when adding medicines for adequate blood sugar control for patients with type 2 diabetes. This study is being conducted by Hui Zheng of the University of Ottawa, Department of Epidemiology and Community Medicine and is being done as part of his PhD thesis. This research is being conducted under the direction and supervision of Dr. George A. Wells, Director at the Cardiovascular Research Methods Centre, University of Ottawa Heart Institute, Canada.

Purpose of this study

Today, China accounts for the largest number of individuals with diabetes and has become the epicenter of diabetes worldwide. To our knowledge, this the is first study to investigate the needs of patients with type 2 diabetes in China in making decisions about their therapies. The results of the study will assist patients in making more informed choices among the therapeutic options available that best fit with their needs.

The purpose of this study is to understand the needs of a patient when deciding on the medicine for their blood sugar control. The results will help identify common needs of patients when deciding on this medicine.

Questions will be posed related to domains such as personal values and preferences, decisional conflict, knowledge and expectations of the treatment of diabetes. These have been adapted from the University of Ottawa's Decision Need Assessment in Population workbook, with added items and questions based on a review of the literature on diabetes decision making, as well as from a discussion with endocrinologists in China.

Your participation

You will be invited to participate in a one-time focus group study with 3 to 5 practitioners for approximately one hour. The focus group session will be scheduled during working hours and conducted in the clinic conference room. The focus group will be co-ordinated by the study research assistant, and Hui Zheng will conduct the interview and two intervewers (H.Z, and a research team member at Fu Wai Hospital) will record in writing the responses to questions about patient decision making needs in choosing medicines for blood sugar control.

Risk

There are no known risks associated with this study.

Benefit

Your participation in the study will help to better understand patient decision making needs when adding medicines for diabetes. This will help physicians to more effectively communicate with patients on their needs during a short clinical visit.

Confidentiality and anonymity

During the session, any options on patient needs will be fully discussed. Given the nature of focus groups, there are limitations to confidentiality and anonymity. We will ask that all participants respect the privacy of others and keep confidential all discussions/opinions of the members of their focus group.

The only personal information collected is a broad age group and sex of the practitioner. This information is not specific enough to identify a particular practitioner and will only be reported in aggregate statistical form.

For the written responses to the questions, the recordings of the focus group responses will only be used in the coding process. The codes/themes identified will be the result of a highly intensive, coded process across the practitioner focus groups, and there will not be specific enough information to identify particular practitioners.

Conservation of data

In Canada, during the study, all original written records will be kept in a locked cabinet of the Thesis Supervisor's research office and the electronic data will be encrypted and stored on a password protected computer in the research office of the Thesis Supervisor. In China, during the study, a copy of all written records will be kept in a locked cabinet of the Co-Investigator's research office and the electronic data will be encrypted and stored on a password protected computer in the research office of the Co-investigator. This will provide for a backup of the records/data at a physically separate location during the course of the study.

The data will be conserved for 5 years after the completion of the study. All written records will be kept in a locked cabinet of the Thesis Supervisor's research office and the electronic data will be encrypted and stored on a password protected usb key in the same locked cabinet. In addition, all written records will be optically scanned onto a usb key along with the electronic data and stored in a separate locked cabinet in the research lab of the Thesis Supervisor.

Compensation

There will be no compensation for your participation in this study.

Voluntary Participation

You are under no obligation to participate in the interview. You may withdraw at any time or refuse to answer any questions, without suffering any negative consequences.

This study has been approved by the Research Ethics Board at University of Ottawa, Canada and Fu Wai Hospital, Beijing, China.

Acceptance

There are two copies of the consent form, one of which is yours to keep.

Participant's signature (*Signature*) Date (*Date*)

Principal Investigator's signature (*Signature*) Date (*Date*)

Appendix 3G: Patient decisional needs when considering treatment intensification for type 2 diabetes: A qualitative study in China

Hui Zheng [1,6], Karine Toupin-April [1,2], Yali An [3], Siyao He [3], Ronald J. Sigal [4], Doug Coyle [1], George A. Wells* [1,5], Guangwei Li* [3]

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Abstract

Aims: This study explored decisional needs of patients with type 2 diabetes in China when considering treatment intensification to achieve good glycemic control, from both the patient's and practitioners' perspectives.

Methods: Interviews were conducted with 35 patients, and individual interviews and focus groups with 28 practitioners in Beijing, China. Topic guides based on the Ottawa Decisional Support Framework were modified for the Chinese context. Two interviewers independently extracted and coded transcripts of their notes into-overarching themes. Content analysis was performed to analyze participants' responses.

Results: Patients (34/35) reported having tried different medications and some (15/35) visited multiple hospitals and consulted different doctors. Patients' knowledge of medications was suboptimal (26/35), and most patients were not aware of their glucose levels (23/35). Although most were receptive to add-on medications, both patients and practitioners reported a range of uncertainty about the decision, and patients wanted more reliable information. Patients (15/35) and practitioners (19/28) recognized the importance of a trusting relationship when adding medications. Both reported similar values and preferences, but these were rarely discussed when adding medications. Although most patients (32/35) reported that they were capable of making a decision on adding medications, few practitioners (6/28) perceived their patients were capable.

Conclusions: Findings suggest a need for reliable information, more discussion about values and preferences and decision support to help engage patients and practitioners in a shared decision-making process. Decision support tools may facilitate the process for patients with type 2 diabetes in China considering add-on medications.

Key words: Patient decisional needs, diabetes, China.

1. Introduction

Along with diet and exercise, most patients with type 2 diabetes mellitus (T2DM) will require pharmacological treatment intensification at some point over their lifetime to maintain good glycemic control [1, 8, 9]. With a notable increase in the number of novel antihyperglycemic agents available, the variety of possible treatment options along with different benefit and safety concerns has increased accordingly [2, 3, 10]. Recognizing these concerns, a patient-centered approach was first recommended by the American Diabetes Association [3, 10] for management of hyperglycemia. A patient-centered approach is a shared decision making process between patients and clinicians when making a medical decision [4]. This means that evidence-based medicine must be customized to fit the specific needs of the patient in the real world [5]. More recently, the International Diabetes Federation report identified that China has the highest number of diabetic cases in the world with 116 million in 2009, and is projected to rise to 140 million by 2030 [1]. The latest Chinese diabetes guidelines introduced, for the first time, the concept of a patient-centered approach [6], however, research in this field is still in its early development and no such China-based studies have been published [7]. This highlights a need to collect first-hand information on patient decision needs, including their needs for information, their values and preferences and their needs for decision support.

The objective of this study was to identify patient decisional needs, from both patients' and practitioners' perspectives, when considering adding on antihyperglycemic agents to achieve adequate glycaemic control for patients with type 2 diabetes in China.

2. Materials and Methods

A qualitative study comprised of patient interviews and practitioner interviews and focus groups was conceived, implemented and conducted to identify patient decisional needs when considering adding on antihyperglycemic agents to achieve adequate glycaemic control. The consolidated criteria for reporting qualitative research (COREQ) was followed for the comprehensive reporting of qualitative studies involving interviews and focus groups.

A tier-3 level hospital (i.e., hospital with various specialties), Fu Wai hospital, was selected for the qualitative study in China mainly for two reasons: 1) patients with T2DM who visited this level of hospital generally come from across the country and presented with more diverse social and geographical backgrounds than other lower level hospitals; and 2) practitioners in such tier-3 level hospitals had experience treating patients with diverse backgrounds and were more likely to engage in a research study.

Following the Ottawa Decisional Support Framework (ODSF) and the Population Needs Assessment guides [11-13], two semi-structured topic guides were developed: one for

patients (Appendix 1) and one for practitioners (Appendix 2). The topic guides included open- and close-ended questions. Topic guides were developed in English and translated into Chinese by members of the research team. They were then modified to ensure relevance and acceptability in the Chinese context through discussions with the endocrinologists at Fu Wai Hospital.

Two interviewers conducted the interviews and focus groups over a two-week period at Fu Wai hospital, Beijing, China. One interviewer (H.Z., male) is an endocrinologist working in the Public Health Agency of Canada with methodology training in quantitative and qualitative methods, and the other interviewer (Y.A., female) is an endocrinologist at Fu Wai Hospital with knowledge of the health care system in China and the patients and practitioners at the hospital but was not the physician for the patients interviewed. A detailed plan of the activities during this two-week period was developed and discussed within the research team in advance of the interviews, namely: a training session with the research team members in Fu Wai Hospital on the interview process; the research assistant at Fu Wai Hospital would contact the participants (i.e., patients and practitioners) two days prior to the date of the interview, introduce the study and provide the information sheet; and the location for the interview was arranged in advance, in particular, considering the convenience of the outpatients on the day of their clinic visit.

The study received ethics approval from the University of Ottawa Research Ethics Board in Canada, and Fu Wai Hospital, Beijing, China.

2.1 Selection of Patients and Practitioners

Based on Guest's field study [14, 15], data saturation likely occurs within the first 12 patient interviews and first 4 practitioner focus groups (5 to 7 practitioners per group). To help ensure that saturation was achieved, the plan was to recruit approximately 25 to 35 patients, since patients attending a tier 3 level hospital, such as the Fu Wai hospital, come from across the country and a wide diversity of backgrounds is expected. A purposive sampling process was followed in which a sample of patients with diverse characteristics was selected [16].

2.2 Interviews and Focus Groups

2.2.1 Patient interviews

Patients with type 2 diabetes over 18 years old were identified in the Endocrinology Clinic at Fu Wai Hospital by a research assistant (RA) who was not directly involved in patient care. Patients who were currently taking at least one antihyperglycemic agent were eligible. However, patients with severe underlying medical conditions, including diabetes-associated kidney dialysis, amputation, or advanced stage of retinopathy, were excluded, given that they may have different decisional needs regarding glucose control, in comparison with patients with relatively mild diabetes-associated complications. The RA identified eligible outpatients from the hospital registry system two days before the clinic visit, and inpatients two days prior to the interview. The RA communicated with the patients by phone and explained the study project, using the study's information sheet and consent form. If the patient agreed and signed the

consent form (either over the phone or on the clinical visit day), a time to meet with the RA about the interview was arranged on the day of the outpatient clinic visit, or at a convenient time for the inpatients. Face-to-face interviews of approximately 40 minutes were conducted in a private meeting room in June 2018.

2.2.2 Practitioner interviews and focus groups

Practitioners associated with the department of endocrinology and with more than one year of clinical experience in diabetes were eligible, including nurses, endocrinologists and other physician specialists. If a practitioner provided informed consent, he/she was added to a list for a focus group if available at the chosen time. Focus groups took approximately one hour in a clinic conference room during working hours. Practitioners who were not available for the focus groups participated in individual 40 minute interviews in the same conference room. All interviews were conducted in June 2018.

2.3 Data Collection

Recruitment and data collection were performed concurrently with the analysis. Two researchers (H.Z., Y.A) interviewed patients (Appendix 1) and practitioners (Appendix 2) with the help of the topic guides. The topic guides were pretested and covered patients' and practitioners' experience with type 2 diabetes and decision-making about add-on medications. Elements that were explored included the way in which patients made the decisions for add-on medications, information patients received and wished they had received, values and preferences which affect their decisions and their decision support

needs. Patients' knowledge of antihyperglycemic medication was assessed using a simple knowledge test that was developed by the research team. Participants' demographic and socioeconomic information were collected. HbA1c results were retrospectively extracted from medical records when patients could not provide them during the interview. Notes were taken by each interviewer but audio recording was not used because it was not deemed acceptable due to the cultural context and participants' concerns. At the end of each interview, the two researchers summarized the information recorded with the participant(s) for accuracy, and afterwards the two researchers reached consensus on the discussions that took place. Data saturation was considered attained when no new ideas could be generated in a category or theme [14, 15].

2.4 Data Analysis

Data analysis was guided by content analysis [17], including reviewing the responses (text data) to each question, extracting potential ideas from the phrases, sentences or paragraphs recorded and grouping thematically relevant codes. Recruitment and data collection were performed concurrently with the analysis. If any new ideas emerged from patients' interviews or practitioners' focus groups or individual interviews, additional codes were created. All interviews were coded by two researchers (H.Z., Y.A). First, the two interviewers (H.Z, A.Y.) independently reviewed open-ended question response (text data) line by line and identified any potential ideas in the phrases, sentences or paragraphs reviewed. They created a code or a phrase. Each code described the meaning of the text data with its idea in simple words. The two

reviewers compared the coded transcripts. If any discrepancy occurred, both interviewers reviewed their initial text data to check their coding, and then discussed the issue and reached consensus. This was done after each face-to-face interview. The interviews were conducted until data saturation was achieved. Saturation was defined as the point at which no new ideas could be generated and contributed to existing ideas or codes in subsequent face-to-face interviews. A similar process was followed after each focus group session. Next, the two interviewers independently generated a second level set of codes based on the list of initial codes, by merging the initial codes with similar meanings. Each second-level code described the meaning of the combined text data with its idea in simple words. Finally, the codes were tabulated and sorted to identify a range of categories or themes.

Descriptive statistics such as percentage, mean, median, standard deviation (SD) and interquartile range (IQR) were used to summarize patient and practitioner demographic and socioeconomic characteristics. For added clarity, simple counts were used to support terms such as *some*, *usually* and *most* when describing narrative accounts [18]. The maximum knowledge score for a medication was 3 (1 for knowing the advantage; 1 for knowing the disadvantage; and 1 for knowing the risk), and for a patient with more than one medication, the average of the knowledge scores was calculated.

3. Results

In total, 35 patients with type 2 diabetes participated in the semi-structured individual interviews, and 28 practitioners providing care to patients with diabetes participated in semi-structured individual interviews and focus group interviews at Fu Wai Hospital. Of the 28 practitioners, 12 practitioners participated in two focus group sessions, 6 in each, and sixteen participated in individual interviews. Only 2 of the 37 patients invited declined because of cancelled clinic visits, and one of the 29 practitioners invited did not participate because of time commitments.

3.1 Study participants

Thirty-five patients (5 inpatients and 30 outpatients) were interviewed (Table1), coming from broad geographic regions in China. Patients presented with a diversity of demographic and socioeconomic characteristics, with varying education, occupation, income, and medical insurance coverage. Clinically, they varied in duration of diabetes, medication history and glycemic control measured by hemoglobin A1c (HbA1c). The mean age was 59 years (SD 10.9 years). Males and females were similarly represented (54% and 46% respectively). Most patients (23/35) did not know their most recent glucose or HbA1c levels, so their HbA1c results were retrospectively determined from medical records.

Twenty-eight practitioners participated in the study: 17 physicians and 11 nurses. Their mean age was 35 years (SD 7 years), and most (23/28) were female. Physicians typically spent an average of 11 to 15 minutes per clinical visit (Table 2).

3.2 Thematic summary

Based on the ODSF [11-13], decisional needs were organized into seven themes: 1) patient experience in using the health care system; 2) patient knowledge and exchange of information about their medications; 3) decisional conflict (uncertainty about the best choice); 4) factors related to decisional conflict; 5) patient values and preferences; 6) role in decision-making; and 7) what patients need to make a better decision. We elaborate on each of the themes below.

3.2.1 Patient experience in using the health care system

Patients' perspective:

All but one patient reported having tried different medications for diabetes, including Western medicine and Traditional Chinese Medicine (TCM). Most patients (30/35) perceived Western medicine as being more effective and less safe in comparison with TCM. Most of the patients (20/30) taking TCM mentioned using them as a holistic treatment for body functions and not necessarily to reduce high blood sugar.

"When my blood sugar level was high, I used Western medications. When my blood sugar [was] back to normal, I preferred to take Traditional Chinese medications because the newspapers said they were made of herbs and they had no side effects."(Patient 10)

Almost half of the patients (15/35) reported visiting different hospitals and consulting with different physicians. Patients reported trusting health care services provided in larger or tier-3 level hospitals, and they mentioned believing medical advice from specialists more than from general practitioners outside tier-3 level hospitals. Nearly all patients (34/35) reported consulting specialists and/or renowned experts in diabetes. Few patients (1/35) mentioned going to see a general practitioner in their community.

"I lived in a small town (in the northern part of Jilin province). I came to Fu Wai Hospital because this is a tier-3 level famous hospital and had very well-known experts in diabetes. I did not trust the doctors in my small town and there were no advanced medical devices like here." (Patient 6)

Younger (10/14) patients were more likely to report visiting multiple hospitals than older (5/21) patients. Similarly, higher educated (11/14) patients were more likely to visit than less educated patients (9/21). The most common sources of information for patients (18/35) were newspapers, magazines, internet, social media and friends, as well as information available in hospitals.

3.2.2 Patient knowledge and exchange of information about their medications

Patients' perspective:

Most patients (26/35) did not correctly answer more than one-third of the questions about their current antihyperglycemic medications; that is, their knowledge score on these medications was ≤ 0.33. Notably, patients who took TCM were more likely to show less knowledge of their medications (0.2) compared to patients who did not take TCM (0.3).

Some patients (5/35) also indicated that practitioners did not provide them with information on the side effects of new drugs.

> *"I had diabetes less than two years and I changed medications many times for diabetes. Every time we added or changed medication, my doctor could not explain its side effects to me" (Patient 20)*

Practitioners' perspective:

Some of the practitioners (8/28) felt that patients had unrealistic expectations of the pharmacological treatment for diabetes. Their patients were looking for medications to "cure" type 2 diabetes, often after hearing about treatments which were reported to be effective in the media.

> *"Patients often came to the clinic and asked for medicine (either Western medicine or TCM) to cure the disease of* type 2 diabetes*. Sometimes, they provide the names of the medicines because they got them from their friends or heard it on TV, or sometimes, they just ask if there are new medicines available." (Practitioner 7)*

3.2.3 Decisional conflict (uncertainty about the best choice)

Patients' perspective:

Given that all the patients were taking at least one antihyperglycemic medication, we asked about their feelings when adding medications to their existing regimen. Although most patients (26/35) reported that they accepted adding medications, a few patients (5/35) reported concerns and negative feelings such as being distressed or upset, worried about what could go wrong, wavering between choices or changing their mind.

> *"My doctor gave me a new drug (for diabetes), but I read some drug company's report on the drug later which mentioned a lot of side effects of this drug. So I did not know what to do and came to the big hospital to ask the expert." (Patient 26)*

Practitioners' perspective:

As with patients, most practitioners (17/28) reported their patients were receptive to add-on medications. However, they mentioned that many patients were uncertain about what to do. Most practitioners (15/28) also observed patients' concerns and negative feelings related to adding medications such as: questioning why they should add-on a medication; being distressed or upset; delaying the decision; worrying about what could go wrong; and feeling physically stressed. Fewer practitioners (5/28) observed other more serious patients' concerns and negative feelings such as: refusing to accept the change of treatment; crying and sadness; reducing the dosage or stopping the prescribed medications without informing their physicians.

"A patient came to the clinic with high glucose level. The patient started to use insulin to control hyperglycemia at the local hospital, but he heard that once he would begin insulin, it would become addictive. So the patient came to our hospital" (Practitioner 11)

3.2.4 Factors related to decisional conflict

Patients' perspective:

When asked about factors that may result in decisional conflict, most patients (25/35) expressed confusion due to the diversity of information on antihyperglycemic medications being provided from various sources such as television, newspapers, internet, other social media and friends. Interviewed patients (15/35) complained that they were lacking reliable information on risks and benefits of the antihyperglycemic drugs that they were interested in taking. Nearly all patients (34/35) reported that consulting specialists and/or renowned experts in tier-3 level hospitals made their decision easier because they trusted their recommendations.

"In my home town, my doctor asked me to take metformin, but the newspaper said the drug harms kidney function so I took traditional Chinese medication but my blood sugar was very high, so I came to the big hospital to find a good drug." (Patient 15)

In addition, some patients (9/35) felt unsupported by their families in making decisions. Some also mentioned the lack of financial support to pay for drugs that were not covered by their insurance, which then had an impact on decision-making.

"I am obese and have diabetes. I heard a new drug can reduce weight and blood sugar, but the drug was expensive and was not covered by my insurance. I want to use it but my family members did not support me financially to use this new drug." (Patient 11)

Some (9/35) felt pressure from others, such as friends with diabetes, to use a novel medication for diabetes.

"My friend with diabetes had started to take a new drug for diabetes and he said the drug was very effective and had no side effects. He said I should use it, but the doctor in my hometown said the drug was not good in my case. So, I came to the big hospital to see famous experts." (Patient 18)

Practitioners' perspective:

The confusion felt by patients about the information on medications was echoed by practitioners. Nearly all practitioners (27/28) mentioned that their patients did not know which source of information was more reliable and which information they could trust.

Practitioners (27/28) also reported that their patients were influenced largely by the pressure from others to make decisions that were not necessarily appropriate for them, which could lead to uncertainty.

"If a patient knows that some of his friends with diabetes are taking a new medication, or if a drug was advertised frequently on television, or had an attractive drug name,

patients often confuse whether they should or should not use the new drug and they may then not know what to do. " (Practitioner 3)

"Patients need more support in decision-making from their families. Also, if some medications are not covered by the patient's current insurance plan or covered partially, family members have to pay out-of-pocket and they will make a big decision." (Practitioner 10)

A trust relationship between patients and practitioners:

Consistently, both patients (15/35) and practitioners (19/28) identified a "trust" relationship is critical when adding antihyperglycemic medication. Interviewed practitioners noted that their patients often accepted an add-on antihyperglycemic medication when these were prescribed by consulting specialists and/or renowned experts in tier-3 level hospitals.

"I came to the big hospital and saw famous doctors for diabetes. If they asked me to take some medication I would do it, but I may not do it if the doctor at my small hometown suggested it to me." (Patient 7)

"Sometimes, we may prescribe the same medication that the patient had been told previously by his or her doctor at local hospital. Patients accepted them when we introduced it." (Practitioner 5).

3.2.5 Patient values and preferences

Patients' perspective:

Most patients (22/35) were concerned about adverse effects of medications, especially on kidneys and the liver. They also worried about medication effectiveness (19/35).

> *"My doctor gave me metformin, but the newspaper said the drug was harmful to kidney and liver function so I really worried about the drug not being good for me." (Patient 22)*

Other common patient worries included: weight gain and hypoglycemia; daily frequency of medication administration; the cost of therapies; and insurance coverage. Notably, female patients (11/14) were more concerned about weight gain than male patients (5/21). Patients with higher incomes above the third quartile (mean= 35,906 RMB) were more concerned about the effectiveness of medications compared to patients with lower incomes below third quartile (mean= 5,147 RMB).

Most patients (25/35) reported that their physicians seldom asked about their concerns when adding medications. Patients (16/25) with a short duration of diabetes were more likely to be asked.

> *"I have type 2 diabetes for more than seven years. When adding medications, my doctor just told me that my blood sugar level was high and I needed to add medications. I worried for my kidney and liver function, but my doctor did not ask my worries when he gave the medication." (Patient 12)*

Practitioners' perspective:

Patient concerns were largely echoed by practitioners. Most practitioners (27/28) noted their patients were often concerned about the safety of medications, in particular the impact on kidney and liver function, the convenience of administration and the cost of medications. However, only a few practitioners (6/28) felt that patients were concerned about medication effectiveness.

> *"Most patients in clinic asked about the negative impact of medicines on kidney and liver function because they often heard from the newspapers and TV that some new drugs had no side effects on kidneys and liver. Patients asked more often about side effects than efficacy of medicines." (Practitioner 19)*

3.2.6 Role in Decision-making

Patients' perspective:

One-third of patients mentioned that they were actively involved in their decisions about add-on medications. One-third mentioned they simply agreed with their health care providers' recommendations. One-third mentioned that the decisions were made by their family members, relatives, friends or even other patients with diabetes. Nearly all patients (32/35) reported that they were capable of making a decision.

Practitioners' perspective:

Practitioners perceived that almost two-thirds of medical decisions were made by physicians and patient's family members and friends combined, without the patients. Few practitioners (8/28) perceived that patients had the ability to make these decisions.

> *"Patient family members play a very important role in decision making, especially for those patients with low income and/or low education. Family members sometimes support patients not only emotionally but also financially." (Practitioner 25).*

3.2.7 What patients need to make a better decision

Patients' perspective:

Most of the interviewed patients (26/35) wanted to have reliable information on risks and benefits of medications. They wished more engagement in decision-making when choosing medications.

Practitioners' perspective:

When practitioners were asked how they could help patients to make a sound clinical decision, practitioners noted that their own knowledge about new medications was important because patients often asked about them. Most practitioners (20/28) said they needed to improve their communication skills and suggested that some examples of successful cases may be good ideas to facilitate the knowledge translation especially during a clinical visit.

> *" It was challenge to clearly explain benefits and risks of medications to patients in such a short clinical visit time period, and it would be better to have successful cases as*

examples or other simple tools to help explain information to patients when adding medications" (Practitioner 2)

In addition, half of the practitioners reported that the support from patient's family was important for making a decision.

4. Discussion

A patient-centered approach for the management of type 2 diabetes has been increasingly recommended in China [6]; however, little is known about patient decisional needs of this population [7]. To our knowledge, this is the first study that explored decisional needs for adults with type 2 diabetes in China who considered treatment intensification. These needs were considered from both the patients' and practitioners' perspectives.

Interviewed patients presented with a diversity of experiences: using various medications, visiting different hospitals and consulting different physicians, especially specialists in diabetes at tier-3 level hospitals.

Most patients did not know their glucose or HbA1c levels and had suboptimal knowledge of medications, illustrated by only one-third of interviewed patients being able to correctly answer questions about their medications. Our results echoed the 2019

report on standards of care for type 2 diabetes in China which related that “the overall proportion of patients who were aware of their level of diabetes control was 38.6%” [6]. Also, in general, patients who took TCM demonstrated less knowledge of their medications. Consistent with the patients’ low level of knowledge, some of the practitioners revealed that patients have unrealistic expectations of the treatment for diabetes, such as believing that some medications can cure diabetes. Some patients also mentioned that practitioners did not provide them with information on the side effects of new drugs. Patients felt they were lacking reliable information on risks and benefits of antihyperglycemic drugs, which may partially explain their low knowledge level of the features of the various medications.

Although most patients reported that they accepted adding medications, some patients and practitioners reported patients’ concerns and negative feelings. These seem to be related to patients’ feeling confused about the contradictory information from various sources of information and ultimately trusting recommendations of experts in tier-3 level hospitals. Other factors that may have played a role included the lack of decision-making support and financial support from their families, as well as pressure from others.

Patients’ trust of experts working in tier-3 level hospitals was an element that helped them make a decision and follow the advice of the medical professionals. Ideally, this trust should be nurtured and established beyond the tier-3 hospitals to the tier-2 and

tier-1 level hospitals. It is well known that renowned experts and specialists commonly practise at tier-3 levels such as the Fu Wai hospital, however there are only 30,000 specialists to deal with 120 million patients with diabetes in China [19]. As reported in our study, specialists can only spend approximately 10-15 minutes per patient visit. Other studies in China found that physicians even spend less than 10 minutes per patient during clinical visits [7]. Today, there is a “trust crisis” in the health care system in China [7, 20, 21]. The ongoing health care reform is intended to focus primarily on patient-centered medical care and to improve the patient and practitioner relationship in the country [22].

Patient values and preferences when adding on medications were largely consistent between patients and practitioners, often focusing on the safety, cost and the convenience of taking the medications. These values may change depending on individuals’ socioeconomic and demographic characteristics; for instance, the perception of weight gain associated with using antihyperglycemic agents seems more concerning to females than males. In our results, practitioners did not rank drug side effects as high as patients. Interestingly, one study in Malaysia showed that patients focused more on the drug side effects and physicians focused more on the efficacy when they considered a treatment [23]. It may be worthwhile to further investigate any discrepancies between practitioners’ and patients’ perspectives regarding patient needs for considering treatment options in this population with T2DM in China.

Making a decision when adding medications involves physicians, patients and, often, other individuals who are family members or relatives, spouses, friends or patients with diabetes. Although patient values and preferences were recognized, they were rarely communicated and most physicians simply told patients that their blood glucose levels were high and they needed add-on medications. Following failure with metformin monotherapy, patients with T2DM face many treatment options from which their physicians can choose. At this stage, the communication between patients, family members and physicians becomes critical to take individual patient values and preferences into consideration [2]. Such communication is necessary for this shared decision making process to happen. However, this communication is not optimal as identified during our interviews, which is consistent with other studies that found physicians in China require better communication skills because of minimal patient communication training in medical school [24, 25].

The current study showed most patients wish to be more engaged in decision-making. These findings are similar to studies in Malaysia [28], China [7], and Japan [29] which found that patients desired greater involvement in medical decision-making. For patients to play a role in a shared decision making process, they need the pertinent information about the specific condition and associated treatment options provided in a clear and understandable format. Using tools such as patient decision aids and decision coaching [26, 27] may help prepare patients, family members and others to engage in decision-

making by providing them with evidence-based information about treatment options and having open conversations with physicians about patients' values and preferences.

To our knowledge, this is the first study to investigate decisional needs of patients with type 2 diabetes in China and provides an in-depth exploration of these needs, from both patient and practitioner perspectives. Some limitations should be considered. First, we could not analyze the results separately for outpatients and inpatients because of the small numbers of inpatients (5/35). Second, the two focus group sessions included both physicians and nurses with the goal of including a diverse selection of practitioners, and the numbers were too small for a separate analysis by physicians versus nurses. Third, the study had no audio transcription of interviews, although the two interviewers (H.Z., Y.A) reviewed notes and reached consensus at the end of each interview while the information was fresh in their minds. Fourth, the values and preferences are specific to patients with T2DM in China and are not necessarily generalizable to other countries and healthcare systems.

The findings from our study suggest that patients with T2DM in China have suboptimal knowledge of antihyperglycemic medications, although they visit various hospitals and see different physicians. Patients want more consistent and clear information on treatment options and wish to be more engaged in making a decision regarding their treatment. On the other hand, practitioners indicated a willingness to participate in a shared decision making process with patients, a sentiment that was also identified in

other studies in China [25]. A patient decision aid may help to facilitate this shared decision making for patients who fail metformin monotherapy and are considering add-on antihyperglycemic medications.

Acknowledges: No specific funding was obtained for this study.

Conflict of interest: None

Research team and Author Contribution:

The principal investigator (H.Z.) is a MD and a PhD Candidate in the School of Epidemiology and Public Health, University of Ottawa. The research team included experts in the field of qualitative and quantitative research (K. T. A., G.A. W.), economic research (D.C.) and endocrinology (physician: G.W.L., Y. A., S.H., R. S.) who provide care to patients with diabetes in China and Canada. Members of this international research team came from the University of Ottawa and the University of Calgary, Canada, and Fu Wai Hospital, China.

H.Z., K.T.A., R.J.S., D.C., G.W. and G.A.W. conceived and designed the research. H.Z. and Y.A. interviewed patients and practitioners, and recorded the data. H.Z. performed the content analysis and statistical analysis, and wrote the first draft of the manuscript. All authors contributed to the writing and revisions of the manuscript.

Table 1. Patient Characteristics

Patient Characteristics		Number	Percentage
Age, years (n=35)			
	Mean ± SD *	60 ± 11	
Patients			
	Inpatients	5	14.3
	Outpatients	30	85.7
Sex (n=35)			
	Male	19	54.3
	Female	16	45.7
Monthly Income, RMB + (n=35)			
	<3000	9	25.7
	3000 – 5000	11	31.4
	5000 – 9000	7	20.0
	> 9000	8	22.9
	Median (IQR ^)	5000 (3000, 8300)	
Occupation (n=34)			
	Accounting	1	2.9
	Architecture	1	2.9
	Business	1	2.9
	CEO	1	2.9
	Civil servant	3	8.8
	Family woman	2	5.9
	Finance	2	5.9
	Lab technician	1	2.9
	Manager	1	2.9
	Real estate	1	2.9
	Retirement	14	41.2
	Self-employed	1	2.9
	Teacher	1	2.9
	Blue-collar Worker	3	8.8
	Police officer	1	2.9
Residence region (n=35)			
	Beijing	18	51.4
	Hai Nan	1	2.9
	He Nan	1	2.9
	He Bei	1	2.9
	Hei Long Jiang	4	11.4
	Ji Lin	2	5.7
	Jiang Su	1	2.9
	Nei Meng	2	5.7
	Shan Dong	2	5.7
	Shan Xi	3	8.6
Diabetes duration, years (n=35)			
	≤ 5	8	22.9
	6 - 9	10	28.6
	10 - 15	9	25.7
	> 15	8	22.9
	Median (IQR ^)	9 (6.0, 9.0)	
HbA1c, % (n=34)			
	≤ 6.5	9	26.5
	6.6-7.3	9	26.5

	7.4-8.7	9		26.5
	> 8.7	7		20.5
	Median (IQR ^)	7.3	(6.0-8.1)	
Insurance coverage (n=35)				
	Urban Employee Basic Medical Insurance	5		14.3
	Urban Resident Basic Medical Insurance / New Rural Cooperative Medical System	21		60.0
	Self-payment	5		14.3
	Other	4		11.4
Education (n=35)				
	No school	2		5.7
	Primary School	5		14.3
	High school	8		22.9
	College	10		28.6
	University	7		20.0
	Graduate Degree	3		8.5
Diabetes treatment (n=35)				
	Metformin	29		82.9
	Insulin	22		62.9
	GLP-1 analogue	8		22.9
	DPP-4 inhibitor	5		14.3
	Acarbose	7		20.0
	Traditional Chinese Medicine	3		8.6
	Sulfonylureas	2		5.7
	Meglitinides	1		2.9

* SD: Standard deviation.

+ RMB: the unit is Chinese Yuan in China (1 US dollar is equal about 6 RMB).

^ IQR: interquartile range.

Table 2. Characteristics of the Interviewed Practitioners

Practitioner Characteristics		Number	Percentage
Age, years (n=28)			
	Mean ± SD *	35 ± 7	
Occupation			
	Nurse	11	39.3
	Physician	17	60.7
Sex (n=28)			
	Male	5	17.9
	Female	23	82.1
Department (n=28)			
	Cardiovascular	3	10.7
	Endocrinology	9	32.1
	General Practitioner	5	17.9
	Nurse	11	39.3
Patients seen/day (n=16 physicians)			
	5-10	5	31.2
	11-20	3	18.8
	21-30	4	25.0
	> 30	4	25.0
Time / patient (n=16 physicians)			
	4-10 minutes	2	12.5
	11-15 minutes	10	62.5
	>15 minutes	4	25.0

* SD: Standard deviation.

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Appendix 1: Patients Interview Topic Guide

QUESTIONNAIRE

1. After diagnosed as diabetes mellitus, what do you think are the most important matters to do? Probe role,
    - see a doctor
    - look for a specific medicine
    - diet and exercise

2. Let's focus on one particular decision.
    - What problem or problems, if any, have you encountered when you are asked to take additional medicines to achieve better blood sugar control?

3. Let's talk about the difficulty you have making this decision about adding therapies for intensive glycemic control. How do you feel when making this decision? Probe role,
    - Constantly thinking about the decision
    - Delaying the decision
    - None of these; I do not feel distressed

4. What things make the decision difficult for you? Probe role,
    - Worried about weight gain
    - daily frequency, or convenience of dose administration and blood glucose monitor
    - Lacking information about options, benefits, risks

5. If you have to make a decision on medication today, could you select three items from the question 4 above that concern you most?

6. Thinking about this decision, what are the options that you have?

7. Who else may be involved in making this decision? Do you usually:
    a. Make the decision for you
    b. Share the decision with you
    - Provide support or advice for you to make the decision on their own

8. How do you usually go about making such a decision? Probe role
    a. Get information on options
    - Get information on the chances of benefits and risks
    - Consider the personal importance of the benefits and risks

9. What would help you to make this decision?

10. What will hinder you (get in the way of) making this decision?

11. Is there anything else that would help overcome these barriers to decision making?

12. I will list possible ways to help some people with a decision, which ones do you think might be useful to you?

Counseling from a health practitioner	If YES, specific what types
Discuss groups of patients facing the same decision	If YES, specify what type of organization or group
Information materials	If YES, specify content. probe role, o General information on diabetes o Product monography o Help considering the personal importance of benefits versus risk
	If YES, specify format. probe role, o Booklet, pamphlets o Internet o WeChat
	If YES, who do you think should prepare information about the decision, probe role, o Pharmacies o Expert medical and health practitioners o Health societies for specific condition (e.g. Diabetes Society)

13. Is there anything else that would help you to do a better job supporting you in decision making?

14. When you visit a clinic, what does your doctor tell you if he or she wants to add medicines for blood sugar control?

15. What additional information you really need or want besides what your doctor told you as described above?

16. Are you taking medicines regularly as your doctors prescribed? Yes or No.

17. If answer is “No”, how often you miss taking your medicines?

18. What do you see as the main advantages/benefits, disadvantages, and risks of the anti-diabetic medications you are taking now?

CHARACTERISTICS OF PATIENTS

19. Age Category
    a. Twenties
    b. Thirties
    c. Forties
    d. Fifties
    e. Sixties or more

20. Sex
    - Female
    - Male

21. Income(salary) per month/year

22. Occupation

23. Duration of experience with health problem

24. What is the highest grade or level of education you completed?
    - Primary school or less
    - High school diploma
    - College diploma/degree
    - University undergraduate degree
    - University graduate degree (Master or PhD)

25. Professional degree. Probe role
    - M.D.
    - Engineer
    - Statistician
    - Others

THANK RESPONDENT

Appendix 2: Practitioner interview topic guide

QUESTIONNAIRE

1. What decisions do patients with type 2 diabetes have to make in your practice?

2. Let us focus on one particular decision:
    - What do patients consider most when adding anti-hyperglycemic therapies to them for glycemic control? Why?

3. Let's talk about the difficulty patients have in making this decision. How do patients feel when making this decision? Probe role,
    - Constantly thinking about the decision
    - Delaying the decision
    - Feeling physically stressed, tense muscles, difficulty sleeping

4. What factors make the decision difficult for patients? Probe role,
    - Worry about weight gain
    - Lacking information about options, benefits, risks
    - Worry about hypoglycemia

5. What do you see as the main options patients have?

6. What do you see as the main advantages/benefits, disadvantages, and risks of the options?

7. What is your usual role in making this decision? (Probe role) Do you usually:
    - Make the decision for the patients
    - Share the decision with the patients
    - Provide support or advice for patients to make the decision on their own

8. What factors make it difficult for you to support your patients' decision making?

9. What factors make it easier for you to support your patients' decision making?

10. Who else besides yourself and the patient is usually involved in making this decision? Probe role,
    - Spouse
    - Family members
    - Friends

11. What is their usual role in making this decision (e.g. the person mentioned above)? (Probe role), Do you usually:
    - Make the decision for the patients
    - Share the decision with the patients
    - Provide support or advice for patients to make the decision on their own

12. How do patients usually go about making such a decision?

Probe role
- Consider the personal importance of the benefits and risks
- Get information on how others go about deciding
- Get support from others

13. What would help patients to make this decision?

14. What will hinder patients (get in the way of) making this decision?

15. Is there anything else that would help overcome barriers to decision making?

16. I will list possible ways to help some people with a decision, which ones do you think might be useful to your patients?

Counseling from a health practitioner	If YES, specific what types
Discuss groups of people facing the same decision	If YES, specify what type of organization or group
Information materials	If YES, specify content. probe role, o General information on diabetes o Product Monograph o Help considering the personal importance of benefits versus risk
	If YES, specify format. Probe role, o Booklet, pamphlets o Internet o WeChat
	If YES, who do you think should prepare information about the decision? Probe role, o Pharmacies o Experts in medicine o Health societies for specific condition (e.g. Diabetes Society)

17. Is there anything else that would help you to do a better job supporting your patients' decision making?

18. Whether patients also discuss or ask other diabetes related risk?

19. How many outpatients you see per day in a clinic

20. On average, how much time do you spend with each patient in a clinic

21. In a clinic, what you explain to a patient when adding medicines for intensive glycaemic control?

22. What you think the patient really need or want to know when you add the medicines?

23. Do you think most of your patients take anti-hyperglycemic medicines regularly as prescribed? Yes or No.

24. If answer is “No”, how often patients miss taking their medications?

CHARACTERISTICS OF PRACTITIONER

25. Age Category
    - Twenties
    - Thirties
    - Forties
    - Fifties
    - Sixties or more

26. Sex
    - Male
    - Female

27. Practice discipline, specify

28. Practice Specialty, specify
    - Nurse
    - Resident physician
    - Attending physician

29. Practice Location, specify

THANK RESPONDENT

Appendix 4A: Literature search strategy

2018 OCT 11

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2018 October 10>, Ovid MEDLINE(R) ALL <1946 to October 10, 2018>

SEARCH STRATEGY	
1	exp Diabetes Mellitus, Type 2/ (336398)
2	Diabetes Mellitus/ (644692)
3	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet*).tw,kw. (355261)
4	(MODY or NIDDM or T2DM).tw,kw. (62932)
5	or/1-4 (1019531)
6	exp Diabetes Mellitus, Type 2/dt (81195)
7	Drug Combinations/ (163882)
8	Drug Therapy, Combination/ (161569)
9	6 and (7 or 8) (4371)
10	Hypoglycemic Agents/ (98171)
11	(antidiabetic? or anti-diabetic? or antihyperglyc?emic? or anti-hyperglyc?emic? or hypoglyc?emic? or antidiabetes or anti-diabetes).tw,kw. (113445)
12	Dipeptidyl-Peptidase IV Inhibitors/ (9869)
13	((DPP4 or DPP 4 or DPP IV) adj1 inhibitor?).tw,kw. (8661)
14	(dipeptidyl-peptidase IV adj2 inhibitor?).tw,kw. (1451)
15	(dipeptidyl-peptidase 4 adj2 inhibitor?).tw,kw. (4624)
16	gliptin?.tw,kw. (634)
17	(alogliptin or nesina or SYR 322 or SYR322 or HSDB 8203 or incresina or vipidia).tw,kw. (1171)
18	JHC049LO86.rn. (214)
19	Linagliptin/ (2304)
20	(linagliptin or BI 1356 or ONDERO or tradjenta or trajenta or trayenta or trazenta).tw,kw. (1891)
21	3X29ZEJ4R2.rn. (313)
22	(saxagliptin or BMS 477118 or BMS477118 or HSDB 8199 or Onglyza or OPC 262).tw,kw. (1958)
23	9GB927LAJW.rn. (305)
24	exp Sitagliptin Phosphate/ (8367)
25	(sitagliptin or EC 690-730-1 or Glactiv or HSDB 7516 or januvia or "mk 0431" or mk0431 or mk 431 or ono 5435 or ristaben or sitagliptine or tesabel or tesavel or xelevia).tw,kw. (6396)
26	TS63EW8X6F.rn. (1169)
27	Sodium-Glucose Transporter 2/ai (1142)
28	(sodium-glucose transporter 2 inhibitor? or sodium-glucose cotransporter 2 inhibitor?).tw,kw. (1476)
29	(sodium-glucose transporter 2 inhibitor? or sodium-glucose co-transporter 2 inhibitor?).tw,kw. (1069)
30	((SGLT-2 or SGLT2) adj inhibitor?).tw,kw. (4824)
31	(sodium dependent glucose transporter 2 inhibitor? or sodium dependent glucose cotransporter 2 inhibitor?).tw,kw. (49)
32	(sodium dependent glucose transporter 2 inhibitor? or sodium dependent glucose co-transporter 2 inhibitor?).tw,kw. (35)
33	gliflozin?.tw,kw. (183)
34	Canagliflozin/ (2375)

35 (canagliflozin or Invokana or JNJ 24831754* or JNJ 28431754 or TA 7284 or Prominad).tw,kw. (2034)
36 0SAC974Z85.rn. (399)
37 (dapagliflozin or BMS 512148 or BMS512148 or edistride or forxiga or farxiga).tw,kw. (2358)
38 1ULL0QJ8UC.rn. (0)
39 (empagliflozin or BI 10773 or BI10773 or Jardiance).tw,kw. (2296)
40 HDC1R2M35U.rn. (406)
41 Sulfonylurea Compounds/ (14453)
42 (sulfonylurea? or sulfonurea? or sulfonyl urea? or sulfonylcarbamide? or sulphonurea? or sulphonylurea?).tw,kw. (24771)
43 Chlorpropamide/ (8095)
44 (adiaben or apo-chlorpropamide or apochlorpropamide or abemide or "arodoc c" or asucrol or ascurol or biabenal or bioglumin or BRN 2218363 or catanil or CCRIS 155 or chlomide or chlormide or chlorodiabina or chloropropamide or chlorpromide or clorpropamide or copamide or chloronase or chlorpromide or clorpropamide or chloropropamide or chlorpropamid or chlorpropamide or chlorpropamidum or clorpropamid or clorpropamida).tw,kw. (3436)
45 (dabinese or deavynfar or diabaril or diabechlor or diabeedol or diabemide or diabenal or diabenese or diabeneza or diabet-pages or diabetoral or diabexan or diabiclor or diabines or diabinese or diabitex or diabitol or diamel ex or dibecon or dynalase or EINECS 202-314-5 or eubetin or glicoben or glisema or glucamide or glycemin or glymese or HSDB 2051 or hypomide or insilange or insogen or insulase).tw,kw. (735)
46 (melormin or meldian or melitase or mellinese or millinese or NCI-C01752 or NSC 44634 or NSC 626720 or neo-toltinon or oradian or P 607 or pamidin or prodiaben or pubetin or stabinol or tesmel or "p chlorobenzolsulphonylglycolic acid nitrile" or para chlorobenzenesulfonylglycolic acid nitrile or parachlorobenzene sulfonylglycolic acid nitrile or U-3818 or U-9818).tw,kw. (170)
47 WTM2C3IL2X.rn. (1815)
48 Gliclazide/ (6494)
49 (gliclazide or diaglyk or diaikron or diabrezide or diamicron or BRN 1657836 or EINECS 244-260-5 or gen-gliclazide or gliklazid or gliclazida or gliclazidum or glimicron or glyade or glyclazide or glycazide or nordialex or predian or S 1702 or S 852 or SE 1702).tw,kw. (3895)
50 G4PX8C4HKV.rn. (844)
51 (glimepiride or amaryl or amarel or BRN 5365754 or CCRIS 7083 or endial or euglim or glemax or glimepirid or glimepirida or glimepiridum or glimerid or glorion or HOE 490 or HOE490 or solosa or "s 80 8490").tw,kw. (3826)
52 6KY687524K.rn. (757)
53 Glyburide/ (29928)
54 (adiab or amecladin or apo-glibenclamide or azuglucon or bastiverit or benclamin or betanase or betanese 5 or BRN 2230085 or calabren or clamide or clibenclamide or cytagon or dangbinol or daonil or debtan or diabasan or diabeta or dibelet or duraglucon or EINECS 233-570-6 or euclamin or euglucan or euglucon or euglykon).tw,kw. (1328)
55 (GBN 5 or gen-glybe or gewaglucon or gilemal or glamide or glencamide or gliban or glibeclamid or glibemid or gliben or glibenbeta or glibenclamid or glibenclamida or glibenclamide or glibenclamidum or glibenhexal or glibenil or glibens or glibesyn or glibet or glibetic or glibil or gliboral or glicem or glidiabet or gliformin or glikeyer or glimel or glimide or glimidstada or glisulin or glitisol or glubate or gluben).tw,kw. (18985)
56 (glucobene or glucohexal or glucolon or glucomid or gluconic or glucoremed or glucoven or glukoreduct or glulo or glyamid or glyben or glybencamidum or glybencenamide or glybenclamid or glybenclamide or glybendamine or glybenzyclamide or glybenzcyclamide or glyburide or glycolande or glycomin or glynase or HB 419 or HB 420 or hemi-daonil or hexaglucon or humedia or insol or lederglib or libanil or lisaglucon or locose or lodulce).tw,kw. (7514)
57 (maninil or manoglucon or med-glionil or melix or micronase or miglucan or nadib or neogluconin or norglicem 5 or normoglucon or orabetic or pira or praeciglucon or prodiabet or renabetic or RP-1127 or

	semi-daonil or semi-euglucon or semi-gliben-puren n or sugril or suraben or tiabet or U 26452 or U-26 452 or UR 606 or yuglucon or xeltic).tw,kw. (751)
58	SX6K58TVWC.rn. (6040)
59	Tolbutamide/ (19000)
60	(abemin or aglicem or aglicid or aglycid or apo-tolbutamide or arcosal or arkozal or artosin or artosina or artozin or beglucin or BRN 1984428 or butamid or butamide or butamidum or CCRIS 592 or "D 860" or diabecid or diaben or diabenyl or diabeton or diabesan or diasulfon or diabetamid or diabetol or diabuton or diatol or dirastan or diasulin or diaval or dolipol or drabet).tw,kw. (666)
61	(EINECS 200-594-3 or fresan or glicemin or glicotron or glycotron or guabeta or glyconon or HLS 831 or HSDB 3393 or hypoglycone or ipoglicone or ipoglucos or mermol or metil glucosulfina or mobenol or NCI-C01763 or NSC 23813 or neo antiglycemikos or neo diabetal or neo norboral or neobellin or neoinsoral).tw,kw. (27)
62	(orabet or oralin or oresan or orezan or orinade or orinase or orinaz or orsinon or osdiabet or oterben or pramidex or proinsul or rastinon or SK-tolbutamide or tarasina or tobutamine or tol ortab or tolbet or tolbugen or tolbusal or tolbutamid or tolbutamida or tolbutamide or tolbutamidum or tolbutone or tolbutamte or tolbutol or tolbutylharnstoff or tolbutylurea or tolglybutamide or tolsiran or tolubetin or toluran or tolurast or tosula or toluina or tolumid or toluvan or tolylsulfonylbutylurea or "U 2043" or willbutamide).tw,kw. (12017)
63	982XCM1FOI.rn. (5227)
64	Thiazolidinediones/ (22582)
65	(thiazolidinedione* or TZD or TZDs).tw,kw. (14005)
66	(pioglitazone* or actos or AD 4833 or piomed or U 72107A or U72 107A or cereluc or glidipion or glita or glitase or glustin or paglitaz or pioglit or sepioglin or zactos).tw,kw. (13614)
67	X4OV71U42S.rn. (3479)
68	(rosiglitazone* or avandia or BRL 49653-C or BRL 49653 or nyracta or rezult or rossini or venvia).tw,kw. (14461)
69	05V02F2KDG.rn. (4081)
70	exp Glucagon-Like Peptide 1/aa (1120)
71	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 analog*).tw,kw. (4248)
72	Glucagon-Like Peptide-1 Receptor/ (5985)
73	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 (receptor? or protein?)).tw,kw. (11326)
74	Receptors, Glucagon/ag (728)
75	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 agonist*).tw,kw. (8916)
76	incretin mimetic*.tw,kw. (867)
77	(dulaglutide or LY-2189265 or LY2189265 or trulicity).tw,kw. (835)
78	WTT295HSY5.rn. (102)
79	(AC 2993 or AC 2993A or AC-2993 or AC002993 or AC2993 or AC2993A or baietta or byetta or bydureon or DA 3091 or exenatide or exendin 4 or HSDB 7789 or LY 2148568 or LY2148568 or PT302 or Ex4 peptide or ITCA 650).tw,kw. (9196)
80	9P1872D4OL.rn. (2134)
81	Liraglutide/ (8051)
82	(liraglutida or liraglutide or liraglutidum or HSDB 8205 or NN-2211 or NN2211 or NNC 90-1170 or saxenda or victoza).tw,kw. (6760)
83	839I73S42A.rn. (1290)
84	Insulin, Long-Acting/ (4639)
85	((long-acting or LA or semilente or semi-lente or slow* acting or intermediate-acting) adj (insulin* or analog*)).tw,kw. (4296)
86	Insulin Detemir/ (3888)
87	(detemir or determir or levemir or NN-304 or NN304).tw,kw. (3202)
88	4FT78T86XV.rn. (517)

89 Insulin Glargine/ (10754)
90 (abasaglar or abasria or basaglar or glargine or HOE-901 or HOE901 or lantus or ly 2963016 or ly2963016 or optisulin or toujeo).tw,kw. (8477)
91 2ZM8CX04RZ.rn. (1608)
92 exp Insulin, Short-Acting/ (2596)
93 ((fast-acting or quick-acting or short-acting or rapid* acting) adj (insulin? or analog*)).tw,kw. (3651)
94 (insulin aspart* or (B28 adj1 insulin?) or (B28 adj1 insulin?) or (B28asp* adj1 insulin?) or NovoLog* or NovoMix* or Novo Mix* or NovoRapid*).tw,kw. (3764)
95 D933668QVX.rn. (617)
96 (lispro or lyspro or humalog or liprolog).tw,kw. (4301)
97 (apidra or glulisine).tw,kw. (1194)
98 7XIY785AZD.rn. (146)
99 exp Insulin, Isophane/ (8575)
100 (actraphan? or berlinsulin or "humulin i" or "humulin n" or insulatard or (insulin? adj3 monotard) or isophane or (insulin? adj2 NPH) or (insulin? adj2 protamine) or isofane or isophan or isophane or isophone or mixtard or novolin or nph iletin or nph umuline or orgasuline or protaphan or protaphane or protophane or prozinc or (zinc adj2 insulin?) or (zinc adj1 protamine)).tw,kw. (7303)
101 2ZM8CX04RZ.rn. (1608)
102 exp Insulin/ (513432)
103 (insulin? adj1 regular).tw,kw. (3221)
104 (insulin? adj1 human).tw,kw. (13899)
105 (nph insulin? or humulin or novolin).tw,kw. (4758)
106 ((insulin? adj1 (pork or porcine or pig or pigs)) or hypurin).tw,kw. (2929)
107 (alogliptin adj3 metformin).tw,kw. (60)
108 (metformin adj2 nesina).tw,kw. (0)
109 (kazano or nesimet or nesina or nesinamet or vipdomet).tw,kw. (113)
110 (linagliptin adj2 metformin).tw,kw. (123)
111 (jentadueto or trajenta duo or trajentamet or trayebta duo or trayenta duo).tw,kw. (44)
112 (saxagliptin adj3 metformin).tw,kw. (215)
113 (komboglyze or kombiglyze or comboglyze or duoglyze).tw,kw. (54)
114 "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"/ (386)
115 (sitagliptin adj3 metformin).tw,kw. (703)
116 (janumet or efficib or gliptamet or Januet or ristfor or velmetia or mk 0431a).tw,kw. (207)
117 (metformin adj3 dapagliflozin).tw,kw. (169)
118 (ebymect or xigduo).tw,kw. (33)
119 (empagliflozin adj3 metformin).tw,kw. (112)
120 (jardiamet or jardiancemet or synjardy).tw,kw. (22)
121 (metformin adj3 rosiglitazone).tw,kw. (918)
122 (avandamet or interac).tw,kw. (359)
123 Glycoside Hydrolase Inhibitors/ (3662)
124 ((alpha-amylase or alpha-glucosidase or glucosidase or glycoside) adj2 inhibitor?).tw,kw. (8655)
125 Acarbose/ (8691)
126 (acarbose or ag 5421 or ag5421 or alpha ghi or bay g 5421 or bay g5421 or glibose or glicobase or glucobay or gluconase or glucor or glumida or prandase or precise or rebose).tw,kw. (372272)
127 T58MSI464G.rn. (1275)
128 (hb 699 or hb699 or meglitinide?).tw,kw. (772)
129 (actulin or ag ee 388 or ag ee388 or ag ee 623 or ag ee623 or enyglid or gluconorm or novonorm or prandin or rapilan or repaglinide or sestrine).tw,kw. (2171)
130 (a 4166 or a4166 or ay 4166 or ay4166 or djn 608 or djn608 or fasticor or glinate or nateglinide or sdz djn 608 or sdz djn608 or senaglinide or starlix or starsis or trazec or "ym 026").tw,kw. (1525)

131	(bay 1099 or bay m 1099 or bay m1099 or bay1099 or diastabol or glyset or miglitol or plumarol).tw,kw. (971)
132	0V5436JAQW.rn. (207)
133	(ao 128 or ao128 or basen or "en 116 077" or en 116077 or "en116 077" or en116077 or glustat or voglibose).tw,kw. (846)
134	or/9-133 (1100013)
135	5 and 134 (276283)
136	(controlled clinical trial or randomized controlled trial).pt. (557317)
137	clinical trials as topic.sh. (184945)
138	(randomi#ed or randomly or RCT$1 or placebo*).tw. (2067603)
139	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (380901)
140	trial.ti. (448696)
141	or/136-140 (2540859)
142	135 and 141 (35600)
143	exp Animals/ not (exp Animals/ and Humans/) (16930534)
144	142 not 143 (22066)
145	Adolescent/ not (exp Adult/ and Adolescent/) (1119010)
146	exp Child/ not (exp Adult/ and exp Child/) (3178347)
147	exp Infant/ not (exp Adult/ and exp Infant/) (1649632)
148	or/145-147 (4032212)
149	144 not 148 (21762)
150	(comment or editorial or interview or news or newspaper article).pt. (1864777)
151	(letter not (letter and randomized controlled trial)).pt. (2031148)
152	149 not (150 or 151) (21336)
153	(2017* or 2018*).dt. (2203954)
154	152 and 153 [UPDATE PERIOD] (1361)
155	154 use medall [MEDLINE UPDATE RECORDS] (1361)
156	diabetes mellitus/ (644692)
157	non insulin dependent diabetes mellitus/ (336213)
158	lipoatrophic diabetes mellitus/ (439)
159	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet*).tw,kw. (355261)
160	(MODY or NIDDM or T2DM).tw,kw. (62932)
161	or/156-160 (1019592)
162	non insulin dependent diabetes mellitus/dt (81157)
163	drug combination/ (99533)
164	162 and 163 (538)
165	antidiabetic agent/ (104340)
166	oral antidiabetic agent/ (17724)
167	(antidiabetic? or anti-diabetic? or antihyperglyc?emic? or anti-hyperglyc?emic? or hypoglyc?emic? or antidiabetes or anti-diabetes).tw,kw. (113445)
168	dipeptidyl peptidase IV inhibitor/ (10825)
169	((DPP4 or DPP 4 or DPP IV) adj1 inhibitor?).tw,kw. (8661)
170	(dipeptidyl-peptidase IV adj2 inhibitor?).tw,kw. (1451)
171	(dipeptidyl-peptidase 4 adj2 inhibitor?).tw,kw. (4624)
172	gliptin?.tw,kw. (634)
173	alogliptin/ (1506)
174	(alogliptin or nesina or SYR 322 or SYR322 or HSDB 8203 or incresina or vipidia).tw,kw. (1171)
175	850649-62-6.rn. (994)
176	850649-61-5.rn. (1312)
177	linagliptin/ (2304)

178 (linagliptin or BI 1356 or ONDERO or tradjenta or trajenta or trayenta or trazenta).tw,kw. (1891)
179 668270-12-0.rn. (1654)
180 saxagliptin/ (2615)
181 (saxagliptin or BMS 477118 or BMS477118 or HSDB 8199 or Onglyza or OPC 262).tw,kw. (1958)
182 361442-04-8.rn. (2280)
183 945667-22-1.rn. (2154)
184 sitagliptin/ (8365)
185 (sitagliptin or EC 690-730-1 or Glactiv or HSDB 7516 or januvia or "mk 0431" or mk0431 or mk 431 or ono 5435 or ristaben or sitagliptine or tesabel or tesavel or xelevia).tw,kw. (6396)
186 486460-32-6.rn. (6010)
187 sodium glucose cotransporter 2 inhibitor/ (2375)
188 (sodium-glucose transporter 2 inhibitor? or sodium-glucose cotransporter 2 inhibitor?).tw,kw. (1476)
189 (sodium-glucose transporter 2 inhibitor? or sodium-glucose co-transporter 2 inhibitor?).tw,kw. (1069)
190 ((SGLT-2 or SGLT2) adj inhibitor?).tw,kw. (4824)
191 (sodium dependent glucose transporter 2 inhibitor? or sodium dependent glucose cotransporter 2 inhibitor?).tw,kw. (49)
192 (sodium dependent glucose transporter 2 inhibitor? or sodium dependent glucose co-transporter 2 inhibitor?).tw,kw. (35)
193 gliflozin?.tw,kw. (183)
194 canagliflozin/ (2375)
195 (canagliflozin or invokana or JNJ 24831754* or JNJ 28431754 or TA 7284 or prominad).tw,kw. (2034)
196 842133-18-0.rn. (1684)
197 dapagliflozin/ (2293)
198 (dapagliflozin or BMS 512148 or BMS512148 or edistride or forxiga or farxiga).tw,kw. (2358)
199 461432-26-8.rn. (1896)
200 empagliflozin/ (2140)
201 (empagliflozin or BI 10773 or BI10773 or jardiance).tw,kw. (2296)
202 864070-44-0.rn. (1914)
203 sulfonylurea derivative/ (9292)
204 (sulfonylurea? or sulfonurea? or sulfonyl urea? or sulfonylcarbamide? or sulphonurea? or sulphonylurea?).tw,kw. (24771)
205 chlorpropamide/ (8095)
206 (adiaben or apo-chlorpropamide or apochlorpropamide or abemide or "arodoc c" or asucrol or ascurol or biabenal or bioglumin or BRN 2218363 or catanil or CCRIS 155 or chlomide or chlormide or chlorodiabina or chloropropamide or chlorpromide or clorpropamide or copamide or chloronase or chlorpromide or clorpropamide or chloropropamide or chlorpropamid or chlorpropamide or chlorpropamidum or clorpropamid or clorpropamida).tw,kw. (3436)
207 (dabinese or deavynfar or diabaril or diabechlor or diabeedol or diabemide or diabenal or diabenese or diabeneza or diabet-pages or diabetoral or diabexan or diabiclor or diabines or diabinese or diabitex or diabitol or diamel ex or dibecon or dynalase or EINECS 202-314-5 or eubetin or glicoben or glisema or glucamide or glycemin or glymese or HSDB 2051 or hypomide or insilange or insogen or insulase).tw,kw. (735)
208 (melormin or meldian or melitase or mellinese or millinese or NCI-C01752 or NSC 44634 or NSC 626720 or neo-toltinon or oradian or P 607 or pamidin or prodiaben or pubetin or stabinol or tesmel or "p chlorobenzolsulphonylglycolic acid nitrile" or para chlorobenzenesulfonylglycolic acid nitrile or parachlorobenzene sulfonylglycolic acid nitrile or U-3818 or U-9818).tw,kw. (170)
209 94-20-2.rn. (5965)
210 gliclazide/ (6494)
211 (gliclazide or diaglyk or diaikron or diabrezide or diamicron or BRN 1657836 or EINECS 244-260-5 or gen-gliclazide or gliklazid or gliclazida or gliclazidum or glimicron or glyade or glyclazide or glycazide or nordialex or predian or S 1702 or S 852 or SE 1702).tw,kw. (3895)

212 21187-98-4.rn. (5343)
213 glimepiride/ (6341)
214 (glimepiride or amaryl or amarel or BRN 5365754 or CCRIS 7083 or endial or euglim or glemax or glimepirid or glimepirida or glimepiridum or glimerid or glorion or HOE 490 or HOE490 or solosa or "s 80 8490").tw,kw. (3826)
215 93479-97-1.rn. (5849)
216 glibenclamide/ (29928)
217 (adiab or amecladin or apo-glibenclamide or azuglucon or bastiverit or benclamin or betanase or betanese 5 or BRN 2230085 or calabren or clamide or clibenclamide or cytagon or dangbinol or daonil or debtan or diabasan or diabeta or dibelet or duraglucon or EINECS 233-570-6 or euclamin or euglucan or euglucon or euglykon).tw,kw. (1328)
218 (GBN 5 or gen-glybe or gewaglucon or gilemal or glamide or glencamide or gliban or glibeclamid or glibemid or gliben or glibenbeta or glibenclamid or glibenclamida or glibenclamide or glibenclamidum or glibenhexal or glibenil or glibens or glibesyn or glibet or glibetic or glibil or gliboral or glicem or glidiabet or gliformin or glikeyer or glimel or glimide or glimidstada or glisulin or glitisol or glubate or gluben).tw,kw. (18985)
219 (glucobene or glucohexal or glucolon or glucomid or gluconic or glucoremed or glucoven or glukoreduct or glulo or glyamid or glyben or glybencamidum or glybencenamide or glybenclamid or glybenclamide or glybendamine or glybenzyclamide or glybenzcyclamide or glyburide or glycolande or glycomin or glynase or HB 419 or HB 420 or hemi-daonil or hexaglucon or humedia or insol or lederglib or libanil or lisaglucon or locose or lodulce).tw,kw. (7514)
220 (maninil or manoglucon or med-glionil or melix or micronase or miglucan or nadib or neogluconin or norglicem 5 or normoglucon or orabetic or pira or praeciglucon or prodiabet or renabetic or RP-1127 or semi-daonil or semi-euglucon or semi-gliben-puren n or sugril or suraben or tiabet or U 26452 or U-26 452 or UR 606 or yuglucon or xeltic).tw,kw. (751)
221 10238-21-8.rn. (22468)
222 tolbutamide/ (19000)
223 (abemin or aglicem or aglicid or aglycid or apo-tolbutamide or arcosal or arkozal or artosin or artosina or artozin or beglucin or BRN 1984428 or butamid or butamide or butamidum or CCRIS 592 or "D 860" or diabecid or diaben or diabenyl or diabeton or diabesan or diasulfon or diabetamid or diabetol or diabuton or diatol or dirastan or diasulin or diaval or dolipol or drabet).tw,kw. (666)
224 (EINECS 200-594-3 or fresan or glicemin or glicotron or glycotron or guabeta or glyconon or HLS 831 or HSDB 3393 or hypoglycone or ipoglicone or ipoglucos or mermol or metil glucosulfina or mobenol or NCI-C01763 or NSC 23813 or neo antiglycemikos or neo diabetal or neo norboral or neobellin or neoinsoral).tw,kw. (27)
225 (orabet or oralin or oresan or orezan or orinade or orinase or orinaz or orsinon or osdiabet or oterben or pramidex or proinsul or rastinon or SK-tolbutamide or tarasina or tobutamine or tol ortab or tolbet or tolbugen or tolbusal or tolbutamid or tolbutamida or tolbutamide or tolbutamidum or tolbutone or tolbutamte or tolbutol or tolbutylharnstoff or tolbutylurea or tolglybutamide or tolsiran or tolubetin or toluran or tolurast or tosula or toluina or tolumid or toluvan or tolylsulfonylbutylurea or "U 2043" or willbutamide).tw,kw. (12017)
226 64-77-7.rn. (12350)
227 2,4 thiazolidinedione derivative/ (12105)
228 (thiazolidinedione* or TZD or TZDs).tw,kw. (14005)
229 pioglitazone/ (17277)
230 (pioglitazone* or actos or AD 4833 or piomed or U 72107A or U72 107A or cereluc or glidipion or glita or glitase or glustin or paglitaz or pioglit or sepioglin or zactos).tw,kw. (13614)
231 112529-15-4.rn. (0)
232 rosiglitazone/ (17486)
233 (rosiglitazone* or avandia or BRL 49653-C or BRL 49653 or nyracta or rezult or rossini or venvia).tw,kw. (14461)

234	155141-29-0.rn. (16077)
235	glucagon like peptide 1 receptor agonist/ (3677)
236	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 analog*).tw,kw. (4248)
237	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 (receptor? or protein?)).tw,kw. (11326)
238	((glucagon-like peptide-1 or GLP-1 or GLP1 or GLP-1R or GLP1R) adj2 agonist*).tw,kw. (8916)
239	incretin mimetic*.tw,kw. (867)
240	dulaglutide/ (825)
241	(dulaglutide or LY-2189265 or LY2189265 or trulicity).tw,kw. (835)
242	923950-08-7.rn. (698)
243	exendin 4/ (9124)
244	(AC 2993 or AC 2993A or AC-2993 or AC002993 or AC2993 or AC2993A or baietta or byetta or bydureon or DA 3091 or exenatide or exendin 4 or HSDB 7789 or LY 2148568 or LY2148568 or PT302 or Ex4 peptide or ITCA 650).tw,kw. (9196)
245	141758-74-9.rn. (7392)
246	liraglutide/ (8051)
247	(liraglutida or liraglutide or liraglutidum or HSDB 8205 or NN-2211 or NN2211 or NNC 90-1170 or saxenda or victoza).tw,kw. (6760)
248	204656-20-2.rn. (5107)
249	long acting insulin/ (4639)
250	((long-acting or LA or semilente or semi-lente or slow* acting or intermediate-acting) adj (insulin* or analog*)).tw,kw. (4296)
251	insulin detemir/ (3888)
252	(detemir or determir or levemir or NN-304 or NN304).tw,kw. (3202)
253	169148-63-4.rn. (2965)
254	insulin glargine/ (10754)
255	(abasaglar or abasria or basaglar or glargine or HOE-901 or HOE901 or lantus or ly 2963016 or ly2963016 or optisulin or toujeo).tw,kw. (8477)
256	160337-95-1.rn. (7819)
257	short acting insulin/ (1249)
258	((fast-acting or quick-acting or short-acting or rapid* acting) adj (insulin? or analog*)).tw,kw. (3651)
259	insulin aspart/ (5319)
260	(insulin aspart* or (B28 adj1 insulin?) or (B28 adj1 insulin?) or (B28asp* adj1 insulin?) or NovoLog* or NovoMix* or Novo Mix* or NovoRapid*).tw,kw. (3764)
261	116094-23-6.rn. (4225)
262	insulin lispro/ (6017)
263	(lispro or lyspro or humalog or liprolog or ly 275585 or ly275585).tw,kw. (4303)
264	133107-64-9.rn. (4726)
265	isophane insulin/ (8567)
266	(actraphan? or berlinsulin or "humulin i" or "humulin n" or insulatard or (insulin? adj3 monotard) or isophane or (insulin? adj2 NPH) or (insulin? adj2 protamine) or isofane or isophan or isophane or isophone or mixtard or novolin or nph iletin or nph umuline or orgasuline or protaphan or protaphane or protophane or prozinc or (zinc adj2 insulin?) or (zinc adj1 protamine)).tw,kw. (7303)
267	9004-17-5.rn. (6861)
268	(insulin? adj1 regular).tw,kw. (3221)
269	human insulin/ (5090)
270	(insulin? adj1 human).tw,kw. (13899)
271	(h tronin or humulin or nazlin).tw,kw. (1962)
272	pig insulin/ (1781)
273	((insulin? adj1 (pork or porcine or pig or pigs)) or hypurin).tw,kw. (2929)
274	alogliptin plus metformin/ (42)

275	(alogliptin adj3 metformin).tw,kw. (60)
276	(metformin adj2 nesina).tw,kw. (0)
277	(kazano or nesimet or nesina or nesinamet or vipdomet).tw,kw. (113)
278	linagliptin plus metformin/ (67)
279	(linagliptin adj2 metformin).tw,kw. (123)
280	(jentadueto or trajenta duo or trajentamet or trayebta duo or trayenta duo).tw,kw. (44)
281	metformin plus saxagliptin/ (108)
282	(saxagliptin adj3 metformin).tw,kw. (215)
283	(komboglyze or kombiglyze or comboglyze or duoglyze).tw,kw. (54)
284	metformin plus sitagliptin/ (379)
285	(sitagliptin adj3 metformin).tw,kw. (703)
286	(janumet or efficib or gliptamet or Januet or ristfor or velmetia or mk 0431a).tw,kw. (207)
287	dapagliflozin plus metformin/ (49)
288	(metformin adj3 dapagliflozin).tw,kw. (169)
289	(ebymect or Xigduo).tw,kw. (33)
290	empagliflozin plus metformin/ (29)
291	(empagliflozin adj3 metformin).tw,kw. (112)
292	(jardiamet or jardiancemet or synjardy).tw,kw. (22)
293	metformin plus rosiglitazone/ (457)
294	(metformin adj3 rosiglitazone).tw,kw. (918)
295	(avandamet or interac).tw,kw. (359)
296	622402-70-4.rn. (0)
297	glycosidase inhibitor/ (1323)
298	((alpha-amylase or alpha-glucosidase or glucosidase or glycoside) adj2 inhibitor?).tw,kw. (8655)
299	acarbose/ (8691)
300	(acarbose or ag 5421 or ag5421 or alpha ghi or bay g 5421 or bay g5421 or glibose or glicobase or glucobay or gluconase or glucor or glumida or prandase or precise or rebose).tw,kw. (372272)
301	56180-94-0.rn. (7079)
302	meglitinide/ (1690)
303	(hb 699 or hb699 or meglitinide?).tw,kw. (772)
304	repaglinide/ (3561)
305	(actulin or ag ee 388 or ag ee388 or ag ee 623 or ag ee623 or enyglid or gluconorm or novonorm or prandin or rapilan or repaglinide or sestrine).tw,kw. (2171)
306	135062-02-1.rn. (3416)
307	nateglinide/ (2547)
308	(a 4166 or a4166 or ay 4166 or ay4166 or djn 608 or djn608 or fasticor or glinate or nateglinide or sdz djn 608 or sdz djn608 or senaglinide or starlix or starsis or trazec or "ym 026").tw,kw. (1525)
309	105816-04-4.rn. (2475)
310	miglitol/ (1472)
311	(bay 1099 or bay m 1099 or bay m1099 or bay1099 or diastabol or glyset or miglitol or plumarol).tw,kw. (971)
312	72432-03-2.rn. (1423)
313	voglibose/ (1101)
314	(ao 128 or ao128 or basen or "en 116 077" or en 116077 or "en116 077" or en116077 or glustat or voglibose).tw,kw. (846)
315	83480-29-9.rn. (1022)
316	or/164-315 (707481)
317	161 and 316 (169312)
318	randomized controlled trial/ or controlled clinical trial/ (1257404)
319	exp "clinical trial (topic)"/ (275391)
320	(randomi#ed or randomly or RCT$1 or placebo*).tw. (2067603)

321	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (380901)
322	trial.ti. (448696)
323	or/318-322 (2829313)
324	317 and 323 (32812)
325	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47637775)
326	exp human/ or exp human experimentation/ or exp human experiment/ (37488600)
327	325 not 326 (10150880)
328	324 not 327 (31656)
329	exp Juvenile/ not (exp Adult/ and exp Juvenile/) (2327849)
330	328 not 329 (31425)
331	editorial.pt. (1047845)
332	letter.pt. not (letter.pt. and randomized controlled trial/) (2026247)
333	330 not (331 or 332) (30886)
334	(2017* or 2018*).dc. (3127449)
335	333 and 334 [UPDATE RECORDS] (3795)
336	335 use emczd [EMBASE UPDATE RECORDS] (3795)
337	155 or 336 [BOTH DATABASES - UPDATE PERIOD] (5156)
338	remove duplicates from 337 (4127) [TOTAL UNIQUE RECORDS – UPDATE PERIOD]
339	338 use medall [MEDLINE UNIQUE RECORDS - UPDATE PERIOD] (1353)
340	338 use emczd [EMBASE UNIQUE RECORDS - UPDATE PERIOD] (2774)

COCHRANE LIBRARY

ID	SEARCH	HITS
#1	[mh "Diabetes Mellitus, Type 2"]	14582
#2	[mh "Diabetes Mellitus"]	6987
#3	((adult or "ketosis-resistant" or matur* or late or ("non-insulin" next depend*) or (noninsulin next depend*) or slow or stable or "type 2" or "type II" or lipoatrophic) near/3 diabet*):ti,ab,kw	28789
#4	(MODY or NIDDM or T2DM):ti,ab,kw	5157
#5	{or #1-#4}	32515
#6	MeSH descriptor: ["Diabetes Mellitus, Type 2"] explode all trees and with qualifier(s): [DT - DT]	5463
#7	MeSH descriptor: ["Drug Combinations"] explode all trees	13155
#8	MeSH descriptor: ["Drug Therapy, Combination"] explode all trees	28531
#9	#6 and (#7 or #8)	1305
#10	MeSH descriptor: ["Hypoglycemic Agents"] explode all trees	7149
#11	(antidiabetic* or (anti next diabetic*) or antihyperglycemic* or antihyperglycaemic* or (anti next hyperglycemic*) or (anti next hyperglycaemic*) or hypoglycemic* or hypoglycaemic* or antidiabetes or (anti next diabetes)):ti,ab,kw	11738

#12	MeSH descriptor: ["Dipeptidyl-Peptidase IV Inhibitors"] explode all trees	493
#13	((DPP4 or "DPP 4" or "DPP IV") near/1 inhibitor*):ti,ab,kw	793
#14	("dipeptidyl-peptidase IV" near/2 inhibitor*):ti,ab,kw	867
#15	("dipeptidyl-peptidase 4" near/2 inhibitor*):ti,ab,kw	513
#16	(gliptin or gliptins):ti,ab,kw	28
#17	(alogliptin or nesina or "SYR 322" or SYR322 or "HSDB 8203" or incresina or vipidia):ti,ab,kw	182
#18	MeSH descriptor: [Linagliptin] explode all tree	187
#19	(linagliptin or "BI 1356" or ONDERO or tradjenta or trajenta or trayenta or trazenta):ti,ab,kw	389
#20	(saxagliptin or "BMS 477118" or BMS477118 or "HSDB 8199" or Onglyza or "OPC 262"):ti,ab,kw	329
#21	MeSH descriptor: ["Sitagliptin Phosphate"] explode all trees	604
#22	(sitagliptin or "EC 690-730-1" or Glactiv or "HSDB 7516" or januvia or "mk 0431" or mk0431 or "mk 431" or "ono 5435" or ristaben or sitagliptine or tesabel or tesavel or xelevia):ti,ab,kw	1221
#23	MeSH descriptor: ["Sodium-Glucose Transporter 2"] explode all trees and with qualifier(s): [AI - AI]	150
#24	(("sodium-glucose transporter 2" or "sodium-glucose cotransporter 2") next inhibitor*):ti,ab,kw	251
#25	(("sodium-glucose transporter 2" or "sodium-glucose co-transporter 2") next inhibitor*):ti,ab,kw	146
#26	(("SGLT-2" or SGLT2) next inhibitor*):ti,ab,kw	467
#27	(("sodium dependent glucose transporter 2" or "sodium dependent glucose cotransporter 2") next inhibitor*):ti,ab,kw	3
#28	(("sodium dependent glucose transporter 2" or "sodium dependent glucose co-transporter 2") next inhibitor*):ti,ab,kw	2
#29	(gliflozin or gliflozins):ti,ab,kw	4
#30	MeSH descriptor: [Canagliflozin] explode all trees	151
#31	(canagliflozin or Invokana or (JNJ next 24831754*) or "JNJ 28431754" or "TA 7284" or Prominad):ti,ab,kw	338
#32	(dapagliflozin or "BMS 512148" or BMS512148 or edistride or forxiga or farxiga):ti,ab,kw	491
#33	(empagliflozin or "BI 10773" or BI10773 or Jardiance):ti,ab,kw	493
#34	MeSH descriptor: ["Sulfonylurea Compounds"] explode all trees	684
#35	(sulfonylurea* or sulfonurea* or (sulfonyl next urea*) or sulfonylcarbamide* or sulphonurea* or sulphonylurea*):ti,ab,kw	2436
#36	MeSH descriptor: [Chlorpropamide] explode all trees	74
#37	(adiaben or "apo-chlorpropamide" or apochlorpropamide or abemide or "arodoc c" or asucrol or ascurol or biabenal or bioglumin or "BRN 2218363" or catanil or "CCRIS 155" or chlomide or chlormide or	129

	chlorodiabina or chloropropamide or chlorpromide or clorpropamide or copamide or chloronase or chlorpromide or clorpropamide or chloropropamide or chlorpropamid or chlorpropamide or chlorpropamidum or clorpropamid or clorpropamida):ti,ab,kw	
#38	(dabinese or deavynfar or diabaril or diabechlor or diabeedol or diabemide or diabenal or diabenese or diabeneza or "diabet-pages" or diabetoral or diabexan or diabiclor or diabines or diabinese or diabitex or diabitol or "diamel ex" or dibecon or dynalase or "EINECS 202-314-5" or eubetin or glicoben or glisema or glucamide or glycemin or glymese or "HSDB 2051" or hypomide or insilange or insogen or insulase):ti,ab,kw	3
#39	(melormin or meldian or melitase or mellinese or millinese or "NCI-C01752" or "NSC 44634" or "NSC 626720" or "neo-toltinon" or oradian or "P 607" or pamidin or prodiaben or pubetin or stabinol or tesmel or "p chlorobenzolsulphonylglycolic acid nitrile" or "para chlorobenzenesulfonylglycolic acid nitrile" or "parachlorobenzene sulfonylglycolic acid nitrile" or "U-3818" or "U-9818"):ti,ab,kw	11
#40	MeSH descriptor: [Gliclazide] explode all trees	197
#41	(gliclazide or diaglyk or diaikron or diabrezide or diamicron or "BRN 1657836" or "EINECS 244-260-5" or "gen-gliclazide" or gliklazid or gliclazida or gliclazidum or glimicron or glyade or glyclazide or glycazide or nordialex or predian or "S 1702" or "S 852" or "SE 1702"):ti,ab,kw	486
#42	(glimepiride or amaryl or amarel or "BRN 5365754" or "CCRIS 7083" or endial or euglim or glemax or glimepirid or glimepirida or glimepiridum or glimerid or glorion or "HOE 490" or HOE490 or solosa or "s 80 8490"):ti,ab,kw	867
#43	MeSH descriptor: [Glyburide] explode all trees	568
#44	(adiab or amecladin or "apo-glibenclamide" or azuglucon or bastiverit or benclamin or betanase or "betanese 5" or "BRN 2230085" or calabren or clamide or clibenclamide or cytagon or dangbinol or daonil or debtan or diabasan or diabeta or dibelet or duraglucon or "EINECS 233-570-6" or euclamin or euglucan or euglucon or euglykon):ti,ab,kw	256
#45	("GBN 5" or "gen-glybe" or gewaglucon or gilemal or glamide or glencamide or gliban or glibeclamid or glibemid or gliben or glibenbeta or glibenclamid or glibenclamida or glibenclamide or glibenclamidum or glibenhexal or glibenil or glibens or glibesyn or glibet or glibetic or glibil or gliboral or glicem or glidiabet or gliformin or glikeyer or glimel or glimide or glimidstada or glisulin or glitisol or glubate or gluben):ti,ab,kw	873
#46	(glucobene or glucohexal or glucolon or glucomid or gluconic or glucoremed or glucoven or glukoreduct or glulo or glyamid or glyben or glybencamidum or glybencenamide or glybenclamid or glybenclamide or glybendamine or glybenzyclamide or glybenzcyclamide or glyburide or glycolande or glycomin or glynase or "HB 419" or "HB 420" or "hemi-daonil" or hexaglucon or humedia or insol or lederglib or libanil or lisaglucon or locose or lodulce):ti,ab,kw	725
#47	(maninil or manoglucon or "med-glionil" or melix or micronase or miglucan or nadib or neogluconin or "norglicem 5" or normoglucon or	21

	orabetic or pira or praeciglucon or prodiabet or renabetic or "RP-1127" or "semi-daonil" or "semi-euglucon" or "semi-gliben-puren n" or sugril or suraben or tiabet or "U 26452" or "U-26 452" or "UR 606" or yuglucon or xeltic):ti,ab,kw	
#48	MeSH descriptor: [Tolbutamide] explode all trees	143
#49	(abemin or aglicem or aglicid or aglycid or "apo-tolbutamide" or arcosal or arkozal or artosin or artosina or artozin or beglucin or "BRN 1984428" or butamid or butamide or butamidum or "CCRIS 592" or "D 860" or diabecid or diaben or diabenyl or diabeton or diabesan or diasulfon or diabetamid or diabetol or diabuton or diatol or dirastan or diasulin or diaval or dolipol or drabet):ti,ab,kw	2
#50	("EINECS 200-594-3" or fresan or glicemin or glicotron or glycotron or guabeta or glyconon or "HLS 831" or "HSDB 3393" or hypoglycone or ipoglicone or ipoglucos or mermol or "metil glucosulfina" or mobenol or "NCI-C01763" or "NSC 23813" or "neo antiglycemikos" or "neo diabetal" or "neo norboral" or neobellin or neoinsoral):ti,ab,kw	0
#51	(orabet or oralin or oresan or orezan or orinade or orinase or orinaz or orsinon or osdiabet or oterben or pramidex or proinsul or rastinon or "SK-tolbutamide" or tarasina or tobutamine or tol ortab or tolbet or tolbugen or tolbusal or tolbutamid or tolbutamida or tolbutamide or tolbutamidum or tolbutone or tolbutamte or tolbutol or tolbutylharnstoff or tolbutylurea or tolglybutamide or tolsiran or tolubetin or toluran or tolurast or tosula or toluina or tolumid or toluvan or tolylsulfonylbutylurea or "U 2043" or willbutamide):ti,ab,kw	247
#52	MeSH descriptor: [Thiazolidinediones] explode all trees	1260
#53	(thiazolidinedione* or TZD or TZDs):ti,ab,kw	1741
#54	(pioglitazone* or actos or "AD 4833" or piomed or "U 72107A" or "U72 107A" or cereluc or glidipion or glita or glitase or glustin or paglitaz or pioglit or sepioglin or zactos):ti,ab,kw	2342
#55	(rosiglitazone* or avandia or "BRL 49653-C" or "BRL 49653" or nyracta or rezult or rossini or venvia):ti,ab,kw	958
#56	MeSH descriptor: ["Glucagon-Like Peptide 1"] explode all trees and with qualifier(s): [AA - AA]	147
#57	(("glucagon-like peptide-1" or "GLP-1" or GLP1 or "GLP-1R" or GLP1R) near/2 analog*):ti,ab,kw	434
#58	MeSH descriptor: ["Glucagon-Like Peptide-1 Receptor"] explode all trees	129
#59	(("glucagon-like peptide-1" or "GLP-1" or GLP1 or "GLP-1R" or GLP1R) near/2 (receptor* or protein*)):ti,ab,kw	963
#60	MeSH descriptor: ["Receptors, Glucagon"] explode all trees and with qualifier(s): [AG - AG]	37
#61	(("glucagon-like peptide-1" or "GLP-1" or GLP1 or "GLP-1R" or GLP1R) near/2 agonist*):ti,ab,kw	829
#62	(incretin next mimetic*):ti,ab,kw	33
#63	(dulaglutide or "LY-2189265" or LY2189265 or trulicity):ti,ab,kw	181

#64	("AC 2993" or "AC 2993A" or "AC-2993" or AC002993 or AC2993 or AC2993A or baietta or byetta or bydureon or "DA 3091" or exenatide or "exendin 4" or "HSDB 7789" or "LY 2148568" or "LY2148568" or PT302 or "Ex4 peptide" or "ITCA 650"):ti,ab,kw	850
#65	MeSH descriptor: [Liraglutide] explode all trees	464
#66	(liraglutida or liraglutide or liraglutidum or "HSDB 8205" or "NN-2211" or NN2211 or "NNC 90-1170" or saxenda or victoza):ti,ab,kw	1138
#67	MeSH descriptor: ["Insulin, Long-Acting"] explode all trees	1525
#68	(("long-acting" or LA or semilente or semi-lente or (slow* next acting) or "intermediate-acting") next (insulin* or analog*)):ti,ab,kw	384
#69	MeSH descriptor: ["Insulin Detemir"] explode all trees	237
#70	(detemir or determir or levemir or "NN-304" or NN304):ti,ab,kw	493
#71	MeSH descriptor: ["Insulin Glargine"] explode all trees	847
#72	(abasaglar or abasria or basaglar or glargine or "HOE-901" or HOE901 or lantus or "ly 2963016" or ly2963016 or optisulin or toujeo):ti,ab,kw	1756
#73	MeSH descriptor: ["Insulin, Short-Acting"] explode all trees	991
#74	(("fast-acting" or "quick-acting" or "short-acting" or (rapid* next acting)) next (insulin* or analog*)):ti,ab,kw	572
#75	((insulin next aspart*) or (B28 near/1 insulin*) or (B28 near/1 insulin*) or (B28asp* near/1 insulin*) or NovoLog* or NovoMix* or (Novo next Mix*) or NovoRapid*):ti,ab,kw	1018
#76	(lispro or lyspro or humalog or liprolog):ti,ab,kw	861
#77	(apidra or glulisine):ti,ab,kw	229
#78	MeSH descriptor: ["Insulin, Isophane"] explode all trees	449
#79	(actraphan* or berlinsulin or "humulin i" or "humulin n" or insulatard or (insulin* near/3 monotard) or isophane or (insulin* near/2 NPH) or (insulin* near/2 protamine) or isofane or isophan or isophane or isophone or mixtard or novolin or "nph iletin" or "nph umuline" or orgasuline or protaphan or protaphane or protophane or prozinc or (zinc near/2 insulin*) or (zinc near/1 protamine)):ti,ab,kw	2171
#80	MeSH descriptor: [Insulin] explode all trees	12597
#81	(insulin* near/1 regular):ti,ab,kw	498
#82	(insulin* near/1 human):ti,ab,kw	3979
#83	((nph next insulin*) or humulin or novolin):ti,ab,kw	513
#84	((insulin* near/1 (pork or porcine or pig or pigs)) or hypurin):ti,ab,kw	206
#85	(alogliptin near/3 metformin):ti,ab,kw	32
#86	(metformin near/2 nesina):ti,ab,kw	0
#87	(kazano or nesimet or nesina or nesinamet or vipdomet):ti,ab,kw	1
#88	(linagliptin near/2 metformin):ti,ab,kw	81
#89	(jentadueto or "trajenta duo" trajentamet or "trayebta duo" or "trayenta duo"):ti,ab,kw	1
#90	(saxagliptin near/3 metformin):ti,ab,kw	107
#91	(komboglyze or kombiglyze or comboglyze or duoglyze):ti,ab,kw	2

#92	MeSH descriptor: ["Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"] explode all trees	2
#93	(sitagliptin near/3 metformin):ti,ab,kw	287
#94	(janumet or efficib or gliptamet or Januet or ristfor or velmetia or "mk 0431a"):ti,ab,kw	10
#95	(metformin near/3 dapagliflozin):ti,ab,kw	97
#96	(ebymect or xigduo):ti,ab,kw	1
#97	(empagliflozin near/3 metformin):ti,ab,kw	59
#98	(jardiamet or jardiancemet or synjardy):ti,ab,kw	0
#99	(metformin near/3 rosiglitazone):ti,ab,kw	221
#100	(avandamet or interac):ti,ab,kw	17
#101	MeSH descriptor: ["Glycoside Hydrolase Inhibitors"] explode all trees	162
#102	(("alpha-amylase" or "alpha-glucosidase" or glucosidase or glycoside) near/2 inhibitor*)	524
#103	MeSH descriptor: [Acarbose] explode all trees	300
#104	(acarbose or "ag 5421" or ag5421 or "alpha ghi" or "bay g 5421" or "bay g5421" or glibose or glicobase or glucobay or gluconase or glucor or glumida or prandase or precise or rebose):ti,ab,kw	4137
#105	("hb 699" or hb699 or meglitinide*):ti,ab,kw	57
#106	(actulin or "ag ee 388" or "ag ee388" or "ag ee 623" or "ag ee623" or enyglid or gluconorm or novonorm or prandin or rapilan or repaglinide or sestrine):ti,ab,kw	267
#107	("a 4166" or a4166 or "ay 4166" or ay4166 or "djn 608" or djn608 or fasticor or glinate or nateglinide or "sdz djn 608" or "sdz djn608" or senaglinide or starlix or starsis or trazec or "ym 026"):ti,ab,kw	186
#108	("bay 1099" or "bay m 1099" or "bay m1099" or bay1099 or diastabol or glyset or miglitol or plumarol):ti,ab,kw	148
#109	("ao 128" or ao128 or basen or "en 116 077" or "en 116077" or "en116 077" or en116077 or glustat or voglibose):ti,ab,kw	165
#110	{or #9-#109}	33422
#111	#5 and #110 with Publication Year from 2017 to 2018, in Trials	1917
#112	#5 and #110 with Cochrane Library publication date Between Jan 2017 and Dec 2018, in Trials	5253
#113	#111 OR #112	5254

CENTRAL - 5254

PubMed

SEARCH	QUERY	ITEMS FOUND
#89	Search #87 AND #88	174

#88	Search publisher[sb] OR 2018/10/01:2018/10/11[edat]	544515
#87	Search #84 NOT (#85 OR #86)	15273
#86	Search letter[pt] NOT (letter[pt] AND randomized controlled trial[pt])	996762
#85	Search comment[pt] OR editorial[pt] OR interview[pt] OR news[pt] OR newspaper article[pt]	1285807
#84	Search #79 NOT #83	15839
#83	Search #80 OR #82 OR #82	1233544
#82	Search Infant[mesh] not (Adult[mesh] and Infant[mesh])	790663
#81	Search Child[mesh] not (Adult[mesh] and Child[mesh])	1133614
#80	Search Adolescent[mesh] not (Adult[mesh] and Adolescent[mesh])	564313
#79	Search #77 NOT #78	15990
#78	Search Animals[mesh] NOT (Animals[mesh] AND humans[mesh])	4503231
#77	Search #75 AND #76	16384
#76	Search #4 AND #69	93004
#75	Search #70 OR #71 or #72 or #73 OR #74	1297011
#74	Search trial [ti]	188195
#73	Search single blind*[tw] OR single mask*[tw] OR single dumm*[tw] OR double blind*[tw] OR double mask*[tw] OR double dumm*[tw] OR triple blind*[tw] OR triple mask*[tw] OR triple dumm*[tw] OR treble blind*[tw] OR treble mask*[tw] OR treble dumm*[tw]	218835
#72	Search randomised[tw] OR randomized[tw] OR randomly[tw] or RCT[tw] OR RCTs[tw] OR placebo*[tw]	1032461
#71	Search "clinical trials as topic"[mesh]	318183
#70	Search controlled clinical trial[pt] OR randomized controlled trial[pt]	557776
#69	Search #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68	433290
#68	Search "ao 128"[tw] OR ao128[tw] OR basen[tw] OR "en 116 077"[tw] OR "en 116077"[tw] OR "en116 077"[tw] OR en116077[tw] OR glustat[tw] OR voglibose[tw]	328
#67	Search "hb 699"[tw] OR hb699[tw] OR meglitinide*[tw] OR actulin[tw] OR "ag ee 388"[tw] OR "ag ee388"[tw] OR "ag ee 623"[tw] OR "ag ee623"[tw] OR enyglid[tw] OR gluconorm[tw] OR novonorm[tw] OR prandin[tw] OR rapilan[tw] OR repaglinide[tw] OR sestrine[tw] OR "a 4166"[tw] OR a4166[tw] OR "ay 4166"[tw] OR ay4166[tw] OR "djn	1720

	608"[tw] OR djn608[tw] OR fasticor[tw] OR glinate[tw] OR nateglinide[tw] OR sdz djn 608[tw] OR sdz djn608[tw] OR senaglinide[tw] OR starlix[tw] OR starsis[tw] OR trazec[tw] OR "ym 026"[tw] OR "bay 1099"[tw] OR "bay m 1099"[tw] OR "bay m1099"[tw] OR bay1099[tw] OR diastabol[tw] OR glyset[tw] OR miglitol[tw] OR plumarol[tw] OR 0V5436JAQW[EC/RN Number]	
#66	Search acarbose[tw] OR "ag 5421"[tw] OR ag5421[tw] OR "alpha ghi"[tw] OR "bay g 5421"[tw] OR "bay g5421"[tw] OR glibose[tw] OR glicobase[tw] OR glucobay[tw] OR gluconase[tw] OR glucor[tw] OR glumida[tw] OR prandase[tw] OR precise[tw] OR rebose[tw] OR T58MSI464G[EC/RN Number]	161588
#65	Search Acarbose[mesh]	1275
#64	Search alpha-amylase inhibitor*[tw] OR alpha-glucosidase inhibitor*[tw] OR glucosidase inhibitor*[tw] OR glycoside inhibitor*[tw]	3335
#63	Search Glycoside Hydrolase Inhibitors[mesh]	2341
#62	Search (sitagliptin[tw] AND metformin[tw]) OR janumet[tw] OR efficib[tw] OR gliptamet[tw] OR Januet[tw] OR ristfor[tw] OR velmetia[tw] OR "mk 0431a"[tw] OR (metformin[tw] AND dapagliflozin[tw]) OR ebymect[tw] OR xigduo[tw] OR (empagliflozin[tw] AND metformin[tw]) OR jardiamet[tw] OR jardiancemet[tw] OR synjardy[tw] OR (metformin[tw] AND rosiglitazone[tw]) OR avandamet[tw] OR interac[tw]	1671
#61	Search "Sitagliptin Phosphate, Metformin Hydrochloride Drug Combination"[mesh]	7
#60	Search (alogliptin[tw] AND metformin[tw]) OR (nesina[tw] AND metformin[tw]) OR kazano[tw] OR nesimet[tw] OR nesina[tw] OR nesinamet[tw] OR vipdomet[tw] OR (linagliptin[tw] AND metformin[tw]) OR jentadueto[tw] OR trajenta duo[tw] OR trajentamet[tw] OR trayebta duo[tw] OR trayenta duo[tw] OR (saxagliptin[tw] AND metformin[tw]) OR komboglyze[tw] OR kombiglyze[tw] OR comboglyze[tw] OR duoglyze[tw]	1758
#59	Search pork insulin*[tw] OR porcine insulin*[tw] OR pig insulin*[tw] OR pigs insulin*[tw] OR hypurin[tw]	8175
#58	Search regular insulin*[tw] OR human insulin*[tw] OR nph insulin*[tw] OR humulin[tw] OR novolin[tw]	8152
#57	Search Insulin [mesh]	177173
#56	Search actraphan*[tw] OR berlinsulin[tw] OR "humulin i"[tw] OR "humulin n"[tw] OR insulatard[tw] OR (insulin*[tw] AND monotard[tw]) OR isophane[tw] OR (insulin*[tw] AND NPH[tw]) OR (insulin*[tw] AND protamine[tw]) OR isofane[tw] OR isophan[tw] OR isophane[tw] OR	3913

	isophone[tw] OR mixtard[tw] OR novolin[tw] OR “nph iletin”[tw] OR nph umuline[tw] OR orgasuline[tw] OR protaphan[tw] OR protaphane[tw] OR protophane[tw] OR prozinc[tw] OR zinc insulin*[tw] OR zinc protamine[tw] OR protamine zinc[tw] OR 2ZM8CX04RZ[EC/RN Number]	
#55	Search Insulin, Isophane[mesh]	992
#54	Search lispro[tw] OR lyspro[tw] OR humalog[tw] OR liprolog[tw] OR apidra[tw] OR glulisine[tw] OR 7XIY785AZD[EC/RN Number]	1491
#55	Search Insulin, Isophane[mesh]	992
#54	Search lispro[tw] OR lyspro[tw] OR humalog[tw] OR liprolog[tw] OR apidra[tw] OR glulisine[tw] OR 7XIY785AZD[EC/RN Number]	1491
#53	Search fast-acting insulin*[tw] OR quick-acting insulin*[tw] OR short-acting insulin*[tw] OR rapid acting insulin*[tw] OR rapidly acting insulin*[tw] OR fast-acting analog*[tw] OR quick-acting analog*[tw] OR short-acting analog*[tw] OR rapid acting analog*[tw] OR rapidly acting analog*[tw] OR insulin aspart*[tw] OR B28 insulin*[tw] OR B28 insulin*[tw] OR B28asp insulin*[tw] OR NovoLog*[tw] OR NovoMix*[tw] OR Novo Mix*[tw] OR NovoRapid*[tw] OR D933668QVX[EC/RN Number]	4382
#52	Search Insulin, Short-Acting[mesh]	1455
#51	Search abasaglar[tw] OR abasria[tw] OR basaglar[tw] OR glargine[tw] OR "HOE-901"[tw] OR HOE901[tw] OR lantus[tw] OR ly 2963016[tw] OR ly2963016[tw] OR optisulin[tw] OR toujeo[tw] OR 2ZM8CX04RZ[EC/RN Number]	2605
#50	Search Insulin Glargine[mesh]	1608
#49	Search detemir[tw] OR determir[tw] OR levemir[tw] OR "NN-304"[tw] OR NN304[tw] OR 4FT78T86XV[EC/RN Number]	970
#48	Search Insulin Detemir[mesh]	517
#47	Search long-acting insulin*[tw] OR LA insulin*[tw] OR semilente insulin*[tw] OR semi-lente insulin*[tw] OR slow acting insulin*[tw] OR slower acting insulin*[tw] OR intermediate-acting insulin*[tw] OR long-acting analog*[tw] OR LA analog*[tw] OR semilente analog*[tw] OR semi-lente analog*[tw] OR slow acting analog*[tw] OR slower acting analog*[tw] OR intermediate-acting analog*[tw]	3977
#46	Search Insulin, Long-Acting[mh:noexp]	2750
#45	Search liraglutida[tw] OR liraglutide[tw] OR liraglutidum[tw] OR "HSDB 8205"[tw] OR "NN-2211"[tw] OR NN2211[tw] OR "NNC 90-1170"[tw] OR saxenda[tw] OR victoza[tw] OR 839I73S42A[EC/RN Number]	2224
#44	Search Liraglutide[mesh]	1291
#43	Search "AC 2993"[tw] OR "AC 2993A"[tw] OR "AC-2993"[tw] OR AC002993[tw] OR AC2993[tw] OR AC2993A[tw] OR baietta[tw] OR	3268

	byetta[tw] OR bydureon[tw] OR "DA 3091"[tw] OR exenatide[tw] OR "exendin 4"[tw] OR "HSDB 7789"[tw] OR LY 2148568[tw] OR LY2148568[tw] OR PT302[tw] OR "Ex4 peptide"[tw] OR "ITCA 650"[tw] OR 9P1872D4OL[EC/RN Number]	
#42	Search glucagon-like peptide-1 agonist*[tw] OR GLP-1 agonist*[tw] OR GLP1 agonist*[tw] OR GLP-1R agonist*[tw] OR GLP1R agonist*[tw] OR incretin mimetic*[tw] OR dulaglutide[tw] OR LY-2189265[tw] OR LY2189265[tw] OR trulicity[tw] OR WTT295HSY5[EC/RN Number]	1534
#41	Search "receptors, glucagon/agonists"[MeSH Terms]	728
#40	Search glucagon-like peptide-1 receptor*[tw] OR GLP-1 receptor*[tw] OR GLP1 receptor*[tw] OR GLP-1R receptor*[tw] OR GLP1R receptor*[tw] OR glucagon-like peptide-1 protein*[tw] OR GLP-protein*[tw] OR GLP1 protein*[tw] OR GLP-1R protein*[tw] OR GLP1R protein*[tw]	7815
#39	Search Glucagon-Like Peptide-1 Receptor[mesh]	2293
#38	Search glucagon-like peptide-1 analog*[tw] OR GLP-1 analog*[tw] OR GLP1 analog*[tw] OR GLP-1R analog*[tw] OR GLP1R analog*[tw]	1641
#37	Search "glucagon like peptide 1/analogs and derivatives"[MeSH]	1120
#36	Search rosiglitazone*[tw] OR avandia[tw] OR "BRL 49653-C"[tw] OR "BRL 49653"[tw] OR nyracta[tw] OR rezult[tw] OR rossini[tw] OR venvia[tw] OR 05V02F2KDG[EC/RN Number]	6142
#35	Search thiazolidinedione*[tw] OR TZD[tw] OR TZDs[tw] OR pioglitazone*[tw] OR actos[tw] OR "AD 4833"[tw] OR piomed[tw] OR "U 72107A"[tw] OR "U72 107A"[tw] OR cereluc[tw] OR glidipion[tw] OR glita[tw] OR glitase[tw] OR glustin[tw] OR paglitaz[tw] OR pioglit[tw] OR sepioglin[tw] OR zactos[tw] OR X4OV71U42S[EC/RN Number]	14534
#34	Search Thiazolidinediones[mesh]	11040
#33	Search abemin[tw] OR aglicem[tw] OR aglicid[tw] OR aglycid[tw] OR apo-tolbutamide[tw] OR arcosal[tw] OR arkozal[tw] OR artosin[tw] OR artosina[tw] OR artozin[tw] OR beglucin[tw] OR "BRN 1984428"[tw] OR butamid[tw] OR butamide[tw] OR butamidum[tw] OR "CCRIS 592"[tw] OR "D 860"[tw] OR diabecid[tw] OR diaben[tw] OR diabenyl[tw] OR diabeton[tw] OR diabesan[tw] OR diasulfon[tw] OR diabetamid[tw] OR diabetol[tw] OR diabuton[tw] OR diatol[tw] OR dirastan[tw] OR diasulin[tw] OR diaval[tw] OR dolipol[tw] OR drabbet[tw] OR EINECS 200-594-3[tw] OR fresan[tw] OR glicemin[tw] OR glicotron[tw] OR glycotron[tw] OR guabeta[tw] OR glyconon[tw] OR "HLS 831"[tw] OR "HSDB 3393"[tw] OR hypoglycone[tw] OR ipoglicone[tw] OR ipoglucos[tw] OR mermol[tw] OR metil glucosulfina[tw] OR mobenol[tw] OR NCI-C01763[tw] OR NSC 23813[tw] OR neo antiglycemikos[tw] OR neo diabetal[tw] OR neo norboral[tw] OR neobellin[tw] OR neoinsoral[tw] OR orabet[tw] OR oralin[tw] OR oresan[tw] OR orezan[tw] OR orinade[tw] OR orinase[tw] OR orinaz[tw]	6775

	OR orsinon[tw] OR osdiabet[tw] OR oterben[tw] OR pramidex[tw] OR proinsul[tw] OR rastinon[tw] OR SK-tolbutamide[tw] OR tarasina[tw] OR tobutamine[tw] OR tol ortab[tw] OR tolbet[tw] OR tolbugen[tw] OR tolbusal[tw] OR tolbutamid[tw] OR tolbutamida[tw] OR tolbutamide[tw] OR tolbutamidum[tw] OR tolbutone[tw] OR tolbutamte[tw] OR tolbutol[tw] OR tolbutylharnstoff[tw] OR tolbutylurea[tw] OR tolglybutamide[tw] OR tolsiran[tw] OR tolubetin[tw] OR toluran[tw] OR tolurast[tw] OR tosula[tw] OR toluina[tw] OR tolumid[tw] OR toluvan[tw] OR tolylsulfonylbutylurea[tw] OR "U 2043"[tw] OR willbutamide[tw] OR 982XCM1FOI[EC/RN Number]	
#32	Search Tolbutamide[mesh]	5227
#31	Search glucobene[tw] OR glucohexal[tw] OR glucolon[tw] OR glucomid[tw] OR gluconic[tw] OR glucoremed[tw] OR glucoven[tw] OR glukoreduct[tw] OR glulo[tw] OR glyamid[tw] OR glyben[tw] OR glybencamidum[tw] OR glybencenamide[tw] OR glybenclamid[tw] OR glybenclamide[tw] OR glybendamine[tw] OR glybenzyclamide[tw] OR glybenzcyclamide[tw] OR glyburide[tw] OR glycolande[tw] OR glycomin[tw] OR glynase[tw] OR "HB 419"[tw] OR "HB 420"[tw] OR hemi-daonil[tw] OR hexaglucon[tw] OR humedia[tw] OR insol[tw] OR lederglib[tw] OR libanil[tw] OR lisaglucon[tw] OR locose[tw] OR lodulce[tw] OR maninil[tw] OR manoglucon[tw] OR med-glionil[tw] OR melix[tw] OR micronase[tw] OR miglucan[tw] OR nadib[tw] OR neogluconin[tw] OR "norglicem 5"[tw] OR normoglucon[tw] OR orabetic[tw] OR pira[tw] OR praeciglucon[tw] OR prodiabet[tw] OR renabetic[tw] OR "RP-1127"[tw] OR semi-daonil[tw] OR semi-euglucon[tw] OR semi-gliben-puren n[tw] OR sugril[tw] OR suraben[tw] OR tiabet[tw] OR "U 26452"[tw] OR "U-26 452"[tw] OR "UR 606"[tw] OR yuglucon[tw] OR xeltic[tw] OR SX6K58TVWC[EC/RN Number]	8827
#30	Search adiab[tw] OR amecladin[tw] OR apo-glibenclamide[tw] OR azuglucon[tw] OR bastiverit[tw] OR benclamin[tw] OR betanase[tw] OR "betanese 5"[tw] OR "BRN 2230085"[tw] OR calabren[tw] OR clamide[tw] OR clibenclamide[tw] OR cytagon[tw] OR dangbinol[tw] OR daonil[tw] OR debtan[tw] OR diabasan[tw] OR diabeta[tw] OR dibelet[tw] OR duraglucon[tw] OR EINECS 233-570-6[tw] OR euclamin[tw] OR euglucan[tw] OR euglucon[tw] OR euglykon[tw] OR "GBN 5"[tw] OR gen-glybe[tw] OR gewaglucon[tw] OR gilemal[tw] OR glamide[tw] OR glencamide[tw] OR gliban[tw] OR glibeclamid[tw] OR glibemid[tw] OR gliben[tw] OR glibenbeta[tw] OR glibenclamid[tw] OR glibenclamida[tw] OR glibenclamide[tw] OR glibenclamidum[tw] OR glibenhexal[tw] OR glibenil[tw] OR glibens[tw] OR glibesyn[tw] OR glibet[tw] OR glibetic[tw] OR glibil[tw] OR gliboral[tw] OR glicem[tw] OR	8018

	glidiabet[tw] OR gliformin[tw] OR glikeyer[tw] OR glimel[tw] OR glimide[tw] OR glimidstada[tw] OR glisulin[tw] OR glitisol[tw] OR glubate[tw] OR gluben[tw]	
#29	Search Glyburide[mesh]	6040
#28	Search glimepiride[tw] OR amaryl[tw] OR amarel[tw] OR "BRN 5365754" [tw] OR "CCRIS 7083" [tw] OR endial[tw] OR euglim[tw] OR glemax[tw] OR glimepirid[tw] OR glimepirida[tw] OR glimepiridum[tw] OR glimerid[tw] OR glorion[tw] OR "HOE 490" [tw] OR HOE490[tw] OR solosa[tw] OR "s 80 8490"[tw] OR 6KY687524K[EC/RN Number]	1290
#27	Search gliclazide[tw] OR diaglyk[tw] OR diaikron[tw] OR diabrezide[tw] OR diamicron[tw] OR "BRN 1657836"[tw] OR EINECS 244-260-5[tw] OR gen-gliclazide[tw] OR gliklazid[tw] OR gliclazida[tw] OR gliclazidum[tw] OR glimicron[tw] OR glyade[tw] OR glyclazide[tw] OR glycazide[tw] OR nordialex[tw] OR predian[tw] OR "S 1702"[tw] OR "S 852"[tw] OR "SE 1702"[tw] OR G4PX8C4HKV[EC/RN Number]	1386
#26	Search Gliclazide[mesh]	844
#25	Search melormin[tw] OR meldian[tw] OR melitase[tw] OR mellinese[tw] OR millinese[tw] OR NCI-C01752[tw] OR "NSC 44634"[tw] OR "NSC 626720"[tw] OR neo-toltinon[tw] OR oradian[tw] OR "P 607"[tw] OR pamidin[tw] OR prodiaben[tw] OR pubetin[tw] OR stabinol[tw] OR tesmel[tw] OR "p chlorobenzolsulphonylglycolic acid nitrile"[tw] OR para chlorobenzenesulfonylglycolic acid nitrile[tw] OR parachlorobenzene sulfonylglycolic acid nitrile[tw] OR "U-3818"[tw] OR "U-9818"[tw] OR WTM2C3IL2X[EC/RN Number]	1858
#24	Search adiaben[tw] OR apo-chlorpropamide[tw] OR apochlorpropamide[tw] OR abemide[tw] OR "arodoc c"[tw] OR asucrol[tw] OR ascurol[tw] OR biabenal[tw] OR bioglumin[tw] OR BRN 2218363[tw] OR catanil[tw] OR "CCRIS 155"[tw] OR chlomide[tw] OR chlormide[tw] OR chlorodiabina[tw] OR chloropropamide[tw] OR chlorpromide[tw] OR clorpropamide[tw] OR copamide[tw] OR chloronase[tw] OR chlorpromide[tw] OR clorpropamide[tw] OR chloropropamide[tw] ORchlorpropamid[tw] OR chlorpropamide[tw] OR chlorpropamidum[tw] OR clorpropamid[tw] OR clorpropamida[tw] OR dabinese[tw] OR deavynfar[tw] OR diabaril[tw] OR diabechlor[tw] OR diabeedol[tw] OR diabemide[tw] OR diabenal[tw] OR diabenese[tw] OR diabeneza[tw] OR diabet-pages[tw] OR diabetoral[tw] OR diabexan[tw] OR diabiclor[tw] OR diabines[tw] OR diabinese[tw] OR diabitex[tw] OR diabitol[tw] OR diamel ex[tw] OR dibecon[tw] OR dynalase[tw] OR EINECS 202-314-5[tw] OR eubetin[tw] OR glicoben[tw] OR glisema[tw]	2089

	OR glucamide[tw] OR glycemin[tw] OR glymese[tw] OR HSDB 2051[tw] OR hypomide[tw] OR insilange[tw] OR insogen[tw] OR insulase[tw]	
#23	Search Chlorpropamide[mesh]	1815
#22	Search sulfonylurea*[tw] OR sulfonurea*[tw] OR sulfonyl urea*[tw] OR sulfonylcarbamide*[tw] OR sulphonurea*[tw] OR sulphonylurea*[tw]	12417
#21	Search Sulfonylurea Compounds[mh:noexp]	5836
#20	Search empagliflozin[tw] OR "BI 10773"[tw] OR BI10773[tw] OR Jardiance[tw] OR HDC1R2M35U[EC/RN Number]	831
#19	Search dapagliflozin[tw] OR "BMS 512148"[tw] OR BMS512148[tw] OR edistride[tw] OR forxiga[tw] OR farxiga[tw] OR 1ULL0QJ8UC[EC/RN Number]	705
#18	Search canagliflozin[tw] OR Invokana[tw] OR JNJ 24831754*[tw] OR "JNJ 28431754"[tw] OR TA 7284[tw] OR Prominad[tw] OR 0SAC974Z85[EC/RN Number]	766
#17	Search Canagliflozin[mesh]	399
#16	Search sodium-glucose transporter 2 inhibitor*[tw] OR sodium-glucose cotransporter 2 inhibitor*[tw] OR sodium-glucose co-transporter 2 inhibitor*[tw] OR sodium-glucose co-transporter 2 inhibitor*[tw] OR SGLT-2 inhibitor*[tw] OR SGLT2 inhibitor*[tw] OR sodium dependent glucose transporter 2 inhibitor*[tw] OR sodium dependent glucose cotransporter 2 inhibitor*[tw] OR sodium dependent glucose transporter 2 inhibitor*[tw] OR sodium dependent glucose co-transporter 2 inhibitor*[tw] OR gliflozin[tw] OR gliflozins[tw]	2368
#15	Search "sodium glucose transporter 2/antagonists and inhibitors"[MeSH Terms]	1144
#14	Search sitagliptin[tw] OR "EC 690-730-1"[tw] OR Glactiv[tw] OR "HSDB 7516"[tw] OR januvia or "mk 0431"[tw] OR mk0431[tw] OR "mk 431"[tw] OR "ono 5435"[tw] OR ristaben[tw] OR sitagliptine[tw] OR tesabel[tw] OR tesavel[tw] OR xelevia[tw] OR TS63EW8X6F[EC/RN Number]	2098
#13	Search Sitagliptin Phosphate[mesh]	1171
#12	Search saxagliptin[tw] OR BMS 477118[tw] OR BMS477118[tw] OR HSDB 8199[tw] OR Onglyza[tw] OR "OPC 262"[tw] OR 9GB927LAJW[EC/RN Number]	628
#11	Search linagliptin[tw] OR "BI 1356"[tw] OR ONDERO[tw] OR tradjenta[tw] OR trajenta[tw] OR trayenta[tw] OR trazenta[tw] OR 3X29ZEJ4R2[EC/RN Number]	604
#10	Search Linagliptin[mesh]	313
#9	Search DPP4 inhibitor*[tw] OR DPP 4 inhibitor*[tw] OR DPP IV inhibitor*[tw] OR dipeptidyl-peptidase IV inhibitor*[tw] OR dipeptidyl-	5393

	peptidase 4 inhibitor*[tw] OR gliptin[tw] OR gliptins[tw] OR alogliptin[tw] OR nesina[tw] OR "SYR 322"[tw] OR SYR322[tw] OR "HSDB 8203"[tw] OR incresina[tw] OR vipidia[tw] OR JHC049LO86[EC/RN Number]	
#8	Search Dipeptidyl-Peptidase IV Inhibitors[mesh]	3209
#7	Search antidiabetic*[tw] OR anti-diabetic*[tw] OR antihyperglycemic*[tw] OR antihyperglycaemic*[tw]OR anti-hyperglycemic*[tw] OR anti-hyperglycaemic*[tw] OR hypoglycemic*[tw] OR hypoglycaemic*[tw] OR antidiabetes*[tw] OR anti-diabetes*[tw]	82376
#6	Search Hypoglycemic Agents[mesh]	61650
#5	Search "diabetes mellitus, type 2/drug therapy"[MeSH] AND (Drug Combinations[mh:noexp] OR Drug Therapy, Combination[mh:noexp])	3740
#4	Search #1 OR #2 OR #3	385460
#3	Search MODY[tw] OR NIDDM[tw] OR T2DM[tw]	23623
#2	Search (adult[tw] OR ketosis-resistant[tw] OR matur*[tw] OR late[tw] OR non-insulin depend*[tw] OR noninsulin depend*[tw] OR slow[tw] OR stable[tw] OR "type 2"[tw] OR "type II"[tw] OR lipoatrophic[tw]) AND diabet*[tw]	315284
#1	Search "Diabetes Mellitus, Type 2" [mesh] OR Diabetes Mellitus [mh:noexp]	222899

NEW DRUGS

Ovid multifile

Database: Embase Classic+Embase <1947 to 2018 October 10>, Ovid MEDLINE(R) ALL <1946 to October 10, 2018>

SEARCH STRATEGY	
1	exp Diabetes Mellitus, Type 2/ (336398)
2	Diabetes Mellitus/ (644692)
3	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet*).tw,kw. (355261)
4	(MODY or NIDDM or T2DM).tw,kw. (62932)
5	or/1-4 (1019531)
6	(metformin adj3 canagliflozin).tw,kw. (90)
7	(invokamet or vokanamet).tw,kw. (32)
8	(albiglutide or albugon or (albumin adj1 GLP 1) or (albumin adj1 glucagon like peptide 1) or eperzan or "gsk 716155" or "gsk 716155a" or gsk716155 or gsk716155a or naliglutide or syncria or tanzeum).tw,kw. (569)

9	bydureon*.tw,kw. (293)
10	or/6-9 (906)
11	5 and 10 (785)
12	(controlled clinical trial or randomized controlled trial).pt. (557317)
13	clinical trials as topic.sh. (184945)
14	(randomi#ed or randomly or RCT$1 or placebo*).tw. (2067603)
15	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (380901)
16	trial.ti. (448696)
17	or/12-16 (2540859)
18	11 and 17 (278)
19	exp Animals/ not (exp Animals/ and Humans/) (16930534)
20	18 not 19 (131)
21	Adolescent/ not (exp Adult/ and Adolescent/) (1119010)
22	exp Child/ not (exp Adult/ and exp Child/) (3178347)
23	exp Infant/ not (exp Adult/ and exp Infant/) (1649632)
24	or/21-23 (4032212)
25	20 not 24 (131)
26	(comment or editorial or interview or news or newspaper article).pt. (1864777)
27	(letter not (letter and randomized controlled trial)).pt. (2031148)
28	25 not (26 or 27) (130)
29	28 use medall [MEDLINE RECORDS] (88)
30	(2017* or 2018*).dt. (2203954)
31	29 and 30 [MEDLINE - UPDATE PERIOD] (33)
32	diabetes mellitus/ (644692)
33	non insulin dependent diabetes mellitus/ (336213)
34	lipoatrophic diabetes mellitus/ (439)
35	((adult or ketosis-resistant or matur* or late or non-insulin depend* or noninsulin depend* or slow or stable or type 2 or type II or lipoatrophic) adj3 diabet*).tw,kw. (355261)
36	(MODY or NIDDM or T2DM).tw,kw. (62932)
37	or/32-36 (1019592)
38	canagliflozin plus metformin/ (42)
39	(metformin adj3 canagliflozin).tw,kw. (90)
40	(invokamet or vokanamet).tw,kw. (32)
41	albiglutide/ (717)
42	(albiglutide or albugon or (albumin adj1 GLP 1) or (albumin adj1 glucagon like peptide 1) or eperzan or "gsk 716155" or "gsk 716155a" or gsk716155 or gsk716155a or naliglutide or syncria or tanzeum).tw,kw. (569)
43	782500-75-8.rn. (630)
44	bydureon*.tw,kw. (293)
45	or/38-44 (1257)
46	37 and 45 (1109)
47	randomized controlled trial/ or controlled clinical trial/ (1257404)
48	exp "clinical trial (topic)"/ (275391)
49	(randomi#ed or randomly or RCT$1 or placebo*).tw. (2067603)
50	((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (380901)
51	trial.ti. (448696)
52	or/47-51 (2829313)

53	46 and 52 (542)
54	exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (47637775)
55	exp human/ or exp human experimentation/ or exp human experiment/ (37488600)
56	54 not 55 (10150880)
57	53 not 56 (540)
58	exp Juvenile/ not (exp Adult/ and exp Juvenile/) (2327849)
59	57 not 58 (537)
60	editorial.pt. (1047845)
61	letter.pt. not (letter.pt. and randomized controlled trial/) (2026247)
62	59 not (60 or 61) (529)
63	62 use emczd [EMBASE RECORDS] (449)
64	(2017* or 2018*).dc. (3127449)
65	63 and 64 [EMBASE UPDATE RECORDS] (122)
66	31 or 65 [BOTH DATABASES - UPDATE PERIOD] (155)
67	remove duplicates from 66 (126) [TOTAL UNIQUE RECORDS]
68	67 use medall [MEDLINE UNIQUE UPDATE RECORDS] (33)
69	67 use emczd [EMBASE UNIQUE UPDATE RECORDS] (93)

ID	SEARCH	HITS
#1	[mh "Diabetes Mellitus, Type 2"]	14582
#2	[mh "Diabetes Mellitus"]	6987
#3	((adult or "ketosis-resistant" or matur* or late or ("non-insulin" next depend*) or (noninsulin next depend*) or slow or stable or "type 2" or "type II" or lipoatrophic) near/3 diabet*):ti,ab,kw	28789
#4	(MODY or NIDDM or T2DM):ti,ab,kw	5157
#5	{or #1-#4}	32515
#6	(metformin near/3 canagliflozin):ti,ab,kw	53
#7	(invokamet or vokanamet):ti,ab,kw	0
#8	(albiglutide or albugon or (albumin near/1 GLP 1) or (albumin near/1 "glucagon like peptide 1") or eperzan or "gsk 716155" or "gsk 716155a" or gsk716155 or gsk716155a or naliglutide or syncria or tanzeum):ti,ab,kw	96
#9	bydureon*:ti,ab,kw	16
#10	{or #6-#9}	164
#11	#5 and #10 with Cochrane Library publication date between Jan 2017 and Dec 2018, in Trials	61
#12	#5 and #10 with Publication Year from 2017 to 2018, in Trials	20
#13	#11 OR #12	61

CENTRAL- 61

PUBMED (NEW RECORDS ONLY)

SEARCH	QUERY	ITEMS FOUND
#29	Search #27 AND #28	8
#28	Search publisher[sb] OR 2018/10/01:2018/10/11	530981
#27	Search #24 NOT (#25 OR #26)	150
#26	Search letter[pt] NOT (letter[pt] AND randomized controlled trial[pt])	996762
#25	Search comment[pt] OR editorial[pt] OR interview[pt] OR news[pt] OR newspaper article[pt]	1285807
#24	Search #19 NOT #23	153
#23	Search #20 OR #21 OR #22	1764651
#22	Search Infant[mesh] not (Adult[mesh] and Infant[mesh])	790663
#21	Search Child[mesh] not (Adult[mesh] and Child[mesh])	1133614
#20	Search Adolescent[mesh] not (Adult[mesh] and Adolescent[mesh])	564313
#19	Search #17 NOT #18	153
#18	Search Animals[mesh] NOT (Animals[mesh] AND humans[mesh])	4503231
#17	Search #10 AND #16	153
#16	Search #11 OR #12 OR #13 OR #14 OR #15	1297011
#15	Search trial [ti]	188195
#14	Search single blind*[tw] OR single mask*[tw] OR single dumm*[tw] OR double blind*[tw] OR double mask*[tw] OR double dumm*[tw] OR triple blind*[tw] OR triple mask*[tw] OR triple dumm*[tw] OR treble blind*[tw] OR treble mask*[tw] OR treble dumm*[tw]	218835
#13	Search randomised[tw] OR randomized[tw] OR randomly[tw] or RCT[tw] OR RCTs[tw] OR placebo*[tw]	1032461
#12	Search "clinical trials as topic"[mesh]	318183
#11	Search controlled clinical trial[pt] OR randomized controlled trial[pt]	557776
#10	Search #4 AND #9	310
#9	Search #5 OR #6 OR #7 OR #8	340
#8	Search bydureon*[tw]	21
#7	Search albiglutide[tw] OR albugon[tw] OR "albumin GLP 1"[tw] OR "GLP 1 albumin"[tw] or "albumin glucagon like peptide 1"[tw] OR "glucagon like peptide 1 albumin"[tw] OR eperzan[tw] OR "gsk 716155"[tw] OR "gsk 716155a"[tw] OR gsk716155[tw] OR gsk716155a[tw] OR naliglutide[tw] OR syncria[tw] OR tanzeum[tw]	160
#6	Search invokamet[tw] OR vokanamet[tw]	4
#5	Search metformin[tw] AND canagliflozin[tw]	159
#4	Search #1 OR #2 OR #3	385460

#3	Search MODY[tw] OR NIDDM[tw] OR T2DM[tw]	23623
#2	Search (adult[tw] OR ketosis-resistant[tw] OR matur*[tw] OR late[tw] OR non-insulin depend*[tw] OR noninsulin depend*[tw] OR slow[tw] OR stable[tw] OR "type 2"[tw] OR "type II"[tw] OR lipoatrophic[tw]) AND diabet*[tw]	315284
#1	Search "Diabetes Mellitus, Type 2" [mesh] OR Diabetes Mellitus [mh:noexp]	222899

Appendix 4B: List of included studies (and company publications)

1. Merker, L. *et al*. Empagliflozin as add-on to metformin in people with type 2 diabetes. *Diabetic Med.* 32, 1555-1567 (2015).

2. Simó, R. *et al*. Long-term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study. *Cardiovascular diabetology* 14, 116 (2015).

3. Weinstock, R. *et al*. Safety and efficacy of once-weekly dulaglutide versus sitagliptin after 2 years in metformin-treated patients with type 2 diabetes (AWARD-5): a randomized, phase III study. *Diabetes, Obesity and Metabolism* 17, 849-858 (2015).

4. Ross, S. *et al*. Efficacy and safety of empagliflozin twice daily versus once daily in patients with type 2 diabetes inadequately controlled on metformin: a 16-week, randomized, placebo-controlled trial. *Diabetes, Obesity and Metabolism* 17, 699-702 (2015).

5. Schernthaner, G. *et al*. Efficacy and tolerability of saxagliptin compared with glimepiride in elderly patients with type 2 diabetes: a randomized, controlled study (GENERATION). *Diabetes, obesity and metabolism* 17, 630-638 (2015).

6. Hansen, L., Iqbal, N., Ekholm, E., Cook, W. & Hirshberg, B. Postprandial dynamics of plasma glucose, insulin, and glucagon in patients with type 2 diabetes treated with saxagliptin plus dapagliflozin add-on to metformin therapy. *Endocrine Practice* 20, 1187-1197 (2014).

7. Anholm, C. *et al*. Adding liraglutide to the backbone therapy of biguanide in patients with coronary artery disease and newly diagnosed type-2 diabetes (the AddHope2 study): a randomised controlled study protocol. *BMJ Open* 4, e005942-2014-005942 (2014).

8. Moon, J. S. *et al*. The effect of glargine versus glimepiride on pancreatic β-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. *Acta Diabetol.* 51, 277-285 (2014).

9. Grandy, S., Langkilde, A., Sugg, J., Parikh, S. & Sjöström, C. Health-related quality of life (EQ-5D) among type 2 diabetes mellitus patients treated with dapagliflozin over 2 years. *Int. J. Clin. Pract.* 68, 486-494 (2014).

10. Gupta, S., Khajuria, V., Tandon, V. R., Mahajan, A. & Gillani, Z. H. Comparative evaluation of efficacy and safety of combination of metformin-vidagliptin versus metfromin-glimepiride in most frequently used doses in patients of type 2 diabetes mellitus with inadequately controlled metformin monotherapy-A randomised open label study. *Perspect. Clin. Res.* 6, 163-168 (2015).

11. Hissa, M. R. N., Cavalcante, L. L. A., Guimarães, S. B. & Hissa, M. N. A 16-week study to compare the effect of vildagliptin versus gliclazide on postprandial lipoprotein concentrations and oxidative stress in patients with type 2 diabetes inadequately controlled with metformin monotherapy. *Diabetology & metabolic syndrome* 7, 62 (2015).

12. Inagaki, N., Kondo, K., Yoshinari, T. & Kuki, H. Efficacy and safety of canagliflozin alone or as add-on to other oral antihyperglycemic drugs in Japanese patients with type 2 diabetes: a 52-week open-label study. *Journal of diabetes investigation* 6, 210-218 (2015).

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Appendix 4C: Study characteristics of included studies

Study design and interventions

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Nauck et al.	2014	United States, Canada, France, Germany, India, Korea, Republic of, Mexico, Poland, Puerto Rico, Romania, Russian Federation, Spain, Taiwan	Parallel	≥ 6 weeks	1098	104 wks	MET≥ 1500+ PLA	MET≥ 1500+ SIT100	MET≥ 1500+ DUL0.75	MET≥ 1500+ DUL1.5	NA
Ross et al.	2015	Europe, North America, Latin America	Parallel	≥ 12 weeks	983	16 weeks	MET1976+ PLA	MET1973+E MP5bid	MET1984+ EMP10 qd	MET1967+E MP12.5bid	MET1909+E MP25qd
Moon et al.	2014	Korea	Parallel	>3 months	75	48 weeks	MET1425.5 + GLM4.3	MET1365.1 +IGA22.8IU	NA		
Gupta et al	2015	India	Parallel	4 months	90	12 weeks	MET1000+G LM4	MET1000+ VID100	NA		
Hissa et al	2015	Brazil	Parallel	≥3 months	36	16 weeks	MET1457+G LL86.8	MET1584+ VIL100	NA		
Inagaki et al	2015	Japan	Parallel	NR	148	52 wk	MET+ CAN100	MET+ CAN200	NA		
Odawara et al	2014	Japan	Parallel	≥10 weeks	139	12 weeks	MET750.0+P LA	MET753.6+ VIL100	NA		
Chen et al	2014	Taiwan	Parallel	8 weeks	55	16 weeks	MET1500+G LY15	MET1500+ ACA300	NA		
Kawamori et al.	2014	Japan	Parallel	12 weeks	130	16 weeks	MET1500+PL A	MET1500+ REP1.5	NA		
White et al.	2014	USA, Germany, Hungary, Puerto Rice	Parallel	at least 8 wk	160	12 wk	MET≥1500+ PLA	MET≥1500+ SAX5	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Kadowaki et al.	2013	Japan	Parallel	≥ 12 wk	149	12 wk	MET500 to 750+PLA	MET500 to 750+SIT50	NA		
Neutel et al.	2013	USA, Israel, Mexico, Argentina	Parallel	4-8 wk	93	4 wk	MET2000	MET1500+SAX5	NA		
Chawla et al.	2013	India	Parallel	1 mo	52	16 wk	MET1865.38 +SIT100	MET1830+PIO30	NA		
Bergenstalet al.	2012	23 countries	Parallel	12 wk	666	156 wk	MET≥1500+ PLA	MET≥1500+ SIT100	MET≥1500 +TAS10QW	MET≥1500+TAS10to20QW	NA
Cho et al.	2010	Korea	Parallel	8 weeks	145	16 weeks	MET1500+PLA	MET1500+ MIT30	NA		
Wang et al.	2015	NR	Parallel	6 mo	90	1 yr	MET+SAX5	MET+ ACA150	NA		
Jin et al.	2015	Republic of Korea	Parallel	≥4 weeks	180	24 wk	MET1500to2000+ SIT100	MET1500to 2000+ ANA200	NA		
Xiao et al.	2015	China	Parallel	≥ 4 weeks	120	24 weeks	MET≥1500+ GLI5to10	MET≥1500+ PIO15 to 45	NA		
Rosenstock et al.	2015	Multicenter	Parallel	8 wk	534	24 wk	MET1500or2000+SAX5	MET1500or 2000+ DAP10	NA		
Rosenstock et al	2015	USA	Parallel		299	12 weeks	MET + PLA	MET+ SOT75	MET+ SOT200	MET+ SOT400QD	MET+ SOT200BID
Kim et al.	2015	Korea	Parallel	≥ 8 weeks	204	16 weeks	MET1407+PLA	MET1486+TEN20	NA		
Kashiwagi et al.	2015	Japan	Parallel	6 weeks	169	24weeks double-blind, up to 52weeks with open-label extension	MET + PLA	MET + IPR50	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Aaboe et al.	2015	Denmark	Parallel	3 months	25	12 weeks	MET≥ 1000+PLA	MET≥1000+ SIT100	NA		
Schumm-Draeger et al	2015	Europe, South Africa	Parallel	≥10 weeks	400	16 weeks	MET≥ 1500+PLA	MET≥1500+ DAP5	MET≥ 1500+DAP 10QD	MET≥1500+D AP5BID	NA
Ji et al	2015	China, Malaysia, Vietnam,	Parallel	8 weeks	678	18 weeks	MET≥1500+ PLA	MET≥1500+ CAN100	MET≥1500 +CAN300	NA	
Gurkan et al.	2014	NR	Parallel	2 months	34	26 weeks	MET2000+E XE20ug	MET2000+I GA	NA		
Del Prato et al	2014	North and South America, Europe, Asia, South Africa, Australia, New Zealand	Parallel	4 weeks	2,639	104 weeks	MET1823.4+ GLI5to20	MET1825.2 +ALO12.5	MET1837. 2+ALO25	NA	
Nandy et al.	2014	USA	Parallel	3 months	49	12 weeks	MET+GLM4	MET+ PLA	MET+ LIR1.8	NA	
Forst et al.	2014	Germany	Parallel	NR	40	12 weeks	MET+GLM1t o4	MET+ LIN5	NA		
Dungan et al.	2014	USA, Czech Republic, Hungary, Mexico, Slovakia, Puerto Rico, Poland, Spain, Romania, Germany	Parallel	3 months	599	26 weeks	MET2068+LI R0.6to1.8	MET2021+ DUL1.5QW	NA		
Ridderstrale et al.	2014	Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Hong Kong, India, Italy, Malaysia, Mexico, the Netherlands, Norway, Philippines, Portugal, South	Parallel	12 weeks	1,549	104 weeks	MET≥1500+ GLM1to4	MET≥1500+ EMP25	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, UK, USA									
Ohira et al.	2014	Japan	Parallel	NR	70	6 months	MET1000	MET500+SIT50	NA		
Ahren et al	2014	United States, Albania, Germany, Hong Kong, Mexico, Peru, Philippines, Russian Federation, South Africa, Spain, United Kingdom	Parallel	3 months	1,049	104 weeks	MET≥1500+GLM2to4	MET≥1500+PLA	MET≥1500+SIT100	MET≥1500+ALB30QW	NA
Derosa et al	2014	Italy	Parallel	≥ 1 month	167	6 months	MET+GLM6	MET+VIL100	NA		
Diamant et al.	2014	Multinational (72 sites)	Parallel	≥ 8 weeks	467	156 weeks (3 years)	MET2000+EXE2mgQW	MET2000+IGA	NA		
Haring et al.	2014	Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the U.S.	Parallel	≥ 12 weeks	1,307	76 weeks (24+52 weeks extension)	MET≥1500+PLA	MET≥1500+EMP10	MET≥1500+EMP25	NA	
Bolli et al	2014	United States, Brazil, Chile, Colombia, Estonia, Germany, Italy, Lithuania, Malaysia, Mexico, Philippines, Poland, Romania, Slovakia, Ukraine	Parallel	NR	482	≥ 76 weeks	MET1943+PLA	MET1968+LIX20ug_1STEP	MET2036+LIX20ug_2STEP	NA	

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Berndt-Zipfel et al.	2013	Germany	Parallel	NR	44	24 weeks	MET+GLM0.5to4	MET+VIL100	NA		
Genovese et al.	2013	Italy	Parallel	3 months	213	24 weeks	MET2550+PLA	MET2550+PIO30to45	NA		
Rosenstock et al.	2013	United States, Argentina, Austria, Brazil, Colombia, Denmark, Finland, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Puerto Rico, Russian Federation, Spain, Sweden	Parallel	NR	639	24-week, then 52-weeks safety extension	MET2058+EXE20ug	MET2020+LIX20ug	NA		
Kim et al	2013	Korea	Parallel	≥ 2 months	34	4 weeks	MET≥1000+GLM2	MET≥1000+SIT100	NA		
Cefalu et al	2013	United States, Argentina, Bulgaria, Canada, Costa Rica, Denmark, Finland, Germany, India, Israel, Korea, Republic of, Mexico, Norway, Philippines, Poland, Puerto Rico, Romania, Russian Federation, Slovakia, Ukraine	Parallel	≥ 10 weeks	1,452	104 weeks total; primary outcome: 52 weeks	MET+GLM5.6	MET+CAN100	MET+CAN300	NA	
Derosa et al	2013	Italy	Parallel	8±2 months	171	12 months	MET2500+PLA	MET2500+EXE20ug	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Henry et al.	2013	US	Parallel	≥3 months	155	PERIOD 1 ONLY: 12-week "active-controlled period"	MET1236.8+EXE10to20ug	MET1403.9+EXE20ug	MET1470.6+EXE40ug	NA	
Ahrén et al.	2013	Australia, Canada, Chile, Czech Republic, Germany, Croatia, Mexico, Morocco, the Philippines, Romania, Russian Federation, South Africa, Spain, Ukraine, U.S., and Venezuela	Parallel	NR	680	24 weeks	MET2001+PLA	MET1969+LIX20AM	MET1943+LIX20PM	NA	
Kapitza et al	2013	Germany	Parallel	≥ 2 week	148	28 days	MET≥1500+LIR0.6to1.8	MET≥1500+LIX10to20ug	NA		
Charbonnel et al.	2013	21 countries	Parallel	≥12 weeks	653	12 weeks in phase 1 and 14 weeks in phase 2, total 26 weeks	MET≥1500+SIT100	MET≥1500+LIR1.2	NA		
Forst et al.	2013	Germany	Parallel	≥3 months	44	24 weeks	MET2000+GLM1to4	MET2000+VIL100	NA		
Rhee et al.	2013	Korea, India	Parallel	4 weeks	425	24 weeks	MET≥1000+SIT100	MET≥1000+GEM50QD	MET≥1000+GEM25BID	NA	

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Wilding et al.	2012	Hungary, Poland, Romania, UK, Italy, US	Parallel	≥6 weeks	343	12 weeks	ME≥1500T+PLA	MET≥1500+IPR12.5	MET≥1500+IPR50	MET≥1500+IPR150	MET≥1500+IPR300
Derosa et al.	2012	Italy	Parallel	8±2 months	167	12 months	MET2500+PLA	MET2500+VIL100	NA		
Hermans et al.	2012	Belgium, France, Germany, Italy, Spain, Turkey, UK	Parallel	4 weeks	286	24 weeks	MET2000or2500	MET1500+SAX5	NA		
Derosa et al.	2012	Italy	Parallel	8 months	178	12 months	MET2500+PLA	MET2500+SIT100	NA		
Guerci et al	2012	NR	Parallel	3 months	38	8 weeks	MET2113+SIT100	MET2115+VIL100	NA		
Monnier et al.	2012	France	Parallel	≥ 12 weeks	21	12 weeks	MET2000+GLM1to4	MET2000+ROS4to8	NA		
Rizzo et al	2012	Italy	Parallel	8 weeks	90	12 weeks	MET2000+SIT100	MET2000+VIL100	NA		
Seino et al.	2012	Japan	Parallel	12 weeks	288	12 week double-blind, with 40 weeks open-label extension for AE's	MET500or750+PLA	MET500or750+ALO12.5	MET500or750+ALO25	NA	
Yang et al	2012	NR	Parallel	10 weeks	395	24 weeks	MET1000or1700+PLA	MET1000or1700+SIT100	NA		
Gallwitz et al	2012	Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland,	Parallel	NR	1,552	104 weeks	MET+GLM	MET+LIN5	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		South Africa, Sweden, UK, USA									
Srivastava et al.	2012	India	Parallel	≥ 3 months	50	18 weeks	MET+GLM1to4	MET+SIT50to200	NA		
Koren et al.	2012	Isreal	Crossover	NR	40	28	MET+GLY5	MET+SIT100	NA		
Pan et al.	2012	China	Parallel	≥ 4 weeks	438	24 weeks	MET≥1500+PLA	MET≥1500+VIL50	MET≥1500+VIL100	NA	
Gallwitz et al.	2012	Austria, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Mexico, Poland, Spain, Switzerland, and the UK	Parallel	NR	1,029	time to treatment failure or 3 years	MET1989+GLM≥1	MET1956+EXE10or20ug	NA		
Aschner et al.	2012	Austria, Brazil, Colombia, Egypt, Greece, Hong Kong, India, Israel, Korea, Lebanon, Mexico, Netherlands, Portugal, Spain, Turkey, UK, USA	Parallel	NR	515	6 months	MET1835+SIT100	MET1852+IGA	NA		
Rosenstock et al.	2012	Argentina, Bulgaria, Canada, Czech Republic, India, Malaysia, Mexico, Poland, Romania, Russia, UK, USA	Parallel	3 months	451	12 weeks	MET1919+PLA	MET1885+SIT100	MET1870+CAN50	MET1903+CAN100	MET1904+CAN200
DeFronzo et al.	2012	United States, Australia, Brazil,	Parallel	≥ 2 months	1,554	26 weeks	MET1937+PLA	MET1902+ALO12.5	MET1851+ALO25	MET1893+PIO15	MET1854+PIO30

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		Bulgaria, Chile, Croatia, Estonia, Guatemala, India, Israel, Latvia, Mexico, New Zealand, Peru, Romania, Russian Federation, Serbia, South Africa, Ukraine									
Bolinder et al.	2012	Bulgaria, Czech Republic, Hungary, Poland, Sweden	Parallel	≥ 12 weeks	182	24 weeks (primary outcome), 102 weeks (extension phase)	MET1901+PLA	MET1989+DAP10	NA		
Fonseca et al.	2012	US, Latin America	Parallel	8 weeks	282	18 weeks	MET2000	MET1500+SAX5	NA		
Wang et al.	2011	Taiwan	Parallel	8weeks	55	16 weeks	MET1500+GLY	MET1500+ACA	NA		
Yang et al.	2011	China, India and South Korea	Parallel	8weeks	570	24 weeks	MET1606+PLA	MET1620+SAX5	NA		
Stephens et al.	2011	UK	Parallel	NR	25	8 weeks	MET1500to3000+GLY2.5	MET1500to3000+REP3	NA		
Petrica et al.	2011	Romania	Parallel	≥ 6 months	78	12 months	MET1700+GLM4	MET1700+PIO30	NA		
Lin et al.	2011	Taiwan	Parallel	at least 8 weeks	51	16 weeks	MET1500+GLY15	MET1500+ACA300	NA		
Terra et al.	2011	Colombia, Germany, Italy, Spain, Sweden, USA	Parallel	2 months	302	12 weeks	MET+PLA	MET+GOS2	MET+GOS5	MET+GOS10	MET+GOS20

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Derosa et al.	2011	Italy	Parallel	NR	111	12 months	MET1000to2000+GLM3to6	MET1000to2000+EXE10to20ug	NA		
Derosa et al.	2011	Italy	Parallel	NR	201	12 month	MET+GLY15	MET+PIO45	NA		
Pfutzner et al.	2011	Germany	Parallel	NR	305	24 weeks	MET1700+GLM2	MET1700+PIO30	NA		
Zinman et al.	2011	Canada, India, South Africa, USA	Parallel	1 week (metformin maintenance period)	245	16 weeks	MET2000+IGA	MET2000+IND3.1QD	MET2000+IND4.5QD	MET2000+IND3.4TW	NA
Heise et al.	2011	France, Germany, Norway, Romania, Spain	Parallel	1 week	178	16 weeks	MET1500or2000+IGA	MET1500or2000+DSP70/30	MET1500or2000+DSP55/45	NA	
Gallwitz et al.	2011	Germany	Parallel	NR	363	26 weeks	MET+EXE20ug	MET+IAM28.4	NA		
Arechavaleta et al.	2011	Austria, Brazil, Chile, Colombia, Costa Rica, Denmark, Ecuador, France, Germany, Guatemala, India, Italy, Korea, Republic of, Malaysia, Mexico, New Zealand, Panama, Peru, Poland, Spain, Switzerland, United Kingdom	Parallel	12 weeks	1,035	30 weeks	MET≥1500+GLM1to6	MET≥1500+SIT100	NA		
Yang et al.	2011	China, South Korea and India	Parallel	≥ 6 week metformin run-in	929	16 weeks	MET2000+GLM4	MET2000+LIR0.6	MET2000+LIR1.2	MET2000+LIR1.8	NA

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
				and maintenance period							
Taskinen et al.	2011	Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden, US	Parallel	12 weeks	701	24 weeks	MET≥1500+ PLA	MET≥1500+ LIN5	NA		
Forst et al.	2010	UK, Germany, France, Slovakia, Ukraine, Sweden	Parallel	NR	333	12 weeks	MET+GLM	MET+PLA	MET + LIN1	MET+LIN5	MET+LIN10
Goke et al.	2010	International	Parallel	8 weeks	858	52 weeks	MET1500to3000+GLI5 to 20	MET1500to3000+ SAX5	NA		
Scheen et al.	2010	Argentina, Belgium, Denmark, France, Italy, Mexico, Norway, South Africa, Sweden	Parallel	8 weeks	801	18 weeks	MET1831.5+ SAX5	MET1826.2 +SIT100	NA		
Stenlof et al.	2010	United States, Israel, Sweden, Mexico, Puerto Rico, Argentina, Italy, and the Philippines.	Parallel	≥ 8 weeks before enrolment and a 4-week MET XR lead-in period before randomization	93	4 weeks	MET1500to2000+PLA	MET1500to2000+SAX5	NA		
Ratner et al.	2010	Brazil, Canada, Poland, Romania, Russian, Ukraine, and US	Parallel	at least 3 months prior to enrolment	542	13 weeks	MET≥1000+ PLA	MET≥1000+ LIX5ug Qd	MET≥1000 +LIX5ugBid	MET≥1000+LIX10ugQd	MET≥1000+ LIX10ug Bid
Bergenstalet al.	2010	United States, India, Mexico	Parallel	2 Months	514	26 weeks	MET1583+SIT100	MET1504+EXE2QW	MET1480+ PIO45	NA	

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Bailey et al.	2010	United States, Canada, Argentina, Mexico, Brazil	Parallel	8 weeks	546	102 weeks (24 weeks with 78wk extension)	MET1861+PLA	MET1792+DAP2.5	MET1854+DAP5	MET1800+DAP10	NA
Filozof et al.	2010	NR	Parallel	4 weeks	1,007	52 weeks	MET≥1500+GLL	MET≥1500+VIL100	NA		
DeFronzo et al.	2010	US	Parallel	6 weeks	141	20 weeks	MET+EXE20ug	MET+ROS4to8	NA		
Pratley et al.	2010	Croatia, Germany, Ireland, Italy, Netherlands, Romania, Serbia, Slovakia, Slovenia, Spain, UK, US, Canada	Parallel	≥ 3 months	665	52 weeks	MET≥1500+SIT100	MET≥1500+LIR1.2	MET≥1500+LIR1.8	NA	
Apovian et al.	2010	US	Parallel	6 weeks	196	24 weeks	MET+PLA	MET+EXE10to20ug	MET+SUL+PLA	MET+SUL+EXE10 to 20ug	NA
Kadoglou et al.	2010	NR	Parallel	4 months	97	14 weeks	MET2550	MET850+ROS8	NA		
Petrica et al.	2009	NR	Parallel	6 months	44	12 months	MET1700+GLM4	MET1700+ROS4	NA		
Scheen et al.	2009	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Slovakia, Sweden,	Parallel	NR	NR	up to 48 months	MET1721+PLA	MET1687+PIO15to45	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		Switzerland, United Kingdom									
Blonde et al.	2009	US	Parallel	≥4 weeks	2,664	12 weeks	MET≥1000+ VIL100	MET≥1000+ TZD	NA		
Defronzo et al.	2009	US, Brazil	Parallel	≥ 8 weeks	745	24 weeks; rescued patients (hypoglycemia) and completers were eligible to continue 42-month long-term phase	MET1500to2500+PBO	MET1500to2500 + SAX2.5	MET1500to2500 + SAX5	MET1500to2500 + SAX10	NA
Home et al.	2007	23 countries in Europe, Australia and New Zealand	Parallel	≥ 8 weeks	524	18 months	MET≤2550+SUL	MET≤2550+ ROS4to8	NA		
Papathanassiou et al.	2009	Greece	Parallel	NR	28	6 months	MET+GLM4	MET+PIO30	NA		
Goodman et al.	2009	Multinational	Parallel	≥ 3 months	370	24 weeks (6 months)	MET≥1500+ PLA	MET≥1500+ VILam 100	MET≥1500 +VILpm 100	MET≥1500+VILtotal100	NA
Bunck et al.	2009	Sweden, Finland, and the Netherlands	Parallel	≥ 2 months	69	156 weeks	MET2058+EXE10to60ug	MET1798+IGA33.6	NA		
Kaku et al.	2009	NR	Parallel	NR (12 weeks observation period before randomization)	169	28 weeks	MET500or750+PLA	MET500or750+PIO	NA		
Nauck et al.	2008	Multinational ("115 sites in 15 countries"	Parallel	≥ 3 months	524	26 weeks	MET1847+PLA	MET1847+ ALO12.5	MET1847+ ALO25	NA	

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Ferrannini et al.	2009	Canada, USA, Europe, and multinational	Parallel	≥ 4 weeks	2,789	2 years	MET1893+GLM4.5	MET11904+VIL100	NA		
Gao et al.	2009	China, India, Korea, Taiwan	Parallel	3 months	472	16 weeks	MET1000to3000+PLA (NOTE: MET+SU+PLA also mixed in. See comments)	MET1000to3000+EXE10to20ug	NA		
Nauck et al.	2009	Argentina, Australia, Belgium, Bulgaria, Croatia, Denmark, Germany, Hungary, India, Ireland, Italy, Netherlands, New Zealand, Norway, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, United Kingdom	Parallel		385	26 weeks	MET1500to2000+PLA	MET1500to2000+GLM4	MET1500to2000+LIR0.6	MET1500to2000+LIR1.2	MET1500to2000+LIR1.8
Scott et al.	2008	Multinational	Parallel	10 weeks	273	18 weeks	MET≥1500+PLA	MET≥1500+SIT100	MET≥1500+ROS8	NA	
Komajda et al.	2008	23 countries in Europe and Australasia	Parallel	NR	926	12 months	MET≤2550+SUL	MET≤2550+ROS4to8	NA		
Khanolkar et al.	2008	United Kingdom	Parallel	≥ 4 weeks	50	24 weeks	MET2000+GLC80	MET2000+ROS4	NA		
Garcia-Soria et al.	2008	US, Mexico, Australia	Parallel	4 weeks	174	4 weeks	MET≥1500+PLA	MET≥1500+DUT100	MET≥1500+DUT200	MET≥1500+DUT400	NA

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Raz et al.	2008	Austria, Israel, Mexico, Peru and United States	Parallel	NR or 6-week run-in	190	30 weeks	MET1500to2550+PLA	MET1500 to2550 + SIT100	NA		
Hamann et al.	2008	Multinational (Europe and Mexico)	Parallel	8 weeks	596	52 weeks	MET2000+SUL	MET2000+ ROS4	NA		
Bolli et al.	2008	Germany, UK, US, Spain, Italy, Switzerland, Austria, South Africa and Australia	Parallel	NR	576	52 weeks (24 weeks+28 weeks extension)	MET≥1500+ VIL100	MET≥1500+ PIO30	NA		
Bosi et al.	2007	US, France, Italy, Sweden	Parallel	4 weeks	544	24 weeks	MET2102+PLA	MET2126+ VIL50	MET2126+ VIL100	NA	
Nauck et al.	2007	NR	Parallel	NR or 8 weeks	1172	52 weeks	MET≥1500+ GLI10.6	MET≥1500+ SIT100	NA		
Brazg et al.	2007	NR	Crossover	≥6 weeks	28	4 weeks x 2	MET≥1500+ PLA	MET≥1500+ SIT100	NA		
Derosa et al.	2007	Italy	Parallel	NR	103	12 months	MET2250+ROS4	MET2250+PIO15	NA		
Charbonnel et al.	2006	France, Israel, US	Parallel	up to 19 weeks	464	24 weeks	MET>1500+ PLA	MET>1500+ SIT100	NA		
Nauck et al.	2006	Europe and Austrlia	Parallel	2 weeks	144	5 weeks	MET2000+PLA	MET2000+ GLM3.75	MET2000+ LIR1.96	NA	
Weissman et al.	2005	US	Parallel	4 to 7 weeks	766	24 weeks	MET2000	MET1000+ ROS8	NA		
Bakris et al.	2006	North America, South America and Europe	Parallel	NR	389	32 weeks	MET1986+GLY13.7	MET1958+ ROS7.2	NA		
Ristic et al.	2006	Canada, France, Italy, Spain, Austria	Parallel	≥2 month	262	1 year	MET1812+GLC80to240	MET1921+ NAT180to540	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Umpierrez et al.	2006	US	Parallel	2 months	210	26 weeks	MET1470to1490+GLM2to8	MET1540to1570+PIO30to45	NA		
Garber et al.	2006	US	Parallel	≥8 weeks	318	24 weeks	MET1509+GLY7.6 (combination tablet)	MET1819+ROS7.1	NA		
Kvapil et al.	2006	Croatia, Czech Republic, Denmark, France, Greece, Hungary, Norway, Poland, Portugal, Russia, Spain		≥1 month			MET1660+GLY1.75to10.75	MET1660+IAS	NA		
Poon et al.	2005	US	Parallel	≥ 3 months	156	28 days	MET+PBO	MET+EXE5ug	MET+EXE10ug	MET+EXE15ug	MET+EXE20ug
Feinglos et al.	2005	United States	Parallel	≥3 months	122	16 weeks	MET1509+GLI2.5	MET1513+PLA	NA		
DeFronzo et al.	2005	United States	Parallel	3 months	336	30 weeks	MET+PLA	MET+EXE10ug	MET+EXE20ug	NA	
Matthews et al.	2005	Multinational	Parallel	NR	630	52 weeks (ID#6199) and 2 years (ID#6104)	MET + GLC212	MET+PIO39	NA		
Ahrén et al.	2004	Sweden, Spain, Germany and Switzerland	Parallel	≥ 3 months	107	52 weeks	MET1500to3000+PLA	MET1500to3000+VIL50	NA		
Schernthaner et al.	2004	10 European countries	Parallel	≥ 3 months	845	27 weeks	MET+GLM2.9	MET+GLL76.2	NA		
Raskin et al.	2003	US	Parallel	NR	192	16 weeks	MET2000+REP3to12	MET2000+NAT180 to 360	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Phillips et al.	2003	Australia and New Zealand	Parallel	4 weeks	83	24 weeks	MET1700+PLA	MET1700+ACA100or200	NA		
Marre et al.	2002	Multinational	Parallel	2 weeks	411	16 weeks	MET1650	MET1250+GLY6.25	MET1150+GLY11.5	NA	
Marre et al.	2002	Multinational	Parallel	≥ 4 weeks	467	24 weeks	MET2000+PLA	MET2000+NAT180	MET2000+NAT360	NA	
Gomez-Perez et al.	2002	Mexico	Parallel	NR	116	6 months	MET2500+PLA	MET2500+ROS4	MET2500+ROS8	NA	
Van Gaal et al.	2001	Belgium, Israel, Astria, Czech	Parallel	≥3 months	153	32 weeks	MET1500or1700or2550+PLA	MET1500or1700or2550+MIG75to300	NA		
Charpentier et al.	2001	France	Parallel	≥ 4 weeks	379	5 months	MET2550+GLM1to6	MET2550+PLA	NA		
Halimi et al.	2000	France	Parallel	850 mg/day for at least 2 months	152	6 months	MET1700or2550 + PLA	MET1700or2550+ACA150or300	NA		
Einhorn et al.	2000	US	Parallel	≥ 30 days	328	16 weeks	MET+PLA	MET+PIO30	NA		
Fonseca et al.	2000	US	Parallel	MET maintenance period phase: for at least 4 weeks (2500mg/d)	348	26 weeks	MET2500+PLA	MET2500+ROS4	MET2500+ROS8	NA	
Moses et al.	1999	Australia	Parallel	4 to 5 weeks	83	4 to 5 months	MET1000to3000+PLA	MET1000to3000+REP1.5to12	PLA+REP1.5to12	NA	
Rosenstock et al.	1998	US	Parallel	56 days	84	24 weeks	MET2000to2500+PLA	MET2000to2500+ACA150to300	NA		
Wolever et al.	1997	Canada	Parallel	NR	83	12 months	MET+PLA	MET+ACA150to600	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Strozik et al.	2015	Poland	Parallel	≥3 months	61	12 weeks	MET1500	MET3000	MET1500+ VIL100	MET3000+ VIL100	NA
Qiu et al.	2014	Canada, Czech Republic, Mexico, Romania, Russia, Slovakia, US	Parallel	≥ 8 weeks	279	18 weeks	MET2131+PL A	MET2137+C AN100	MET2128+ CAN300	NA	
Gaal et al.	2014	United States, Australia, Brazil, Canada, Chile, Germany, Guatemala, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine	Parallel	≥ 3 months	319	24 weeks	MET1937+SI T100	MET1985+L IX20ug	NA		
Bhandare et al.	2013	India	Parallel	≥2 months	73	12 weeks	MET2000	MET1000+ VIL100	NA		
Raskin et al.	2007	US	Parallel	≥3 months	157	28 weeks	MET1500to2 550+ IAS80	MET1500to 2550+ IGA49	NA		
Leiter et al.	2005	Canada	Parallel	≥3 months	236	32 weeks	MET1500to2 000	MET1500+ ROS4to8	NA		
Kilo et al.	2003	US	Parallel	4 weeks	140	12 weeks	MET2200+NI N	MET2200+I AM	MET2200+ NIR	NA	
Ohira et al.	2014	Japan	Parallel	NR	60	6 months	MET500+GL M1	MET500+PI O15	NA		
Yang et al.	2015	China, India, South Korea	Parallel	≥8 weeks	445	24 weeks	MET≥1500+ PLA	MET≥1500+ DAP5	MET≥1500 +DAP10	NA	
Merck Sharp & Dohme Corp et al.	2015	Argentina, Canada, Croatia, Estonia, Georgia, Hungary, Israel, Malaysia, Philippines, Poland,	Parallel	12 weeks	642	24 weeks	MET≥1500+S IT100	MET≥1500+ OMA25 QW	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		Romania, South Africa, USA									
Daiichi Sankyo Inc et al.	2009	Colombia, Mexico, US	Parallel	NR	169	16 weeks	MET+ SIT100	MET+ ROS4	NA		
Merck Sharp & Dohme Corp et al.	2012	Croatia, Germany, Hungary, South Korea, Lebanon, Lithuania, Malaysia, Poland, Romania, US	Parallel	12 weeks	751	54 weeks	MET≥1500+ GLM1to6	MET≥1500+ OMA25 QW	NA		
NCT record	2010 (last update d)	"Not provided", France is listed as a "Removed Location Countries"	Parallel	NR	84	36 months	MET2000+G LC80to320	MET2000+ ROS4to8	NA		
NCT record	2015 last update	Republic of Korea	Parallel	NR	228	16 weeks	MET+ VIL100	MET+ PIO30	NA		
NCT record	2015 (last update)	EUROPE: Czech Republic, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, United Kingdom	Parallel	≥90 days	404	26 weeks	MET1000to3 000 + LIR1.8	MET1000to 3000 + 20ug	NA		
NCT record	2016 (last update)	China, Beijing	Parallel	60 days	368	26 weeks	MET>1000+S IT100	MET>1000+ LIR1.8	NR		
Lavalle-Gonzalez et al.	2013	Argentina, Bulgaria, Colombia, Czech Republic, Estonia, Greece, India, Italy, Latvia, Malaysia, Mexico, Peru,	Parallel	8 weeks	1,284	52 weeks	MET≥1500+ PLA	MET≥1500+ SIT100	MET≥1500 +CAN100	MET≥1500+C AN300	NA

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		Poland, Portugal, Russia, Singapore, Slovakia, Sweden, Thailand, Turkey, Ukraine, USA									
Chen et al.	NA	China	Parallel	≥ 12 weeks	120	12 weeks	MET1500+PLA	MET1500+PGL0.1	MET1500+PGL0.2	NA	
Henry et al.	2018	US	Parallel	≥ 8 weeks	48	4 weeks	MET1977.1+PLA	MET1977.1+DAP10	NA		
Ridderstråle et al.	2018	Argentina,Canada,Colombia, Czech Republic, finland, great Britain, Hong Kong, India, Italy, Malaysia, Mexico, Netherlands, Norway, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, US	Parallel	≥ 12 weeks	1,549	208 weeks	MET≥1500+GLM2.71	MET≥1500+EMP25	NA		
Yin et al.	2018	China	Parallel	≥ 8 weeks	45	16 weeks	MET≥1500+EXE0.02	MET≥1500+IGA	NR		
Müller-Wieland et al.	2018	Germany, the Czech Republic, Hungary, Poland and Slovakia.	Parallel	≥ 8 weeks	939	52 weeks	MET1500to2500+GLM4.6	MET1500to2500+SAX5+DAP10	MET1500to2500+DAP10	NA	
Otterbeck et al.	2011	USA	Parallel	NR	2,627	12 weeks	MET≥1000+VIL100	MET≥1000+TZD	NA		
Fofonka et al.	2018	Brazil	Parallel	NR	13	12 weeks	MET1700+GLY10	MET1478+VIL100			

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Pratley et al.	2018	Argentina, Canada, Coombia, Mexico, Czech Republic, Hungary, Israel, Poland, Romania, Russian Federation, Slovakia, Ukraine, Malaysia, Philippines, New Zealand, Bulgaria, Italy Finland, Thailand, and the USA,	Parallel	≥ 8 weeks	1233	52 weeks	MET≥1500+SIT100	MET≥1500+SIT100+ERT5	MET≥1500+SIT100+ERT15	MET≥1500+ERT5	MET≥1500+ERT15
Parthan et al.	2018	India	Parallel	≥ 6 weeks	30	24 weeks	MET2000+PLA	MET2000+LIN5	MET2000+VOG0.6	NA	
Yin et al.	2018	China	Parallel	≥ 8 weeks	45	16 weeks	MET≥1500+EXE0.02	MET≥1500+IGA	NA		
Kim et al.	2017	Korea	Parallel	≥ 4 weeks	31	16 weeks	MET≥1000+VIL100	MET≥1000+PIO15	NA		
Min et al.	2017	Korea and Taiwan	Parallel	≥ 8 weeks	171	24 weeks	MET≥1000+PLA	MET≥1000+IPR50	NA		
Hollander et al.	2018	Argentina, Canada, Czech Republic, Hungary, South Korea, Lithuania, Mexico, the Philippines, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, Ukraine,	Parallel	≥ 8 weeks	1,326	52 weeks	MET≥1500+GLM3	MET≥1500+ERT5	MET≥1500+ERT15	NA	

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
		and the USA									
Jameshorani et al.	2017	Iran	Parallel	NR	160	12 weeks	MET+ SIT100	MET+ PIO30	NA		
Shi et al.	2017	China	Parallel	NR	36	12 weeks	MET1500to2000+EXE0.02	MET1500to2000+ACA150to300	NA		
Vianna et al.	2018	Brazil	Parallel	≥ 12 weeks	42	24 weeks	MET1742.9+GLC72.6	MET1640.9+VIL100	NA		
Gadde et al.	2017	US	Parallel	≥ 8 weeks	365	28 weeks	MET≥1500+PLA	MET≥1500+SIT100	NA		
Frias et al.	2017	US	Parallel	≥ 12 weeks	71	12 weeks	MET+PLA	MET+LIR1.8	NA		
Du et al.	2017	China	Parallel	≥ 8 weeks	488	24 weeks	MET≥1500+SAX5	MET≥1500+ACA150 to300	NA		
Handelsman et al.	2017	Argentina, Croatia, Germany, Hungary, Korea, Lebanon, Lithuania, Malaysia, Mexico, Poland, Romania, and the USA.	Parallel	≥ 8 weeks	751	54 weeks	MET≥1500+GLM2.6	MET≥1500+OMA25 QW	NA		
Shankar et al.	2017	NR	Parallel	≥ 12 weeks	402	24 weeks	MET≥1500+PLA	MET≥1500+OMA25QW	NA		
Dei Cas et al.	2017	Italy	Parallel	≥ 12 weeks	64	48 weeks	MET≥1500+GLY5to10	MET≥1500+VIL100	NA		
Kim et a;/	2017	Korea	Parallel	NR	34	12 weeks	MET1500+GLM2	MET1500+VIL100	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Goldenberg et al.	2017	Argentina, Canada, Croatia, Estonia, Georgia, Hungary, Israel, Malaysia, Philippines, Poland, Romania, South Africa and the USA	Parallel	≥ 12 weeks	642	24 weeks	MET≥1500+SIT100	MET≥1500+OMA25QW	NA		
Hong et al.	2017	Korea	Parallel	≥ 12 weeks	222	24 weeks	MET≥1000+SIT100	MET≥1000+EVO5	NA		
Gurkan et al.	2017	Turkey	Parallel	≥ 8 weeks	34	26 weeks	MET2000+EXE0.02	MET2000+IGA	NA		
Tinahones et al.	2017	Argentina, Australia, Canada, Germany, Italy, Portugal, Russia, Spain, the Ukraine and the USA	Parallel	≥12 weeks	256	24 weeks	MET≥1500+EMP10+PLA	MET≥1500+EMP10+LIN5	NA		
Pan et al.	2017	China	Parallel	≥ 12 weeks	197	16 weeks	MET1484+PLA	MET1472+ALO25	NA		
Frias et al.	2017	US	Parallel	≥ 8 weeks	117	10 weeks	MET1875+PLA	MET1925+EXE2QW	NA		
Younis et al.	2017	Israel	Parallel	≥ 2 weeks	60	12 weeks	MET850to2550+PLA	MET850to2550+VIL25or50	NA		
Rosenstock et al.	2018	Internationl	Parallel	≥ 8 weeks	621	26 weeks	MET≥2000+PLA	MET≥2000+ERT5	NA		
Wang et al.	2016	China, Philippines, and Malaysia	Parallel	≥ 6 weeks	306	24 weeks	MET≥1500+PLA	MET≥1500+LIN5	NA		
Frías et al.	2016	Six countries	Parallel	≥ 8 weeks	695	28 weeks	MET≥1500+DAP10	MET≥1500+EXE2QW	NA		
Asti et al.	2016	Italy	Parallel	NR	128	16 weeks	MET+SAX5	MET+SIT100	NA		

Author	Year	Country	Design	Duration of stable background therapy	No. Randomized	Trt. duration	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Kim et al.	2016	Korea	Parallel	≥ 4 weeks	228	16 weeks	MET≥1000+ VIL100	MET≥1000+ PIO15	NA		
Frías et al.	2017	US	Parallel	≥12 weeks	117	10 weeks	MET1875+PL A	MET1925+E XE2QW	NA		
Amin et al.	2015	Canada, India, Korea, Mexico, and US	Parallel	≥ 6 weeks	328	12 weeks	MET1500+PL A	MET1500+S IT100	MET1500+ ERT25	MET1500+ER T10	MET1500+E RT5
Del Prato et al.	2015	10 countries	Parallel	≥ 8 weeks	814	208 weeks	MET1892.8+ GLI5to20	MET1884+ DAP2.5to10	NA		
Banerji et al	2010	USA	Parallel	≥ 4 weeks	NR	12 weeks	MET1485+VI L100	MET1442+T ZD	NA		
Lu et al.	2016	Korea and Taiwan	Parallel	≥ 8 weeks	171	24 weeks	MET≥1500+ PLA	MET≥1500+ IPR50	NA		

Appendix 4D: Inclusion criteria and criteria for inadequate control for included studies

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Nauck et al.	2014	18 to 75 years, T2DM, HbA1c > 8% and ≤ 9.5% (diet and exercise alone) or ≥ 7% and ≤ 9.5% (on oral antihyperglycemic medication monotherapy or combination therapy), BMI 25 to 40 kg/m2, stable weight during the 3-month period before study	An HbA1c value of 8% (64 mmol/mol) and 9.5% (80 mmol/mol) on diet and exercise alone or 7% (53 mmol/mol) and 9.5% (80 mmol/mol) on oral antihyperglycemic medication (OAM) monotherapy or combination therapy (metformin plus another OAM)
Ross et al.	2015	Adults with T2DM, BMI ≤45 kg/m2, HbA1c ≥7 and ≤10% on diet and exercise with stable metformin IR (≥1500 mg/day)	HbA1C 7-10% on metformin at screening
Moon et al.	2014	18 to 75 years, T2DM, HbA1c 7.5–12.0 % on metformin (>1,000 mg/d), BMI <35 kg/m2	HbA1c 7.5–12.0 % on metformin
Gupta et al.	2015	Uncomplicated T2DM with or without stable co-morbid conditions, HbA1c ≥ 6.5% on metformin (1000-2500 mg/d), fasting blood glucose ≥ 126 mg/dl, post prandial blood glucose ≥200 mg/dl	HbA1c ≥ 6.5% on metformin
Hissa et al	2015	18 to 70 years, T2DM, HbA1c > 7.5 % on metformin (≥1,000 mg/d), BMI ≥ 22 and ≤ 40 kg/m2.	HbA1c > 7.5 %
Inagaki et al.	2015	Outpatients, ≥ 20 years, T2DM for at least 3 mo, HbA1c ≥7.0 to ≤10.0% (monotherapy) or ≥7.0 to ≤10.6% (combination therapy) were eligible for the present study. Patients who had used a sulfonylurea (glimepiride, gliclazide or glibenclamide), a glinide (nateglinide or mitiglinide), an a-glucosidase inhibitor (a-GI; voglibose, miglitol or acarbose), a biguanide (metformin), a thiazolidinedione (pioglitazone) or a dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin, vildagliptin or alogliptin) for ≥83 days before week 0 were eligible for combination therapy in the present study.	≥7.0 to ≤10.0% (monotherapy, baseline diet/exercise only) or ≥7.0 to ≤10.6% (combination therapy, baseline diet/exercise+1 OAD)
Odawara et al.	2014	≥20 to <75 years, T2DM, BMI ≥20 to ≤35 kg/m2, HbA1c ≥7.0% to ≤10.0%, inadequately controlled on diet, exercise and metformin	HbA1C 7-10% on metformin
Chen et al.	2014	Outpatients, 30-70 years, T2DM, HbA1c 7.0 to 11.0% on mono- or dual- OAD therapy	HbA1C 7-11% on metformin
Kawamori et al.	2014	> 20 years, T2DM, HbA1c 6.9–9.4% on metformin (750, 1,500 or 2,250 mg/d) in addition to diet and exercise	HbA1c 6.9–9.4% on metformin
White et al.	2014	18 to 78 years, HbA1c level 7.0%–10.0%, stable metformin IR monotherapy (≥1500 mg/d), fasting C-peptide value ≥0.8 ng/mL, BMI ≤45.0 kg/m2	HbA1C 7.0-10.0%
Kadowaki et al.	2013	20 to <75 years, T2DM	HbA1c > 6.9 and < 10.5%

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Neutel et al.	2013	18 to 78 years, T2DM, HbA1c 7.5–11.5% (metformin IR or XR ≥850 and ≤1,500 mg), fasting C-peptide ≥1.0 ng/mL, BMI ≤40 kg/m2 at screening."	HbA1C 7.5-11.5%
Chawla et al.	2013	≥ 18 years, T2DM, HbA1c 7.5-11% (metformin monotherapy ≥ 1500 mg/d), fasting plasma glucose ≥140 mg/dL	HbA1C 7.5-11%
Bergenstal et al.	2012	18 to 75 years, T2DM, HbA1c ≥7.0% to ≤10.0% (metformin ≥1,500 mg/d or maximally tolerated dose, BMI ≥25 kg/m2 ([23 for Asians) to ≤45 kg/m2	HbA1C 7.0-10.0%
Cho et al.	2010	30 to 70 years, T2DM, duration of diabetes of <10 yr, BMI 20–35 kg/m2, HbA1c 7.5–11%	HbA1c >7.0% at the end of the metformin run-in phase
Wang et al.	2015	Outpatients, > 60 years, FBG >8.5 mmol/L, HbA1c >7.5% on metformin	NR
Jin et al.	2015	19 to 75 years, T2DM for at least 3 months, HbA1c 7.0-10.0 % (metformin ≥1000 mg/d), fasting blood glucose of ≤270 mg/dL	HbA1c between 7.0-10.0 % on metformin monotherapy of ≥1000 mg/day for ≥ 4 weeks
Xiao et al.	2015	T2DM, HbA1c ≥ 7.0% on metformin	HbA1C ≥ 7% on metformin
Rosenstock et al.	2015	≥18 years, T2DM, HbA1c ≥8.0% and ≤12.0% on metformin (≥1,500 mg/day), Cpeptide concentrations ≥1.0 ng/mL, BMI ≤45.0 kg/m2	HbA1C >=8.0% and <=12.0%
Rosenstock et al.	2015	18 to 75 years, T2DM, fasting plasma glucose < 270 mg/dL, metformin (> 1500 mg/d)	HbA1C 7–10.5%
Kim et al.	2015	T2DM, HbA1c 7.0–10.0%, metformin (≥1000 mg/day)	HbA1C 7-10% on metformin
Kashiwagi et al.	2015	≥ 20 years, T2DM, HbA1c 7.4–9.9% on metformin, BMI 20.0–45.0 kg/m2	HbA1C 7.4-9.9% and a BMI 20.0-45.0 kg/m^2
Aaboe et al.	2015	Outpatients, ≥18 years; HbA1c 7.0–10.0%, metformin (≥1000 g/d), BMI ≥25 kg/m2	HbA1C 7.0-10.0%
Schumm-Draeger et al.	2015	18 to 77 years, T2DM, HbA1c ≥6.7 and ≤10.5%, metformin (≥1500 mg/d)	HbA1C 6.7-10.5%
Ji et al.	2015	Women, ≥ 18 and ≤80 years, T2DM HbA1c ≥7.0 and ≤10.5%, metformin or metformin+sulphonylurea (both at maximum or near-maximum effective doses)	glycated haemoglobin (HbA1c) ≥7.0 and ≤10.5%
Gurkan et al.	2014	40 to 70 years, T2DM, HbA1c 7–9.5%, BMI 25–45 kg/m2, metformin (2.1 g/d)	NR

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Del Prato et al.	2014	18 to 80 years, T2DM, BMI ≥23 and ≤45 kg/m2 (Asian ≥20 and ≤35 kg/m2), HbA1c 7.0–9.0% with fasting plasma glucose <15.3 mmol/l on stable metformin (≥1500 mg or maximum tolerated dose [MTD]), or HbA1c of 7.5–10% on metformin <1500 mg without documented MTD, with HbA1c values 7.0–9.0% and FPG <15.3 mmol/l after metformin stabilization (≥1500 mg or MTD)	"(i) glycated haemoglobin (HbA1c) level 7.0–9.0% with fasting plasma glucose (FPG) <15.3 mmol/l on stable metformin (≥1500 mg or maximum tolerated dose [MTD]), or (ii) HbA1c of 7.5–10% on metformin <1500 mg without documented MTD, with HbA1c values 7.0–9.0% and FPG <15.3 mmol/l after metformin stabilization (≥1500 mg or MTD) for 8 weeks."
Nandy et al.	2014	40 to70 years, BMI ≥ 40kg/m2, T2DM, HbA1c of 6.5%–9.0%, lifestyle changes alone or metformin	NR
Forst et al.	2014	45 to 75 years, T2DM, HbA1c 6.5–8.5% on metformin	HbA1C 6.5–8.5% on metformin
Dungan et al.	2014	≥18 years of age, T2DM diet and exercise and metformin (>=1500 mg/d), HbA1c value of ≥7·0% to ≤10·0%, stable weight (±5%) for at least 3 mo, BMI ≤45 kg/m2	NR
Ridderstrale et al.	2014	≥18 years T2DM, BMI <= 45 kg/m², HbA1c 7–10%, metformin immediate release (≥1500 mg/d, maximum tolerated dose, or maximum dose according to the local label)	HbA1C 7-10%
Ohira et al.	2014	T2DM, inadequately controlled despite on-going treatment with metformin 500 mg/d	NR
Ahren et al.	2014	≥18 years, T2DM, inadequate glycemic control on metformin (≥1,500 mg or maximum tolerated dose), HbA1c 7.0% to 10.0%, BMI 20–45 kg/m2; creatinine clearance >60 mL/min, and normal thyroid-stimulating hormone concentration or were clinically euthyroid	HbA1C 7.0-10.0% on metformin
Derosa et al.	2014	≥ 18 years, T2DM, inadequately controlled T2DM, HbA1c 7.0%–9.0% on metformin	HbA1c 7.0% - 9.0% on metformin
Diamant et al.	2014	≥18 years, T2DM, suboptimum glycaemic control, HbA1c 7·1–11·0% on maximum tolerated doses of metformin alone or with a sulfonylurea, stable bodyweight for at least 3 months, BMI 25–45 kg/m² (23–45 kg/m² in South Korea and Taiwan)."	HbA1c 7·1–11·0%
Haring et al.	2014	≥ 18 years, BMI ≤ 45 kg/m2, inadequately controlled T2DM, HbA1c ≥ 7% to ≤ 10% despite diet and exercise program and stable immediate release metformin	HbA1c ≥ 7% to ≤ 10% on diet and exercise program and metformin
Bolli et al.	2014	24 to 79 years, T2DM (≥ 1 year since diagnosis), metformin (1.5 g/d), HbA1c 7–10%	HbA1c 7–10% , inclusive, on metformin
Berndt-Zipfel et al.	2013	30 to 80 years, HbA1c 6.5 to 9.5% on metformin	HbA1C 6.5-9.5% on metformin
Genovese et al.	2013	35 to75 years, T2DM taking metformin (2000-3000 mg/d), reduced HDL-C levels (<40 mg/dl in males, <50 mg/dl in females), irrespective of statin treatment, central obesity (waist circumference ≥94 cm for men, ≥80 cm for women)	NR

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Rosenstock et al.	2013	21 to 84 years, T2DM, taking metformin (≥1.5 g/d), HbA1c 7–10%	HbA1c 7–10% (between 53 and 86 mmol/mol) on metformin
Kim et al.	2013	18 to 80 years, T2DM for <10 yr, HbA1c 6.5–8.0%, BMI 20–30 kg/m2.	HbA1C 6.5-8.0% on metformin
Cefalu et al.	2013	18 to 80 years, T2DM, HbA1c 7·0–9·5%, metformin (≥2000 mg/d or ≥1500 mg/d if unable to tolerate a higher dose). Participants takin gmetformin in combination with one other oral non-thiazolidinedione antihyperglycaemic drug at screening discontinued the second antihyperglycaemic drug and, if needed, had their metformin dose increased"	A1C of 7 to 9.5% on metformin
Derosa et al.	2013	>18 years, T2DM, naïve to treatment, poor glycemic control (HbA1c >7.5%), BMI ≥25, weight <34.9 kg·m−2	HbA1C >7.5%
Henry et al.	2013	18 to 70 years, T2DM for a minimum of 6 mo, stable dose of metformin for at least 3 mo, HbA1C ≥7% and ≤10%, FPG <240 mg/dL, BMI ≤40 kg/m^2, stable body weight for 3 mo prior to study entry	NR
Ahren et al.	2013	T2DM, inadequately controlled on metformin (≥1.5 g/d), HbA1c 7–10%	HbA1c 7–10% on metformin
Kapitza et al.	2013	37 to 74 years, T2DM, HbA1c 6.5%–9.0%, on meformin ≥1.5 g/d	HbA1C 6.5-9.0% on metformin
Charbonnel et al.	2013	18 to 79 years, T2DM on metformin (≥1,500 mg/d), HbA1c ≥7.0% and ≤11.0%, fasting finger stick glucose <15 mmol/l	HbA1C 7-11% on metformin
Forst et al.	2013	30 to 80 years, T2DM, HbA1c > 6.5% to ≤ 9.5%. Patients with cardiovascular preconditions (CHD or MI): HbA1c > 7.0% ≤ 9.5%, metformin at maximal or maximal tolerated dosage	HbA1C > 6.5 and ≤9.5% on metformin; HbA1C > 7.0 and ≤9.5% for patients with cardiovascular preconditions
Rhee et al.	2013	18 to 75 years, T2DM, metformin (1000 mg/d or higher)	NR
Wilding et al.	2012	≥18 years, T2DM for ≥6 months, HbA1c of 7.0–9.5%, metformin (≥1500 mg/d), had received routine advice about diet and exercise as part of their usual clinical care, BMI 20–45 kg/m2	HbA1C 7.0-9.5%
Derosa et al.	2012	"Caucasian", > 18 years, T2DM for 6 months, treatment naıeve, poor glycemic control, HbA1c level > 63.9 mmol/mol to < 96.7 mmol/mol, BMI >= 25 to < 30 kg/m2	HbA1C 63.9-96.7 mmol/mol
Hermans et al.	2012	> 18 years, T2DM, insufficient glycaemic control on submaximal metformin (1500-1700 mg/d; HbA1c 7.0%– 10.0%)	HbA1C 7.0-10.0%
Derosa et al.	2012	"Caucasian", > 18 years, T2DM drug-naı¨ve, poor glycemic control, HbA1c level >8.0%, BMI ≥25, and <30 kg/m2	HbA1C >8.0%
Guerci et al.	2012	18 to 80 years, BMI 22–45 kg/m2, T2DM, HbA1c 6.5–8.0% on metformin (maximum tolerated daily dose of at least 1500 mg)	HbA1C 6.5-8.0%

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Monnier et al.	2012	T2DM, inadequate glycemic control, HbA1c level >7% on metformin monotherapy (1,700 to 3,000 mg/d) provided that HbA1c was not greater than 9%	HbA1c level >7% on metformin
Rizzo et al.	2012	T2DM, without adequate glycemic control (HbA1c >7.5%) on metformin treatment at maximal dose (2,000 mg/d)	HbA1C >7.5%
Seino et al.	2012	≥20 and <65 years, T2DM, HbA1c value ≥6.9 to <10.4% on metformin plus specific dietary and exercise therapies."	HbA1C 6.9-10.4%
Yang et al.	2012	Chinese, 18–78 years, T2DM, inadequate glycemic control (i.e. HbA1c ≥7.5% and ≤11.0%) while on metformin monotherapy (1000 or 1700 mg⁄d)	HbA1C 7.5-11 %
Gallwitz et al.	2012	18 to 80 years, T2DM, metformin at a stable dose (1500 mg/d or more or a maximum tolerated dose less than 1500 mg/d) alone or with one other oral antidiabetic drug, HbA1c 6·5–10·0% (on metformin alone) or 6·0–9·0% (on metformin and one additional oral antidiabetic drug), BMI 40 kg/m² or less	HbA1C 6.0-9.0%
Srivastava et al.	2012	>18 years, T2DM, using metformin with inadequate glycemic control (HbA1C >7% and <10%)	HbA1C levels > 7% and < 10% on metformin
Koren et al.	2012	18 to 75 years, T2DM, inadequate glycemic control (HbA1c > 7%) on metformin	(HbA1c > 7%
Pan et al.	2012	18 to 78 years, T2DM, inadequately controlled by metformin, HbA1c 7.0–10.0% (at least 1500 mg/d), BMI 20–40 kg/m2, fasting plasma glucose < 270 mg/dl (15 mmol/l)	HbA1c of 7.0–10.0%
Gallwitz et al.	2012	18 to 85 years, T2DM, BMI ≥ 25 kg/m² to < 40 kg/m², maximum tolerated doses of metformin, and suboptimum glycaemic control, HbA1c 6·5% andm ore or 9·0% and less	HbA1c 6·5% and more or 9·0% and less.
Aschner et al.	2012	35 to 70 years, T2DM for at least 6 mo, HbA1c of 7% or greater and less than 11%, BMI 25 kg/m² to 45 kg/m²	HbA1C 7-11%
Rosenstock et al.	2012	18 to 65 years, T2DM for at least 3 months, HbA1C >=7% and <=10.5%, metformin monotherapy (>=1,500 mg/d),stable body weight, BMI 25–45 kg/m2 (24–45 kg/m2 for those of Asian descent), serum creatinine levels <1.5 mg/dL for men and <1.4 mg/dL for women	HbA1C 7-10.5%
DeFronzo et al.	2012	18 to 80 years, BMI 23 to 45 kg/m2; fasting C-peptide ≥ 0.26 nmol/liter, T2DM, inadequately controlled by metformin monotherapy (≥1500 mg/d), systolic/diastolic blood pressure no greater than 160/100 mm Hg, hemoglobin of at least 12 g/dl for men and at least 10 g/dl for women, alanine aminotransferase no more than 2.5 times the upper limit of normal, TSH no greater than the upper limit of normal, serum creatinine below 133 umol/liter (for men) or below 124 umol/liter (for women)	HbA1c 7.5 to 10%,n metformin

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Bolinder et al.	2012	Women aged 55–75 years who were postmenopausal for at least 5 yr or men aged 30 –75 yr; T2DM, HbA1c 6.5– 8.5%; fasting plasma glucose <= 240 mg/dl, BMI 25 kg/m2 or higher; weight no higher than 120 kg, metformin (at least 1500 mg/d)	HbA1c ≥6.5% and ≤8.5%
Fonseca et al.	2012	Adults, T2DM, inadequate glycaemic control, HbA1c, 7.5–11.0%, metformin (850–1500 mg/d), fasting C-peptide levels ≥1.0 ng/ml, BMI ≤45 kg/m2.	HbA1C 7.5-11.0%
Wang et al.	2011	Outpatients, 30-70 years, T2DM, mono- or dual OAD therapy HbA1c 7.0% to 11.0%	HbA1C 7.0-11.0%
Yang et al.	2011	≥18 years, T2DM, HbA1c 7.0–10.0% on metformin (1500 mg/d), C-peptide level 0.33 nmol/L	HbA1C 7.0-10.0%
Stephens et al.	2011	40 to 70 years, T2DM (diagnosed after the age of 40 years with no history of ketosis), nonsmokers (≥12 months), monotherapy with metformin (1.5–3.0 g/d), HbA1c 7.5–10.5%	HbA1C 7.5-10.5% on metformin
Petrica et al.	2011	T2DM for at least 5 yr), poor glycaemic control (HbA1c > 7%) on metformin	HbA1c > 7%
Lin et al.	2011	Outpatients, 30–70 years, T2DM, treated with one or two oral antidiabetic drugs, HbA1c 7.0% to 11.0%.	HbA1C 7% to 11% on one or two oral antidiabetic drugs; The baseline HbA1c level and reduction of HbA1c value during this 8-week run-in period were not different between the two groups.
Terra et al.	2011	18 to 70 years, T2DM, inadequate glycaemic control, HbA1c > 7 % to < 11 % on metformin, BMI >25 kg/m2 and <45 kg/m2	HbA1C 7% to 11%
Derosa et al.	2011	≥18 years, T2DM, poor glycemic control, HbA1c >8.0%, BMI ≥25 and <30 kg/m2, metformin (1000–2000 mg/day) and were intolerant to metformin at the highest dosages (2500–3000 mg/day	HbA1C >8.0%
Derosa et al.	2011	"Caucasian", ≥18 years, T2DM, uncontrolled T2DM, HbA1C >7.0% on diet, physical activity, and metformin (mean dosage: 1700±850 mg/d). "	HbA1C >7.0%
Pfutzner et al.	2011	18 to 75 years, T2DM, metformin (individually maximal tolerated dosage), HbA1c of ≥6.5%, HDL cholesterol ≤1.03 mmol/L (40 mg/dL) and/or triglycerides ≥1.7 mmol/L (150 mg/dL)	NR
Zinman et al.	2011	18 to 75 years, T2DM for at least 3 mo, HbA1C 7·0–11·0%, BMI 23–42 kg/m², insulin-naive, treated with one or two oral antidiabetic drugs (metformin, α-glucosidase inhibitors, sulphonylurea, or meglitindes) for more than 2 months at stable half-maximum to maximum allowed doses.	HbA1C 7% to10% on one or two oral antidiabetics drugs (metformin, α-glucosidase inhibitors, sulpho nylurea, or meglitindes)

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Heise et al.	2011	18–75 years, T2DM, HbA1C 7–11%, BMI of 25–37 kg/m2 , insulin-naïve (no previous insulin treatment or insulin treatment for <=14 days in the 3 months prior to trial), treated with up to two OADs in the 2 months prior to trial at stable maximum doses or at least half maximum allowed doses	A1C of 7% to 11%
Gallwitz et al.	2011	Adults, T2DM, HbA1C 6.5–10.0%	HbA1C 6.5% to 10.0% on metformin
Arechavaleta et al	2011	≥18 years, T2DM, with inadequate glycaemic control, HbA1c ≥ 6.5 and ≤9.0% on metformin (≥1500 mg/d) as well as diet and exercise	HbA1C 6.5% to 9.0% on metformin
Yang et al.	2011	18 to 80 years (18–75 years for Chinese subjects), T2DM, one or more oral antidiabetic drugs (OADs) for at least 3 months, HbA1c level ≥7.0% and ≤11.0% for subjects on OAD monotherapy or ≥7.0% and ≤10.0% for subjects on OAD combination therapy, BMI ≤45.0 kg/m2	HbA1c ≥7.0% and ≤11.0% on metformin
Taskinen et al.	2011	18 to 80 years, T2DM, BMI ≤40 kg/m2, metformin (≥1500 mg/day or maximum tolerated dose) and not more than one other oral antidiabetes medication, HbA1c 7.0% to10.0%	HbA1C 7.0% to 10.0% on metformin and not more than one other oral antidiabetes medication
Forst et al.	2010	21 to 75 years, T2DM for at least 3 months, BMI 25 to 40 kg⁄m2, inadequate glycaemic control despite treated with metformin alone or with metformin and one other oral hypoglycaemic agent other than rosiglitazone or pioglitazone. For patients previously treated with metformin and one other oral anti-diabetic drug, inadequate glycaemic control was defined as HbA1c level 7.0% to 9.0%; for patients previously treated with metformin alone, inadequate glycaemic control was defined as HbA1c from 7.5% to 10.0%	HbA1C 7.5% to 10%
Goke et al.	2010	≥18 years, T2DM, HbA1c > 6.5% to 10.0% on metformin≥1500 mg⁄d)	HbA1C 6.5% to 10.0%
Scheen et al.	2010	≥18 years, T2DM, uncontrolled (HbA1c 6.5% to 10.0%) despite metformin (≥1500 mg)	HbA1C 6.5% to 10.0%
Stenlof et al.	2010	18 to 77 years, T2DM, inadequate glycemic control (HbA1c 7% to 10%) on metformin immediate release (IR) or metformin XR 1500 mg per day, BMI ≤40 kg/m2, fasting C-peptide concentration 1 ng/mL (0.33 nmol/L)	HbA1C 7% to 10% on metformin
Ratner et al.	2010	30 to75 years, T2DM of at least 1 year's duration, inadequately controlled [HbA1c ≥7.0 and <9.0% on metformin (≥ 1000 mg⁄d)	HbA1c ≥7.0 and < 9.0% on metformin
Bergenstal et al.	2010	≥18 years T2DM, otherwise healthy, HbA1c of 7·1–11·0% on metformin, BMI 25–45 kg/m²	HbA1c of 7·1% to 11·0% on metformin
Bailey et al.	2010	18 to 77 years, T2DM, HbA1c 7–10%, C-peptide concentration 0·34 nmol/L or more, BMI 45 kg/m² or less, metformin (≥1500 mg/d)	HbA1C 7% to 10%
Filozof et al.	2010	18 to 78 years, T2DM, HbA1c7.5% to 11.0%, metformin (≥1500 mg /d)	HbA1C 7.5% to 11.0%

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DeFronzo et al.	2010	18 to 75 years, BMI 25–40 kg/m2, stable body weight for at least 6 months, HbA1C 6.8–10.0%, metformin, absence of islet cell autoantibodies	NR
Pratley et al.	2010	18 to 80 years, T2DM, HbA1c 7·5% to10·0%, BMI 45·0 kg/m² or lower, metformin (≥1500 mg/d)	HbA1C 7.5% to 10.0%
Apovian et al.	2010	18 to 75 years, T2DM, metformin or a sulfonylurea, HbA1c 6.6%-10.0%, BMI 25-39.9 kg/m2, stable body weight (not varying by 5% for at least 6 months before screening)	NR
Kadoglou et al.	2010	Inadequaate control on metformin (850 mg/d), HbA1c >6.5%, BMI >25 kg/m2	HbA1C >6.5%
Petrica et al.	2009	T2DM for at least 5 years, poor glycemic control, HbA1c >7% on metformin	HbA1C >7%
Scheen et al.	2009	35 to 75 years, T2DM, HBA1c > 6·5% despite diet alone or oral glucose-lowering agents with or without insulin	HBA1c > 6·5%
Blonde et al.	2009	18 to 80 years, T2DM, inadequately controlled HbA1c of 7–10% on metformin (≥1000 mg/day), BMI 22–41 kg/m2, fasting plasma glucose (FPG) <270 mg/dl (15 mmol/l)	HbA1C 7% to10%
Defronzo et al.	2009	18 to 77 years, T2DM, HbA1C ≥7.0 and ≤ 10.0%; metformin (≥1500 mg/d, but not > 2550 mg/d), fasting C-peptide concentration ≥1.0 ng/ml, BMI ≤40 kg/m2.	A1C ≥ 7.0 and ≤10.0%
Home et al.	2007	40 to 75 years, T2DM, inadequately controlled, metformin or sulphonylureas, BMI > 25.0 kg/m2, HbA1C > 7.0–9.0%	HbA1c > 7.0% to 9.0%
Papathanassiou et al.	2009	T2DM, A1c>6.5% on metformin, normal liver enzymes and renal function	A1c>6.5%
Goodman et al.	2009	18 to 78 years, HbA1c 7.5-11%, metformin (≥1500 mg/d), BMI 22-40 kg/m2, FPG <270 mg/dl (<15 mmol/l)	HbA1c 7.5% to 11%
Bunck et al.	2009	30 to 75 years, HbA1C 6.5% to 9.5%, BMI 25–40 kg/m2, metformin	HbA1C 6.5% to 9.5% on metformin
Kaku et al.	2009	≥20 and <65 years, T2DM, treated with diet and exercise, but no antidiabetic drugs other than metformin	HbA1C 6.5% to 10%
Nauck et al.	2008	18-80 years, "historical" diagnosis of T2DM, inadequate glycaemic control, HbA1c 7.0% to 10.0% despite metformin (≥1500 mg/d), BMI 23 to 45 kg⁄m2, C-peptide concentration ≥ 0.26 nmol⁄l (0.8 ng⁄ml), serum creatinine < 1.5 mg⁄dl (men) or < 1.4 mg⁄dl (women), fasting plasma glucose (FPG) < 275 mg⁄dl (< 15.3 mmol⁄l)	HbA1c 7.0% to 10.0%
Ferrannini et al.	2009	18 to 73 years, T2DM, HbA1c 6.5–8.5%, metformin (1500 mg/d), BMI 22–45 kg/m2	HbA1c 6.5% to 8.5%
Gao et al.	2009	21 to 75 years, treated immediate release metformin (>=1000 mg/d), met (≥1000 mg/d) and SU; or SU/Met combination therapy, HbA1c 7.1% and 11.0%, BMI >21 kg/m2 and <35 kg/m2.	A1c ≥ 7% to ≤11%
Nauck et al.	2009	18 to 80 years, T2DM, HbA1C 7 to 11%, BMI ≤40 kg/m2	HbA1c 7 % to 11%

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Scott et al.	2008	18 to 75 years, T2DM, metformin (≥1500 mg/d), inadequate glycaemic control (A1C ≥7 and ≤11%)	HbA1c 7% to 11%
Komajda et al.	2008	40 to 75 years, T2DM, BMI > 25.0 kg/m2 and HbA1c 7.1–9.0%, on maximum permitted or tolerated doses of metformin or a sulfonylurea (glibenclamide [glyburide], glimepiride or gliclazide), BP < 180/105 mmHg	HbA1c 7.1% to 9.0% on metformin or sulfonylurea monotherapy
Khanolkar et al.	2008	T2DM, sub-optimal glycaemic control (HbA1c > 6.5%) on metformin	HbA1c > 6.5% on metformin
Garcia-Soria et al.	2008	T2DM for >6 months but <10 years, metformin alone (≥1500 mg/d or highest tolerated dose) or in combination with a glitazone (any labelled dose)	NR
Raz et al	2008	18 to 78 years, T2DM, metformin monotherapy or any other single OHA, or being treated with metformin in combination with another OHA, HbA1c value 8% to 11%	HbA1c 8% to 11% on metformin
Hamann et al.	2008	Overweight (BMI ≥25 kg/m2), T2DM, HbA1C ≥7% and <10%, metformin (≥850 mg/day)	HbA1c 7% to 10%
Bolli et al.	2008	18 to 77 years, T2DM, HbA1C 7.5–11.0%, metformin (≥1500 mg/d), BMI 22–45 kg/m2, fasting plasma glucose (FPG) of <15 mmol/l	HbA1c of 7.5% to 11.0% at the screening visit while receiving a stable dose of metformin ≥ 1500 mg/day (inadequately controlled with prior metformin monotherapy)
Bosi et al.	2007	18 to 78 years, T2DM, metformin (≥1,500 mg/d), HbA1c 7.5% to 11.0%, BMI 22–45 kg/m2, FPG <15 mmol/l	A1C 7.5% to 11.0% on metformin
Nauck et al.	2007	18 to 78 years, T2DM, not on an OHA, OHA monotherapy, or metformin in combination with another OHA	HbA1c 6.5% and 10% after the metformin dose-stable period (8-wk run-in)
Brazg et al.	2007	25 to 75 years, T2DM, inadequate glycaemic control, metformin (≥1500 mg/d) HbA1c ≥6.5% and <10%, fasting plasma glucose (FPG) ≤240 mg/dl at screening	on a stable dose of 1500 mg/day for 6 weeks prior to the screening visit and an haemoglobin A1c (HbA1c) 6.5% and <10% and fasting plasma glucose (FPG) 240 mg/dl)
Derosa et al.	2007	"Caucasian", ≥ 18 yearsr, T2DM, poor glycaemic control (HbA1c >7.5%) or experienced adverse effects with diet and oral hypoglycaemic agents, such as SU or metformin, and diagnosed metabolic syndrome and triglyceridaemia (triglycerides Tg ≥1.70 mmol/L10), hypertension (systolic/diastolic blood pressure, ≥30/≥85 mmHg), fasting C-peptide level >0.33 nmol/L, BMI 25.0–28.1 kg/m2	HbA1C >7.5%
Charbonnel et al.	2006	18 to 78 years, T2DM, inadequate glycemic control, HbA1c ≥7 and ≤10% on metformin (≥1,500 mg/d)	≥7% and ≤10% HbA1c

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Nauck et al.	2006	18 to 70 years, T2DM for a minimum of 1 yr, treated with at least 50% of maximum dose of one or two OHA(s) (except TZD), BMI 25–40 kg/m2, HbA1c 8–13 %, fasting plasma glucose (FPG) ≥10 mmol/L	at least 50 % of maximum dose of one or two OHA(s) (except a TZD)
Goldstein et al.	2005	18 to 75 yr, T2DM, HbA1c of 6.5%–8.5% for subjects having received prior combination treatment (MET + SU) and 7%–10% for drug naive or prior monotherapy subjects; fasting plasma glucose (FPG) of 7.0–15.0 mmol/L (126– 270 mg/dL); and a body mass index (BMI) ≥ 27 kg/m2. Previous treatment could include either diet and exercise or oral therapy (acarbose, SU, MET or MET + SU). Any subject previously receiving MET or MET + SU must have received MET ≤ 1000 mg/day for at least 3 months prior to study entry. Subjects must have stopped previous treatment with TZDs at least 3 months prior to screening.	HbA1c of 6.5%–8.5% for subjects having received prior combination treatment (MET + SU) and 7%–10% for drug naive or prior monotherapy subjects
Bakris et al.	2006	40 to 80 years, T2DM, previously treated with diet and exercise alone, a single oral antidiaetic agent, or combination oral antidiabetic therapy; capillary fasting plasma glucose (FPG) levels > 6.6 mmol/l at visit 3; able to tolerate MET at a minimum dose of 1 g/day.	fasting plasma glucose (FPG) levels > 6 mmol/l on previous treatment with diet and exercise alone, a single oral antidiabetic agent, or combination oral antidiabetic therapy, baseline HbA1c is 8.3-8.5 %.
Ristic et al.	2006	T2DM for ≥ 6 months, inadequately controlled on metformin (>=1000 mg/d) and diet and exercise, HbA1C 6.8–9.0%, BMI 20-35 kg/m2	A1c 6.8% to9.0%
Umpierrez et al	2006	18 to 79 years, T2DM for at least 6 months, metformin (1-2.5 g/d) or extended release metformin (0.5 - 2.0 g/d), BMI ≥ 24, HbA1C 7.5 - 10%, FPG 126 - 235 mg/dL (7-13 mmol/L), C-peptide concentration ≥ 0.27 nmol/L	A1C 7.5% to 10% on Metformin
Garber et al.	2006	20 to 78 years with T2DM requiring oral therapy, metformin (1500 mg/d), HbA1C >7.0 and ≤12.0%, BMI ≥23 and ≤45 kg/m2.	A1c > 7.0% to ≤12% on metformin
Kvapil et al.	2006	Not adequately controlled on metformin (850mg/d), HbA1c 7.5% to 13.0%	
Poon et al.	2005	18 to 65 year, T2DM, HbA1C 6.8-9.0% on metformin, FPG < 240 mg/dl, BMI 27-45 kg/m2, stable body wieght, no clinically relevant abnormal laboratory test values	NR
Feinglos et al.	2005	30 to 81 years, T2DM for at least 6 months, HbA1c 7.0% to 8.5%, inadequate controlled metformin (≥ 1000 mg/d), BMI 27-38 kg/m2	A1c 7.0% to 8.5% on metformin
DeFronzo et al.	2005	19 to 78 years, T2DM, meformin, FPG <13.3 mmol/l (<240 mg/dl), BMI 27–45 kg/m2, HbA1C 7.1–11.0%, metformin (≥1,500 mg/d), stable weight stable for 3 months, no clinically significant abnormal laboratory test values (>25% outside normal laboratory values).	A1c 7.1% to 11%

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Matthews et al.	2005	35 to75 years, HbA1c ≥7.5% or ≤11.0%; fasting C-peptide of ≥1.5 ng/mL (0.50 nmol/L) and stable or worsening glycaemic control for ≥3 months prior to screening	"inadequately managed with metformin alone (at ≥50% of the maximum recommended dose or at the maximum tolerated dose for ≥3 months), were screened"
Ahrén et al.	2004	≥ 30 years, T2DM for at least 6 mo, HbA1c 7.0 to 9.5% on metformin, BMI 20-35 kg/m2	HbA1C 7.0% to 9.5% on metformin
Schernthaner et al.	2004	>35 years, T2DM, diet alone or in combination with metformin or an α-glucosidase inhibitor (acarbose or miglitol), HbA1c 6·9% to 11·5%	glycated haemoglobin (HbA1c) between 6·9% to 11·5%, and have been treated for at least 3 months with diet alone or in combination with metformin or an α-glucosidase inhibitor (acarbose or miglitol)
Raskin et al.	2003	>18 years, T2DM for at least 3 months and BMI values of 24–42 kg/m2. Subjects were stratified by baseline HbA1c value (9% or 9%). Enrolled patients had HbA1c values 7% and 12% in previous monotherapy with a sulfonylurea (at 25% of the maximum dose), metformin (1,000 mg/day), or low-dose Glucovance (glyburide 2.5 mg and metformin 500 mg).	HbA1c values 7% and 12% in previous monotherapy with a sulfonylurea (at 25% of the maximum dose), metformin (1,000 mg/day), or low-dose Glucovance (glyburide 2.5 mg and metformin 500 mg).
Phillips et al.	2003	≥40 years, T2DM for 6 mo or longer, insufficiently controlled by metformin, BMI 25–35 kg/m2, HbA1c 6.8–10.2%	HbA1C 7% to 10% on metformin
Marre et al.	2002	>18 years, T2DM, FPG ≥ 7 mmol/l (126 mg/dl) despite metformin (≥850 mg b.i.d. or ≥500 mg t.i.d.) and diet and exercise, BMI < 40 kg/m2	NR
Marre et al.	2002	≥ 30 years, T2DM for ≥ 6 mo, metformin (>1500 mg/d), BMI 20-35 kg/m2, HbA1C 6.8-11%	A1c: 6.8% to 11%
Gomez-Perez et al.	2002	40 to 80 years, T2DM, fasting C-peptide level ≥0.8 ng/ml, fasting plasma glucose level ≥140 mg/dl and ≤300 mg/dl at weeks 0 and 2 of the metformin maintenance period	Not reported
Van Gaal et al.	2001	30-75 yr, T2DM of at least I yr, inadequately controled by diet and metformin, HbA1c≥7.5 - ≤10.5, BMI 23-40 kg/m2, stable body weight (<5% change) over the 3 months preseding enrolment	Met > 3 monhts, A1c≥7.5%
Charpentier et al.	2001	35 to 70 years newly diagnosed (< 1 yr) T2DM, inadequatley controlled, metformin monotherapy, FBG 7.8-13.9 mmol/L, serum creatinine < 110 umol/L, BMI ≥ 23.0 kg/m2 (women) or ≥ 25.0 kg/m2 (men), no evidence or history of spontaneous weight loss or ketonuriaassociated with glucosuria	fasting blood glucose (FBG) criteria (7.8 mmol/l < FBG < 13.9 mmol/l)

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Halimi et al.	2000	30 to 70 years, T2DM diagnosed at least 1 yr before study, BMI ≥ 25.0 and ≤35.0 kg/m2, poor glycemic control (A1C = >7.0% and <11.0%) on metformin (850 mg/d), serum creatinine level < 135 µmol/l, transaminases, alkaline phophatase and bilirubin liver function parameters less than twice the upper limit of normal, a γ-GT liver function test less than three times the upper limit of normal, and a fasting C-peptide value of ≥ 0.20 µg/l	"Poor glycaemic control was defined as an HbA1c level >7.0 and ≤11.0% for any assay performed during the previous 3 months"
Einhorn et al.	2000	HbA1C value ≥ 8.0% on metformin, BMI 25 to 45 kg/m2, fasting C-peptide level >1.0 ng/mL	glycated hemoglobin [HbA1C] ≥ 8.0%, fasting C-peptide ~1.0 ng/mL) who had been receiving a stable regimen of metformin for ≥ 30 days.
Fonseca et al.	2000	40 to 80 years, T2DM, FPG concentrations 7.8 to 16.7 mmol/L (140 and 300 mg/dL) on metformin (2.5 g/d), fasting C-peptide >= 0.27 nmol/L (0.8 ng/mL), BMI 22 to 38, stable weight (no more than 10% change between screening and baseline)	"FPG concentration range, 7.7-16.7 mmol/L [140-300mg/dL]"
Moses et al.	1999	40 to 75 years, T2DM, HbA1C >7.1% on metformin (1-3 g/day), BMI ≥21 kg/m2.	HbA1C > 7.1%
Rosenstock et al.	1998	> 30 years, T2DM, inadequately controlled on diet and metformin (2,000 or 2,500 mg/d), no other pharmacological therapy for type 2 diabetes was allowed for at least 56 days before screening, HbA1 c between 7 and 10%, stable body weight (within 3 kg) for at least 4 weeks	HbA1C 7% to 10%
Wolever et al.	1997	≥ 18 years, T2DM for at least 6 mo, HbA1C > 7%, except for patients in the diet only group (>6.5%).	HbA1C > 7.0% for treatment groups, >6.5% for diet alone subgroup
Strozik et al.	2015	T2DM, HbA1c 7.5%, metformin (1500 mg/d), BMI 25–35 kg/m2	Not reported
Qiu et al.	2014	18 to 80 years, T2DM, inadequate glycemic control (HbA1c ≥7.0% [53 mmol/mol] and ≤10.5% [91 mmol/mol]) on metformin monotherapy (≥2000 mg/day, or ≥1500 mg/day if unable to tolerate a higher dose), fasting plasma glucose <15 mmol/L at Week -2, and fasting fingerstick glucose ≥6.1 and <15 mmol/L on Day 1."	HbA1C 7.0% to 10.5%
Gaal et al.	2014	Obese (BMI ≥ 30 kg/m2), ≥ 18 to < 50 years, T2DM diagnosed at least 1 year before screening, insufficiently controlled with metformin (1.5 g/d), HbA1c ≥7.0% and ≤10%	HbA1c ≥ 7.0% and ≤ 10%
Bhandare et al.	2013	>18 years, HbA1c > 6.5%, fasting plasma glucose (FPG) < 270 mg/dL, metformin (1000 mg/d), inadequate glycaemic control	HbA1C >6.5% on metformin
Raskin et al.	2007	18 to 75 years, insulin naïve, BMI < 40 kg/m2, body weight < 125 kg (275 lbs), HbA1c ≥ 8%, metformin (≥ 1000 mg/d) as a single agent or in OAD combination therapy	HbA1c≥8%, and to have been previously treated with metformin≥1000 mg/day, as a single agent or in OAD combination therapy, for at least 3 months before the trial
Leiter et al.	2005	20 to 80 years, T2D, FPG ≥7 mmol/l, HbA1C ≤9.5%, metformin (≤1700 mg/d)	FPG >7.0 mmol/l and ≤14.0 mmlol/l plus A1C ≤ 9.5%

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Kilo et al.	2003	≥18 years, T2DM, body weight ≤ 100 kg, BMI ≤ 40 kg/m2, naive insulin treatment, inadequate glycemic control (A1C ≥ 7.5%), metformin as monotherapy or in combinationwith a sulfonylurea or repaglinide, FBG > 126mg/dl (FPG>6.99mmol/l)	not able to achieve the FBG target of 90 – 126 mg/dl on metformin only
Ohira et al.	2014	T2DM, HbA1c > 7.0%, metformin (500 mg/d)	HbA1c > 7.0% on metformin
Yang et al.	2015	≥18 yr, inadequately controlled T2DM (HbA1c ≥7.5% and ≤10.5%), metformin monotherapy (≥1500 mg/d)	HbA1C 7.5% to 10.5%
Merck Sharp & Dohme Corp.	2015	T2DM, metformin (≥1500 mg/d)	NR
Daiichi Sankyo Inc.	2009	HbA1C 7.0% to 10.0% on metformin, may be withdrawn from other (non-metformin) drugs if HbA1C is 6.5% to 9.5 % at screening	HbA1C 7% to 10% (6.5% to 9.5% if on other OADs)
Merck Sharp & Dohme Corp.	2012	T2DM, metformin (≥1500 mg/d), inadequate glycemic control	NR
NCT record	2010 (last updated)	40 to 75 years, T2DM for at least 1 yr, metformin (1.5 to 3g), 6.5% < HbA1c > 8%, 25 < BMI < 35	6.5% < HbA1c > 8% on metformin
NCT record	2015 last update	18 to 80 years, HbA1c 7 to 11%, FPG < 270 mg/dL (15 mmol/L)	A1C 7% to 11%
NCT record	2015 (last update)	T2DM, metformin (at least 1000 mg/day and up to 3000 mg/day), HbA1c 7.5 - 10.5%, BMI >= 20 kg/m^2	HbA1c 7.5 % to 10.5%
NCT record	2016 (last update)	>= 18 yr, T2DM, metformin (at least 1500 mg/d or maximum tolerated dose above or equal to 1000 mg/d), HbA1c 7.0-10.0%, BMI <= 45.0 kg/m2	HbA1c 7.0% to10.0%
Lavalle-Gonzalez et al.	2013	18 to 80 years, inadequate glycaemic control (HbA1c ≥7.0% to ≤10.5%), metformin (≥2,000 mg/day [or ≥1,500 mg/day if unable to tolerate higher dose]), fasting plasma glucose, < 15 mmol/l, fasting fingerstick glucose ≥6.1 mmol/l and <15 mmol/l on day 1.	HbA1C 7.0% to10.5%
Chen et al.	NA	20 to 70 years, BMI 19 to 35 kg/m2; T2DM, metformin (≥1500 mg/d), HbA1c 7.0% to 11%	HbA1c 7.5% to 11% during screening or HbA1c 7.0% to11% before randomization
Henry et al.	2018	18 to 75years, T2DM, BMI ≤45 kg/m2, metformin ((≥1500 mg/d), HbA1c7.5% to 10.5%	HbA1c ≥7.5% and ≤10.5% on metformin
Ridderstråle et al.	2018	Adults with T2DM, BMI ≤45 kg/m2, metformin ((≥1500 mg/d), HbA1c7.o% to 10.0%	HbA1c; 7% to 10% (53-86 mmol/mol)
Yin et al.	2018	18 to 70 years, T2DM, BMI ≥24 kg/m2, metformin ((≥1500 mg/d), HbA1c7.o% to 10.0%	HbA1c between 7.0 % and 10.0%
Müller-Wieland et al.	2018	18 to 75 years, T2DM, BMI ≤45 kg/m2, metformin ((≥1500 mg/d), HbA1c7.5% to 10.5%	HbA1c; 7.5% to 10.5%
Otterbeck et al.	2011	18 to 80 years, T2DM, on stable dose of metformin, HbA1c 7% to 10%	HbA1c; 7% to 10% on stable doses of metformin

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Fofonka et al.	2018	≥18 years, T2DM, metformin, HbA1c between 7.5% and 10%	HbA1c 7.5% to 10%
Pratley et al.	2018	≥18 years, T2DM, metformin monotherapy ≥1500 mg/d, HbA1c ≥7.5% and ≤11.0% (≥58 and ≤97 mmol/mol).	HbA1c ≥7.5% and ≤11.0% (≥58 and ≤97 mmol/mol)
Parthan et al.	2018	30 to 65 years, T2DM, metformin 2000mg/day, HbA1c < 7.5% (< 58.0 mmol/mol)	HbA1c < 7.5% (< 58.0 mmol/mol)
Yin et al.	2018	19 to 70 years, T2DM, BMI ≥24 kg/m^2, Metformin ≥1500mg/day, HbA1c 7.0% to 10.0%	HbA1c level between 7.0% and 10.0%
Kim et al.	2017	>18 years, T2DM, metformin ≥1,000 mg/ day, HbA1c ≥7%, and <10%.	HbA1c ≥7%, and <10%
Min et al.	2017	≥20 years, T2DM, BMI 20.0 to 45.0 kg/m^2, metformin ≥1,500 mg/day (or ≥1,000 mg/day if higher doses were not administered due to safety concerns), HbA1c 7% to 10%	HbA1c 7% to 10%
Hollander et al.	2018	≥18 years, T2DM, metformin≥ 1500 mg/day, HbA1c ≥ 7.0% and ≤ 9.0% [≥ 53 and ≤ 75 mmol/mol].	HbA1c ≥ 7.0% and ≤9.0%
Jameshorani et al.	2017	30 to 60 years, T2DM, BMI 25 to 35 kg/m^2, actively treated with metformin, HbA1c 8% to 9.5%.	HbA1c ≥8% and ≤9.5%
Shi et al.	2017	18 to 65 years, T2DM, BMI≥28 kg/m^2, metformin, HbAlc <8.0%	HbAlc≥8.0%
Vianna et al.	2018	≥40 years, T2DM, postmenopausal women, on stable metformin, HbA1c ≥6.5%	HbA1c ≥ 6.5% and < 9.0%
Gadde et al.	2017	≥18 years, T2DM, BMI ≤45 kg/m^2 and stable body weight (≤3% variation for ≥3 months before screening), metformin ≥1500 mg/d, HbA1c 7.1% to 11.0%, fasting plasma glucose (FPG) <280 mg/ dL at screening	HbA1c 7.1% to 11.0%
Frias et al.	2017	18 to 70 years, T2DM, BMI 27 to 44 kg/m^2, on stable metformin, HbA1c 7.2% to 10.5%, FPG < 250 mg/dL.	HbA1c ≥ 7.2% and ≤ 10.5%
Du et al.	2017	≥18 years, T2DM, metformin ≥1500 mg/d, HbA1c 7.5% to 11.0%, FPG ≤ 13.3 mmol/L.	HbA1c 7.5% to 11.0%
Handelsman et al.	2017	≥ 18 years, T2DM, metformin ≥1500 mg/day, HbA1c ≥6.5% and ≤9.0%, and a fasting finger-stick glucose >7.0 mmol/L (126 mg/dL) and <14.4 mmol/L (260 mg/dL) at randomization."	HbA1c ≥6.5% and 9.0%
Shankar et al.	2017	≥18 years, T2DM, metformin ≥ 1500 mg/day, Hb A1c 7.0% to 10.5%.	HbA1c 7.0% to 10.5%
Dei Cas et al.	2017	≥35 years, T2DM, BMI ≥ 20 or ≤40 kg/m2, metformin ≥ 1500 mg/day, HbA1c 7.0% to 9.0%.	HbA1c 7% to 9%
Kim et al.	2017	20 to 70 years, T2DM, BMI 20–35 kg/m2, metformin 1000–2000 mg/day, HbA1c 7.0–10%, FBG <250 mg/dL (13.9 mmol/L)."	HbA1c 7.0% to 10%
Goldenberg et al.	2017	≥18 years, T2DM, metformin ≥1500 mg/day, HbA1c ≥6.5% and ≤9.0%, a fasting fingerstick glucose >7.2 and <14.4 mmol/L.	HbA1c ≥6.5% and ≤9.0%
Hong et al.	2017	≥18 years, T2DM, BMI≤ 40.0 kg/m2, metformin ≥1000 mg/day, HbA1c ≥6.5% and< 11.0%	HbA1c 6.5% ≤ and < 11.0%

Author	YEAR	INCLUSION CRITERIA	CRITERIA FOR INADEQUATE CONTROL
Gurkan et al.	2017	40 to 70 years, T2DM, BMI 25–45 kg/m2, metformin ≥2000 mg/day, HbA1c 7%–9.5% (53–80 mmol/mol).	HbA1c 7% to 9.5%
Tinahones et al.	2017	≥18 years, T2DM, BMI ≤ 45 kg/m2, metformin ≥1500 mg/day, HbA1c ≥8.0% and ≤10.5%.	HbA1c ≥8.0% and ≤10.5%
Pan et al.	2017	18 to 75 years, T2DM, BMI 20-45 kg/m2, HbA1c 7.0 % to 10.0 %, metformin ≥1000 mg/day, SBP ≤ 180/≤110mmHg, and serum creatinine <132.6 µmol/L in men and <123.8 µmol/L in women.	HbA1c 7.0 % to 10.0 % (inclusive)
Frias et al.	2017	18 to 75 years, T2DM, BMI ≤45 kg/m2, metformin≥1500 mg/day, HbA1c 7.0% and 10.0% (53 and 86 mmol/mol)	HbA1c 7% to 10.0%
Younis et al.	2017	≥21 years, T2DM, documented coronary artery disease >30 days, oral anti-diabetic mono-therapy, HbA1c ≥6.5%,	HbA1c ≥6.5 and ≤7.5%
Rosenstock et al.	2018	≥18 years, T2DM, BMI 18.0 to 40.0 kg/m2, metforrmin ≥1500 mg/day, HbA1c, 7.0%-10.5%.	HbA1c, 7.0% to 10.5%
Wang et al.	2016	18 to 80 years, T2DM, BMI ≤45 kg/m2, metformin ≥1500 mg/day , HbA1c 7.0%–10.0%	HbA1c 7.0% to 10.0%
Frías et al.	2016	≥18 years, T2DM, metformin ≥1500 mg/day, HbA1c 8·0–12·0% [64–108 mmol/mol].	HbA1c 8·0% to 12·0%
Asti et al.	2016	≥18 years, T2DM, mean age 64.3 years [standard deviation (SD) ±8.4], metformin, HbA1c >7.5% and FPG >140 mg/dL	HbA1c >7.5% and fasting glucose (FPG) >140 mg/dL
Kim et al.	2016	18 to 80 years, T2DM, metformin ≥1,000 mg/day, HbA1c 7.0% to 11.0%, FPG <270 mg/dL	HbA1c,7.0% to 11.0% with a stable dose of metformin (≥1,000 mg/day)
Amin et al	2015	18 to 70 years, T2DM, BMI 23–45 kg/m2, on stable metformin, HbA1c 7.0–11.0%.	HbA1c 7.0% to 11.0% (if on metformin monotherapy) or 6.5% to9.5% (if on metformin plus one OAD, excluding thiazolidinediones)
Del Prato	2015	≥ 18 years, T2DM, metformin, HbA1c >6.5% and ≤10%	HbA1c >6.5% and ≤10%
Banerji et al.	2010	≥ 18 years, T2DM, BMI 22–41 kg/m2, GFR >80 mL/min/1.73 m2, metformin (≥1,000 mg/day, HbA1c 7.0% to 10.0%, FPG <270 mg/dL	HbA1c of 7% to 10%
Lu et al.	2016	≥20 years, T2DM, BMI 20-45kg/m2, metformin ≥1,500 mg/day (or ≥1,000 mg/day if higher doses were not administered due to safety concerns), HbA1c between 7% to 10%.	HbA1c 7% to 10%

Appendix 4E1: Risk of bias assessment

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Nauck et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Ross et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Moon et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gupta et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Hissa et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Inagaki et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Odawara et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Chen et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Kawamori et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
White et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kadowaki et al. 2013	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Neutel et al. 2013	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Chawla et al. 2013	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Bergenstal et al. 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Cho et al. 2010	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Wang et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Jin et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Xiao et al.2015	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Rosenstock et al. 2015	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Rosenstock et al. 2015	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	Yes (low risk of bias)
Kim et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kashiwagi e al. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Aaboe et al. 2015	Unclear	Unclear	Yes (low risk of bias)	Unclear	Not applicable

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Schumm-Draeger et al. 2015	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ji et al. 2015	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gurkan et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Unclear	Not applicable
Del Prato et al. 2014	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Nandy et al. 2014	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Forst et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Dungan et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ridderstrale et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ohira et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Unclear	Not applicable
Ahren et al 2014	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Derosa et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Unclear	Unclear
Diamant et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Haring et al. 2014	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Bolli et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Berndt-Zipfel et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Genovese et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Rosenstock et al. 2013	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kim et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Cefalu et al 2013	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Derosa et al 2013	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Henry et al 2013	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ahren et al 2013	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kapitza et al 2013	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Charbonnel et al. 2013	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Forst et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Rhee et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Wilding et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Derosa et al. 2012	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Hermans et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Derosa et al. 2012	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Guerci et al. 2012	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Monnier et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Rizzo et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Seino et al 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Yang et al. 2012	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gallwitz et al. 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Srivastava et al. 2012	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Unclear	Unclear
Koren et al. 2012	No (high risk of bias)	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Unclear
Pan et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gallwitz et al. 2012	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Aschner et al. 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Rosenstock et al. 2012	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
DeFronzo et al. 2012	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Bolinder et al. 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Fonseca et al. 2012	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Wang et al 2011	Yes (low risk of bias)	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Yang et al. 2011	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Stephens st al. 2011	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Petrica et al. 2011	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Terra et al. 2011	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Derosa et al. 2011	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Derosa et al. 2011	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Pfutzner et al. 2011	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Zinman et al. 2011	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Heise et al. 2011	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Gallwitz et al 2011	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Arechavaleta et al 2011	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Yang et al 2011	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Taskinen et al 2011	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Forst et al. 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Goke et al. 2010	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Scheen et al. 2010	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Stenlof et al 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ratner et al. 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Bergenstal et al 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Bailey et al. 2010	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Filozof et al 2010	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
DeFronzo et al. 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Pratley et al. 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Apovian et al. 2010	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kadoglou et al. 2010	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	Not applicable
Petrica et al. 2009	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Scheen et al. 2009	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Blonde et al. 2009	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Defronzo et al. 2009	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Unclear	Unclear
Home et al. 2009	No (high risk of bias)	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Papathanassiou et al 2009	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Goodman et al 2009	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Bunck et al 2009	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kaku et al 2009	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Nauck et al 2008	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ferrannini et al. 2009	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gao et al. 2009	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Nauck et al. 2009	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Scott et al 2008	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	Not applicable
Komajda et al. 2008	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Khanolkar et al. 2008	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Garcia-Soria et al. 2008	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Raz et al 2009	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Hamann et al 2008	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Unclear	Yes (low risk of bias)
Bolli et al 2008	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Home et al. 2007	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Bosi et al. 2007	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Nauck et al. 2007	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Brazg et al. 2007	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
Derosa et al. 2007	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Charbonnel et al. 2006	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Nauck et al. 2006	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Ristic et al. 2006	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Umpierrez et al. 2006	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Garber et al. 2006	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Kvapil et al.2006	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Poon et al. 2005	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Feinglos et al. 2005	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
DeFronzo et al. 2006	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Matthews et al. 2005	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ahrén et al. 2004	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Schernthaner et al. 2004	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Philips et al. 2003	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Marre et al. 2002	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Marre et al. 2002	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gomez-Perez et al. 2002	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Van Gaal et al. 2001	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Charpentier et al. 2001	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Halimi et al. 2000	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Unclear	Unclear
Einhorn et al. 2000	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Fonseca et al. 2000	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Moses et al. 1999	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Rosenstock et al. 1998	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Wolever et al. 1997	Unclear	Unclear	Yes (low risk of bias)	Unclear	Unclear
Strozik et al. 2015	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Unclear	Unclear
Qiu et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gaal et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Bhandare et al. 2013	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Raskin et al. 2007	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Leiter et al. 2005	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kilo et al. 2003	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ohira et al. 2014	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Yang et al. 2015	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
21399 Merck Sharp & Dohme Corp. 2015	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
21508 Daiichi Sankyo Inc. 2009	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Not applicable
21509 Merck Sharp & Dohme Corp. 2012	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
21577 NCT record (last updated)	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
21670 NCT record (last updated)	Unclear	Unclear	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
22053 NCT record (last updated)	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Chen et al. 2016	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Henry et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Ridderstråle et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Yin et al. 2018	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Müller-Wieland et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Otterbeck et al. 2011	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Fofonka et al. 2018	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Pratley et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Parthan et al. 2018	Unclear	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Yin et al. 2018	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kim et al. 2017	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Hollander et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Jameshorani et al. 2018	No (high risk of bias)	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Shi et al. 2017	Yes (low risk of bias)	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Vianna et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gadde et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Frias et al. 2017	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Du et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Handelsman et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Shankar et al. 2017	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Dei Cas et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kim et al. 2017	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Goldenberg et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Hong et al. 2017	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Gurkan et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Tinahones et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Pan et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Frias et al. 2017	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Younis et al. 2017	Unclear	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Rosenstock et al. 2018	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Wang et al. 2016	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Frías et al. 2016	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Asti et al. 2016	Unclear	No (high risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Kim et al. 2016	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Amin et al. 2015	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Studies	Adequate sequence generation2	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data for efficacy	Incomplete outcome data for safety
Del Prato et al. 2015	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	No (high risk of bias)	No (high risk of bias)
Banerji et al. 2010	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)
Lu et al. 2016	Unclear	Unclear	Yes (low risk of bias)	Yes (low risk of bias)	Yes (low risk of bias)

Appendix 4E2: Corresponding GRADE assessment of quality of evidence on overall risk of bias for each study

Studies	Overall risk of bias (ROB)	
Nauck et al. 2014	High ROB	
Ross et al. 2015		Not High ROB
Moon et al. 2014		Not High ROB
Gupta et al. 2015		Not High ROB
Hissa et al. 2015		Not High ROB
Inagaki et al. 2015		Not High ROB
Odawara et al. 2014		Not High ROB
Chen et al. 2014		Not High ROB
Kawamori et al. 2014		Not High ROB
White et al. 2014		Not High ROB
Kadowaki et al. 2013		Not High ROB
Neutel et al. 2013		Not High ROB
Chawla et al. 2013		Not High ROB
Bergenstal et al. 2012	High ROB	
Cho et al. 2010		Not High ROB
Wang et al. 2015		Not High ROB
Jin et al. 2015		Not High ROB
Xiao et al.2015		Not High ROB
Rosenstock et al. 2015		Not High ROB
Rosenstock et al. 2015	High ROB	
Kim et al. 2015		Not High ROB
Kashiwagi e al. 2015		Not High ROB
Aaboe et al. 2015		Not High ROB

Studies	Overall risk of bias (ROB)	
Schumm-Draeger et al. 2015		Not High ROB
Ji et al. 2015		Not High ROB
Gurkan et al. 2014		Not High ROB
Del Prato et al. 2014	High ROB	
Nandy et al. 2014		Not High ROB
Forst et al. 2014		Not High ROB
Dungan et al. 2014		Not High ROB
Ridderstrale et al. 2014		Not High ROB
Ohira et al. 2014		Not High ROB
Ahren et al 2014	High ROB	
Derosa et al. 2014		Not High ROB
Diamant et al. 2014		Not High ROB
Haring et al. 2014		Not High ROB
Bolli et al. 2014		Not High ROB
Berndt-Zipfel et al. 2013		Not High ROB
Genovese et al. 2013		Not High ROB
Rosenstock et al. 2013		Not High ROB
Kim et al. 2013		Not High ROB
Cefalu et al 2013		Not High ROB
Derosa et al 2013		Not High ROB
Henry et al 2013		Not High ROB
Ahren et al 2013		Not High ROB
Kapitza et al 2013		Not High ROB
Charbonnel et al. 2013	High ROB	
Forst et al. 2013		Not High ROB
Rhee et al. 2013		Not High ROB

Studies	Overall risk of bias (ROB)	
Wilding et al. 2012		Not High ROB
Derosa et al. 2012		Not High ROB
Hermans et al. 2012		Not High ROB
Derosa et al. 2012		Not High ROB
Guerci et al. 2012		Not High ROB
Monnier et al. 2012		Not High ROB
Rizzo et al. 2012		Not High ROB
Seino et al 2012		Not High ROB
Yang et al. 2012		Not High ROB
Gallwitz et al. 2012	High ROB	
Srivastava et al. 2012		Not High ROB
Koren et al. 2012	High ROB	
Pan et al. 2012		Not High ROB
Gallwitz et al. 2012	High ROB	
Aschner et al. 2012		Not High ROB
Rosenstock et al. 2012		Not High ROB
DeFronzo et al. 2012	High ROB	
Bolinder et al. 2012		Not High ROB
Fonseca et al. 2012		Not High ROB
Wang et al 2011	High ROB	
Yang et al. 2011		Not High ROB
Stephens st al. 2011		Not High ROB
Petrica et al. 2011		Not High ROB
Terra et al. 2011	High ROB	
Derosa et al. 2011		Not High ROB
Derosa et al. 2011	High ROB	

Studies	Overall risk of bias (ROB)	
Pfutzner et al. 2011		Not High ROB
Zinman et al. 2011		Not High ROB
Heise et al. 2011	High ROB	
Gallwitz et al 2011		Not High ROB
Arechavaleta et al 2011		Not High ROB
Yang et al 2011		Not High ROB
Taskinen et al 2011		Not High ROB
Forst et al. 2010	High ROB	
Goke et al. 2010		Not High ROB
Scheen et al. 2010		Not High ROB
Stenlof et al 2010		Not High ROB
Ratner et al. 2010	High ROB	
Bergenstal et al 2010		Not High ROB
Bailey et al. 2010		Not High ROB
Filozof et al 2010	High ROB	
DeFronzo et al. 2010	High ROB	
Pratley et al. 2010	High ROB	
Apovian et al. 2010		Not High ROB
Kadoglou et al. 2010	High ROB	
Petrica et al. 2009		Not High ROB
Scheen et al. 2009		Not High ROB
Blonde et al. 2009	High ROB	
Defronzo et al. 2009		Not High ROB
Home et al. 2009	High ROB	
Papathanassiou et al 2009	High ROB	
Goodman et al 2009		Not High ROB

Studies	Overall risk of bias (ROB)	
Bunck et al 2009		Not High ROB
Kaku et al 2009	High ROB	
Nauck et al 2008		Not High ROB
Ferrannini et al. 2009		Not High ROB
Gao et al. 2009	High ROB	
Nauck et al. 2009		Not High ROB
Scott et al 2008	High ROB	
Komajda et al. 2008		Not High ROB
Khanolkar et al. 2008		Not High ROB
Garcia-Soria et al. 2008		Not High ROB
Raz et al 2009		Not High ROB
Hamann et al 2008		Not High ROB
Bolli et al 2008		Not High ROB
Home et al. 2007		Not High ROB
Bosi et al. 2007		Not High ROB
Nauck et al. 2007	High ROB	
Brazg et al. 2007		Not High ROB
Derosa et al. 2007		Not High ROB
Charbonnel et al. 2006		Not High ROB
Nauck et al. 2006	High ROB	
Ristic et al. 2006	High ROB	
Umpierrez et al. 2006		Not High ROB
Garber et al. 2006		Not High ROB
Kvapil et al.2006		Not High ROB
Poon et al. 2005	High ROB	
Feinglos et al. 2005		Not High ROB

Studies	Overall risk of bias (ROB)	
DeFronzo et al. 2006		Not High ROB
Matthews et al. 2005		Not High ROB
Ahrén et al. 2004		Not High ROB
Schernthaner et al. 2004		Not High ROB
Philips et al. 2003	High ROB	
Marre et al. 2002		Not High ROB
Marre et al. 2002		Not High ROB
Gomez-Perez et al. 2002	High ROB	
Van Gaal et al. 2001	High ROB	
Charpentier et al. 2001		Not High ROB
Halimi et al. 2000		Not High ROB
Einhorn et al. 2000	High ROB	
Fonseca et al. 2000		Not High ROB
Moses et al. 1999		Not High ROB
Rosenstock et al. 1998		Not High ROB
Wolever et al. 1997		Not High ROB
Strozik et al. 2015		Not High ROB
Qiu et al. 2014		Not High ROB
Gaal et al. 2014		Not High ROB
Bhandare et al. 2013		Not High ROB
Raskin et al. 2007		Not High ROB
Leiter et al. 2005		Not High ROB
Kilo et al. 2003		Not High ROB
Ohira et al. 2014		Not High ROB
Yang et al. 2015		Not High ROB
21399 Merck Sharp & Dohme Corp. 2015		Not High ROB

Studies	Overall risk of bias (ROB)	
21508 Daiichi Sankyo Inc. 2009		Not High ROB
21509 Merck Sharp & Dohme Corp. 2012		Not High ROB
21577 NCT record (last updated)	High ROB	
21670 NCT record (last updated)	High ROB	
22053 NCT record (last updated)		Not High ROB
Chen et al. 2016		Not High ROB
Henry et al. 2018		Not High ROB
Ridderstråle et al. 2018	High ROB	
Yin et al. 2018		Not High ROB
Müller-Wieland et al. 2018		Not High ROB
Otterbeck et al. 2011	High ROB	
Fofonka et al. 2018		Not High ROB
Pratley et al. 2018		Not High ROB
Parthan et al. 2018	High ROB	
Yin et al. 2018		Not High ROB
Kim et al. 2017		Not High ROB
Hollander et al. 2018		Not High ROB
Jameshorani et al. 2018	High ROB	
Shi et al. 2017		Not High ROB
Vianna et al. 2018		Not High ROB
Gadde et al. 2017		Not High ROB
Frias et al. 2017		Not High ROB
Du et al. 2017		Not High ROB
Handelsman et al. 2017		Not High ROB
Shankar et al. 2017		Not High ROB
Dei Cas et al. 2017		Not High ROB

Studies	Overall risk of bias (ROB)	
Kim et al. 2017		Not High ROB
Goldenberg et al. 2017		Not High ROB
Hong et al. 2017		Not High ROB
Gurkan et al. 2017		Not High ROB
Tinahones et al. 2017		Not High ROB
Pan et al. 2017		Not High ROB
Frias et al. 2017		Not High ROB
Younis et al. 2017	High ROB	
Rosenstock et al. 2018		Not High ROB
Wang et al. 2016		Not High ROB
Frías et al. 2016		Not High ROB
Asti et al. 2016	High ROB	
Kim et al. 2016		Not High ROB
Amin et al. 2015		Not High ROB
Del Prato et al. 2015	High ROB	
Banerji et al. 2010		Not High ROB
Lu et al. 2016		Not High ROB

Appendix 4F: Funding information

NR=not reported

Author	Year	Registration number	Country	Sponsor
Nauck et al.	2014	NCT00734474	United States, Canada, France, Germany, India, Korea, Republic of, Mexico, Poland, Puerto Rico, Romania, Russian Federation, Spain, Taiwan	Eli Lilly and Company
Ross et al.	2015	eudract number 2012-000905-53	Europe, North America, Latin America	Boehringer Ingelheim and Eli Lilly and Company
Moon et al.	2014	NCT00562172	Korea	NR
Gupta et al.	2015	NR	India	NR
Hiss et al.	2015	NR	Brazil	Novartis
Inagaki et al.	2015	NCT01387737	Japan	Mitsubishi Tanabe Pharma Corporation
Odawara et al.	2014	NCT01497522	Japan	Novartis Pharma K.K
Chen et al.	2014	NCT00417729	Taiwan	Taichung Veterans General Hospital, Taichung, Taiwan and Bayer Schering Pharma, Taiwan Branch.
Kawamori et al.	2014	JapicCTI-101202 and JapicCTI-101203	Japan	Dainippon Sumitomo Pharma Co., Ltd.
White et al.	2014	NCT00885378	US, Germany, Hungary, Puerto Rice	Bristol-Myers Squibb and AstraZeneca
Kadowaki et al.	2013	NCT00363948	Japan	Ono Pharmaceutical Co. Ltd
Neutel et al.	2013	NCT00918138	US, Israel, Mexico, Argentina	Bristol-Myers Squibb and AstraZeneca
Chawla et al.	2013	NR	India	NR
Bergenstal et al.	2012	NCT00754988	23 countries	NR
Cho et al.	2010	NCT01037842	Korea	Choongwae Pharma Corporation, Korea
Wang et al.	2015	NR	NR	NR
Jin et al.	2015	NCT01529541	the Republic of Korea	JW Pharmaceutical
Xiao et al.	2015	NR	China	The National Science Foundation of Anhui Province
Rosenstock et al.	2015	NCT01606007	Multicenter	Bristol-Myers Squibb and AstraZeneca
Rosenstock et al	2015	NCT01376557	USA	Lexicon Pharmaceuticals
Kim et al.	2015	NCT01805830	Korea	Handok Inc., Seoul, Republic of Korea

Author	Year	Registration number	Country	Sponsor
Kashiwagi et al	2015	NCT01135433	Japan	Astellas Pharma Inc.
Aaboe et al	2015	NCT00411411	Denmark	Merck & Co., Inc.
Schumm-Draeger et al.	2015	NCT01217892	Europe, South Africa	Bristol-Myers Squibb and AstraZeneca
Ji et al.	2015	NCT01381900	China, Malaysia, Vietnam,	Janssen Research & Development, LLC
Gurkan et al.	2014	NR	NR	NR
Del Prato et al.	2014	NCT00856284	North and South America, Europe, Asia, South Africa, Australia, New Zealand	Takeda Developmnet Center Americas, Inc.
Nandy et al.	2014	NCT00620282	USA	
Forst et al.	2014	NCT01547104	Germany	Marcus Borchert
Dungan et al.	2014	NCT01624259	USA, Czech Republic, Hungary, Mexico, Slovakia, Puerto Rico, Poland, Spain, Romania, Germany	Eli Lilly and Company
Ridderstrale et al.	2014	NCT01167881	Argentina, Austria, Canada, Colombia, Czech Republic, Finland, Hong Kong, India, Italy, Malaysia, Mexico, the Netherlands, Norway, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, UK, USA	Boehringer Ingelheim and Eli Lilly
Ohira et al.	2014	NR	Japan	NR
Ahren et al.	2014	NCT00838903	United States, Albania, Germany, Hong Kong, Mexico, Peru, Philippines, Russian Federation, South Africa, Spain, United Kingdom	GlaxoSmithKline
Derosa et al.	2014	NR	Italy	NR
Diamant et al.	2014	NCT00641056	Multinational (72 sites)	Amylin Pharmaceuticals and Eli Lilly
Haring et al	2014	NCT01159600, NCT01289990 (extension)	Canada, China, France, Germany, India, Korea, Mexico, Slovakia, Slovenia, Taiwan, Turkey, and the U.S.	Boehringer Ingelheim and Eli Lilly
Bolli et al.	2014	NCT 00763451	United States, Brazil, Chile, Colombia, Estonia, Germany, Italy, Lithuania, Malaysia, Mexico, Philippines, Poland, Romania, Slovakia, Ukraine	Sanofi
Berndt-Zipfel et al.	2013	NR	Germany	Novartis
Genovese et al.	2013	NCT00772174	Italy	Takeda Italia SpA
Rosenstock et al.	2013	NCT00707031	United States, Argentina, Austria, Brazil, Colombia, Denmark, Finland, Germany, Greece, Hungary, Italy, Netherlands, Norway, Poland, Puerto Rico, Russian Federation, Spain, Sweden	Sanofi
Kim et al.	2013	NCT00699322	Korea	Merck

Author	Year	Registration number	Country	Sponsor
Cefalu et al.	2013	NCT00968812	United States, Argentina, Bulgaria, Canada, Costa Rica, Denmark, Finland, Germany, India, Israel, Korea, Republic of, Mexico, Norway, Philippines, Poland, Puerto Rico, Romania, Russian Federation, Slovakia, Ukraine	Janssen Research & Development, LLC
Derosa et al.	2013	NR	Italy	NR
Henry et al.	2013	NCT00943917	USA	Intarcia Therapeutics
Ahren et al.	2013	NCT00712673	Australia, Canada, Chile, Czech Republic, Germany, Croatia, Mexico, Morocco, the Philippines, Romania, Russian Federation, South Africa, Spain, Ukraine, U.S., and Venezuela	Sanofi
Kapitza et al.	2013	NCT01175473	Germany	Sanofi
Charbonnel et al.	2013	NCT01296412	21 countries	Merck Sharp & Dohme Corp.
Forst et al.	2013	NCT01565096	Germany	Novartis Pharma GmbH Nurnberg
Rhee et al.	2013	NCT00562172	Korea, India	LG Life Sciences Ltd.
Wilding et al.	2012	NCT01117584	Hungary, Poland, Romania, UK, Italy, USA	Astellas Pharma Inc. and Kotobuki Pharmaceutical Co.Ltd.
Derosa et al.	2012	NR	Italy	NR
Hermans et al.	2012	NCT01006590	Belgium, France, Germany, Italy, Spain, Turkey, UK	AstraZeneca, Bristol-Myers Squibb
Derosa et al.	2012	NR	Italy	NR
Guerci et al.	2012	NCT01193296	NR	Novartis
Monnier et al.	2012	NCT00318656	France	Glaxo Smith Kline Laboratories
Rizzo et al.	2012	NR	Italy	NR
Seino et al.	2012	NCT01318109	Japan	Takeda
Yang et al.	2012	NCT00813995	NR	Merck Sharp & Dohme Corp.
Gallwitz et al.	2012	NCT00622284	Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, UK, USA	Boehringer Ingelheim
Srivastava et al.	2012	NR	India	NR
Koren et al.	2012	NR	Isreal	NR
Pan et al.	2012	NR	China	Novartis Beijing, China
Gallwitz et al.	2012	NCT00359762	Austria, Czech Republic, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Mexico, Poland, Spain, Switzerland, and the UK	AstraZeneca
Aschner et al.	2012	NCT00751114	Austria, Brazil, Colombia, Egypt, Greece, Hong Kong, India, Israel, Korea, Lebanon, Mexico, Netherlands, Portugal, Spain, Turkey, UK, USA	Sanofi

Author	Year	Registration number	Country	Sponsor
Rosenstock et al.	2012	NCT00642278	Argentina, Bulgaria, Canada, Czech Republic, India, Malaysia, Mexico, Poland, Romania, Russia, UK, USA	Janssen Global Services, LLC
DeFronzo et al.	2012	NCT00328627	United States, Australia, Brazil, Bulgaria, Chile, Croatia, Estonia, Guatemala, India, Israel, Latvia, Mexico, New Zealand, Peru, Romania, Russian Federation, Serbia, South Africa, Ukraine	Takeda
Bolinder et al.	2012	NCT00855166	Bulgaria, Czech Republic, Hungary, Poland, Sweden	AstraZeneca
Fonseca et al.	2012	NCT00960076	USA, Latin America	AstraZeneca, Bristol-Myers Squibb
Wang et al.	2011	NR	Taiwan	Research grant from the National Science Council (Taiwan), Veterans General Hospitals University System of Taiwan Joint Research Program, and Bayer Schering Pharma
Yang et al.	2011	NCT00661362	China, India and South Korea	AstraZeneca LP and Bristol-Myers Squibb
Stephens et al.	2011	NR	UK	Novo Nordisk
Petrica et al.	2011	NR	Romania	NR
Lin et al.	2011	NR	Taiwan	The National Science Council, Taiwan; Veterans General Hospitals University System of Taiwan Joint Research Program; and Bayer Schering Pharma, Taiwan Branch.
Terra et al.	2011	NCT00473525	Colombia, Germany, Italy, Spain, Sweden, USA	Pfizer Inc.
Derosa et al.	2011	NR	Italy	NR
Derosa et al.	2011	NR	Italy	NR
Pfutzner et al.	2011	NCT00770653	Germany	Takeda Pharma
Zinman et al.	2011	NCT00611884	Canada, India, South Africa, USA	Novo Nordisk A/S
Heise et al.	2011	NCT00614055	France, Germany, Norway, Romania, Spain	Novo Nordisk A/S
Gallwitz et al.	2011	NCT00434954	Germany	AstraZeneca
Arechavaleta et al.	2011	NCT00701090	Austria, Brazil, Chile, Colombia, Costa Rica, Denmark, Ecuador, France, Germany, Guatemala, India, Italy, Korea, Republic of, Malaysia, Mexico, New Zealand, Panama, Peru, Poland, Spain, Switzerland, United Kingdom	Merck Sharp & Dohme Corp.
Yang et al.	2011	NR	China, South Korea and India	Novo Nordisk
Taskinen et al.	2011	NCT00601250	Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden, USA	Boehringer Ingelheim
Forst et al.	2010	NCT00309608	UK, Germany, France, Slovakia, Ukraine, Sweden	Boehringer Ingelheim
Goke et al.	2010	NR	International	Bristol-Myers Squibb and AstraZeneca
Scheen et al.	2010	NCT00666458	Argentina, Belgium, Denmark, France, Italy, Mexico, Norway, South Africa, Sweden	AstraZeneca and Bristol-Myers Squibb

Author	Year	Registration number	Country	Sponsor
Stenlof et al.	2010	NR	the United States, Israel, Sweden, Mexico, Puerto Rico, Argentina, Italy, and the Philippines.	Bristol-Myers Squibb and AstraZeneca
Ratner et al.	2010	NR	Brazil, Canada, Poland, Romania, Russian, Ukraine, and USA	sanofi-aventis
Bergenstal et al.	2010	NCT00637273	United States, India, Mexico	Amylin Pharmaceuticals and Eli Lilly
Bailey et al.	2010	NCT00528879	USA, Canada, Argentina, Mexico, Brazil	Bristol-Myers Squibb and AstraZeneca
Filozof et al.	2010	NR	NR	Novartis
DeFronzo et al.	2010	NCT00135330	USA	AstraZeneca, Eli Lilly
Pratley et al.	2010	NCT00700817	Croatia, Germany, Ireland, Italy, Netherlands, Romania, Serbia, Slovakia, Slovenia, Spain, UK, USA, Canada	Novo Nordisk
Apovian et al.	2010	NR	US	Lilly USA, LLC
Kadoglou et al.	2010	NCT00373178	NR	European Social Fund and National Resources-(EPEAEK II) "PYTHAGORAS II" and Alexander S Onassis Public Benefit Foundation
Petrica et al.	2009	NR	NR	NR
Scheen et al.	2009	ISRCTN, NCT00174993	Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Slovakia, Sweden, Switzerland, United Kingdom	Takeda
Blonde et al.	2009	NCT00396227	US	Novartis
Defronzo et al.	2009	NCT00121667	US, Brazil	Bristol-Myers Squibb; AstraZeneca
Home et al.	2007	NR	23 countries in Europe, Australia and New Zealand	GlaxoSmithKline
Papathanassiou et al.	2009	NR	Greece	University of Ioannina
Goodman et al.	2009	NR	Multinational	Supported by Novartis Pharmaceuticals Corporation
Bunck et al.	2009	NCT00097500	Sweden, Finland, and the Netherlands	Amylin Pharmaceuticals and Eli Lilly and Company
Kaku et al.	2009	UMIN000001110	NR	Takeda
Nauck et al.	2008	NCT00286442	Multinational ("115 sites in 15 countries"	Takeda Global Research & Development Cente
Ferrannini et al.	2009	NCT00106340	Canada, USA, Europe, and multinational	Novartis Pharmaceuticals
Gao et al.	2009	NCT00324363	China, India, Korea, Taiwan	Amylin Pharmaceuticals; Eli Lilly and Company
Nauck et al.	2009	NCT00318461	Argentina, Australia, Belgium, Bulgaria, Croatia, Denmark, Germany, Hungary, India, Ireland, Italy, Netherlands, New Zealand, Norway, Romania, Russian Federation, Slovakia, South Africa, Spain, Sweden, United Kingdom	Novo Nordisk

Author	Year	Registration number	Country	Sponsor
Scott et al.	2008	NCT00541775	Multinational	Merck
Komajda et al.	2008	NCT00379769	23 countries in Europe and Australasia	GlaxoSmithKline
Khanolkar et al.	2008	NR	United Kingdom	NR
Garcia-Soria et al.	2008	NR	US, Mexico, Australia	Phenomix Corporation
Raz et al.	2008	NCT00337610	Austria, Israel, Mexico, Peru and United States	Merck & Co., Inc.
Hamann et al.	2008	NR	Multinational (Europe and Mexico)	NR
Bolli et al.	2008	NCT 00237237	Germany, UK, US, Spain, Italy, Switzerland, Austria, South Africa and Australia	Novartis Pharmaceuticals Corporation
Bosi et al.	2007	NCT00099892	US, France, Italy, Sweden	Novartis Pharmaceuticals Corporation
Nauck et al.	2007	NCT00094770	NR	Merck & Co.
Brazg et al.	2007	NR	NR	byMerck & Co., Inc.
Derosa et al.	2007	NR	Italy	NR
Charbonnel et al.	2006	NCT00086515 (note: NCT in publication is missing a zero)	France, Israel, US	Sponsored by Merck Research Laboratory
Nauck et al.	2006	NR	Europe and Austrlia	NR
Goldstein et al.	2005	NR	US	GlaxoSmithKline Pharmaceuticals
Bakris et al.	2006	NR	North America, South America and Europe	GlaxoSmithKline Pharmaceuticals
Ristic et al.	2006	NR	Canada, France, Italy, Spain, Austria	Sponsored by Novartis Pharma
Umpierrez et al.	2006	NR	US	Sanof-aventis
Garber et al.	2006	NR	US	Authors from Bristol-Meyers Squibb
Kvapil et al.	2006	NR	Croatia, Czech Republic, Denmark, France, Greece, Hungary, Norway, Poland, Portugal, Russia, Spain	
Poon et al.	2005	NR	US	Amylin Pharmaceuticals
Feinglos et al.	2005	NR	United States	Pfizer Inc
DeFronzo et al.	2005	Nr	United States	Amylin pharmaceuticals; Eli Lilly and Co.
Matthews et al.	2005	NR	Multinational	Takeda Euro R&D; Eli Lilly and Co.
Ahrén et al.	2004	NR	Sweden, Spain, Germany and Switzerland	Swedish Research Council
Schernthaner et al.	2004	NR	10 European countries	Grant from the Institut de Recherches Internationales Servier, Courbevoie, France
Raskin et al.	2003	NR	US	NovoNordisk Pharmaceuticals
Phillips et al.	2003	NR	Australia and New Zealand	Bayer AG, Leverkusen, Germany
Marre et al.	2002	NR	Multinational	Merck Lipha
Marre et al.	2002	NR	Multinational	Novartis Pharma AG
Gomez-Perez et al.	2002	NR	Mexico	NR

Author	Year	Registration number	Country	Sponsor
Van Gaal et al.	2001	NR	Belgium, Israel, Astria, Czech	Bayer and Sanofi-Synthelab
Charpentier et al.	2001	NR	France	Hoechst Marion Roussel
Halimi et al.	2000	NR	France	Authors from Bayer
Einhorn et al.	2000		US	Takeda Pharmaceuticals America
Fonseca et al.	2000	NR	US	SmithKline Beecham Pharmaceuticals
Moses et al.	1999	NR	Australia	Novo Nordisk
Rosenstock et al.	1998	NR	USA	Bayer Corporation
Wolever et al.	1997	NR	Canada	Bayer Canada, Inc.
Strozik et al.	2015	NR	Poland	"This study was not founded by any Pharmaceuticals Corporation"
Qiu et al.	2014	NCT01340664	Canada, Czech Republic, Mexico, Romania, Russia, Slovakia, USA	Janssen Research & Development LLC
Gaal et al.	2014	NCT00976937	United States, Australia, Brazil, Canada, Chile, Germany, Guatemala, Mexico, Peru, Poland, Romania, Russian Federation, Ukraine	Sanofi
Bhandare et al.	2013	NR	India	NR
Raskin et al.	2007	NR	USA	Support from Novo Nordisk
Leiter et al.	2005	NR	Canada	GlaxoSmithKline
Kilo et al.	2003	NR	USA	Nova Nordick
Ohira et al.	2014	NR	Japan	NR
Yang et al.	2015	NCT01095666	China, India, South Korea	Bristol-Myers Squibb and AstraZeneca
Merck Sharp & Dohme Corp.	2015	NCT01841697	Argentina, Canada, Croatia, Estonia, Georgia, Hungary, Israel, Malaysia, Philippines, Poland, Romania, South Africa, USA	Merck Sharp & Dohme Corp.
Daiichi Sankyo Inc.	2009	NCT00484419	Colombia, Mexico, US	Daiichi Sankyo Inc.
Merck Sharp & Dohme Corp.	2012	NCT01682759	Croatia, Germany, Hungary, South Korea, Lebanon, Lithuania, Malaysia, Poland, Romania, US	Merck Sharp & Dohme Corp.
NCT record	2010 (last updated)	NCT00367055	"Not provided", France is listed as a "Removed Location Countries"	GlaxoSmithKline
NCT record	2015 last update	NCT01882907	Republic of Korea	Pusan National University Hospital
NCT record	2015 (last update)	NCT01973231	EUROPE: Czech Republic, Finland, France, Germany, Hungary, Italy, Latvia, Lithuania, United Kingdom	Novo Nordisk A/S
NCT record	2016 (last update)	NCT02008682	China, Beijing	Novo Nordisk A/S

Author	Year	Registration number	Country	Sponsor
Lavalle-Gonzalez	2013	NCT01106677	Argentina, Bulgaria, Colombia, Czech Republic, Estonia, Greece, India, Italy, Latvia, Malaysia, Mexico, Peru, Poland, Portugal, Russia, Singapore, Slovakia, Sweden, Thailand, Turkey, Ukraine, USA	Janssen Research & Development, LLC
Chen	NA	NCT01965509	China	Hansoh Pharmaceutical Co., Ltd. (Jiangsu)
Henry et al	2018	NCT02429258	US	AstraZeneca
Ridderstråle et al	2018	NCT01167881	Argentina, Canada, Colombia, Czech Republic, finland, Great Britain, Hong Kong, India, Italy, Malaysia, Mexico, Netherlands, Norway, Philippines, Portugal, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, US	Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance.
Yin et al	2018	NCT02325960	China	AstraZeneca Investment (China) Co., Ltd.
Müller-Wieland et al.	2018	NCT02471404	Germ any, the Czech Republic, Hungary, Poland and Slovakia.	AstraZeneca
Otterbeck et al.	2011	NR	US	Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA.
Fofonka et al.	2018	NCT01867502	Brizal	Novartis
Pratley et al.	2018	NCT02099110	Argentina, Canada, Coombia, Mexico, Czech Republic, Hungary, Israel, Poland, Romania, Russian Federation, Slovakia, Ukraine, Malaysia, Philippines, New Zealand Bulgaria, Italy Finland, Thailand, US	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NewJersey, in collaboration with Pfizer Inc.
Parthan et al.	2018	NCT02097342	India	NR
Yin et al.	2018	NCT02325960	China	AstraZeneca Investment (China) Co., Ltd.
Kim et al.	2017	NCT01339143	Korea	Novartis Korea. the Ministry of Health and Welfare, Republic of Korea (grant number: HI14C2750).
Min et al.	2017	NCT01505426	Korea and Taiwan	Astellas Pharma Inc., Japan
Hollander et al.	2018	NCT01999218	Argentina, Canada, Czech Republic, Hungary, South Korea, Lithuania, Mexico, the Philippines, Poland, Romania, Russia, Slovakia, South Africa, Taiwan, Ukraine, US	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, in collaboration with Pfizer Inc.
Jameshorani et al.	2017	IRCT2015061619554N4	Iran	This research did not receive any financial support
Shi et al.	2017	ChiCTR-OPC-16008152	China	partly funded by the Provincialinnovation team Discipline Construction Project"
Vianna et al.	2018	NCT01679899	Brazil	Novartis Pharmaceuticals (Grant # CLAF237ABR02T.

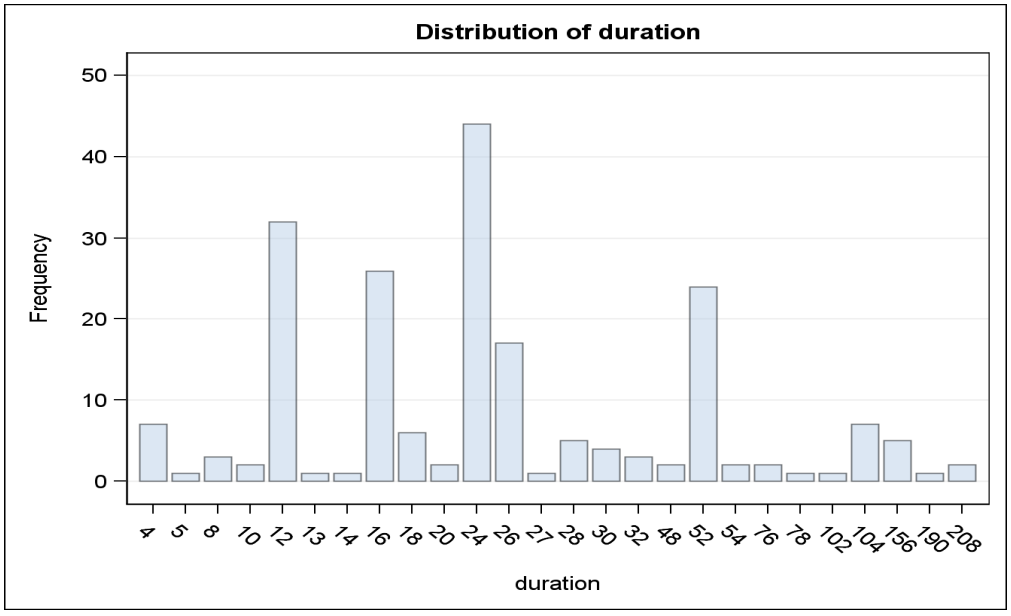
Author	Year	Registration number	Country	Sponsor
Gadde et al.	2017	NCT01652729	US	AstraZeneca
Frias et al.	2017	NCT02205528	US	Novo Nordisk A/S
Du et al.	2017	NCT02243176	China	AstraZeneca
Handelsman et al.	2017	NCT01682759	Argentina, Croatia, Germany, Hungary, Korea, Lebanon, Lithuania, Malaysia, Mexico, Poland, Romania, US	Merck & Co., Inc., Kenilworth, NJ, US
Shankar et al.	2017	NCT01755156	NR	Merck & Co., Inc., Kenilworth, NJ, US.
Dei Cas et al.	2017	NCT01822548	Italy	Research program Regione-Emilia Romagna-University 2007–2009; Italian Ministry of Health Ricerca Finalizzata GR-2011-02347600; unconditional grant from Novartis Italia.
Kim et al.	2017	NCT01404676	Korea	Novartis (#CLAF237AKR08T).
Goldenberg et al.	2017	NCT01841697	Argentina, Canada, Croatia, Estonia, Georgia, Hungary, Israel, Malaysia, Philippines, Poland, Romania, South Africa, US	Merck & Co., Inc., Kenilworth, New Jersey
Hong et al.	2017	NCT02949193	Korea	Dong-A ST Co., Ltd, Seoul, Republic of Korea
Gurkan et al.	2017	NR	Turkey	NR
Tinahones et al.	2017	NCT01778049	Argentina, Australia, Canada, Germany, Italy, Portugal, Russia, Spain, Ukraine, US	Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance
Pan et al.	2017	NCT01289119	China	Takeda Pharmaceutical Company (Beijing, China)
Frias et al.	2017	NCT02288273	US	AstraZeneca
Younis et al.	2017	NCT01604213	Israel	Novartis
Rosenstock et al.	2018	NCT02033889	International	Pfizer, Inc. and Merck & Co., Inc.
Wang et al.	2016	NCT01215097	China, The Philippines, and Malaysia	Boehringer Ingelheim Pharma GmbH & Co
Frías et al.	2016	NCT02229396	Six countries	AstraZeneca
Asti et al.	2016	NR	Italy	NR
Kim et al.	2016	NCT01882907	Korea	Novartis Pharmaceuticals Corporation
Amin et al.	2015	NCT01059825	Canada, India, Korea, Mexico, and the US	Pfizer
Del Prato et al.	2015	NCT00660907	10 countries	Bristol-Myers Squibb and AstraZeneca7357
Banerji et al.	2010	NCT00396627	US	Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, US
Lu et al.	2016	NCT01505426	Korea and Taiwan	Astellas Pharma Inc., Japan

Appendix 4G: Network meta-analysis - sensitivity analysis on duration of treatment period and zero event counts

Network meta-analyses were conducted for 23 of the clinical outcomes (8 continuous outcomes and 15 dichotomous outcomes) for the antihyperglycemic class comparisons. The choice of outcomes for NMA was based on clinical relevance and the sufficiency of the data available to derive robust and consistent network meta-analysis models. This appendix provides results of sensitivity analyses that were conducted in conjunction with these network meta-analyses.

In particular, the duration of the study treatment period of the included randomized controlled trials ranged from 4 to 208 weeks. With such a wide range in the treatment periods, sensitivity analyses were conducted to assess the effect of the treatment period on the results of the network meta-analysis for the 23 study outcomes of interest. The frequency distribution of the number of trials by duration of the treatment period is displayed in Figure 4G.1. The most frequent treatment period for the trials was 12 weeks, 24 weeks, 16 weeks and 52 weeks, and 168 (83.2%) of the trials had a treatment duration between 12 and 52 weeks.

Figure 4G.1: Distribution of the number of studies by duration of treatment period



Similarly, a number of dichotomous outcomes from several studies could not be included directly in the network meta-analyses because zero events in one or both study arms were reported and an adjustment for the zero counts was needed. As part of the analysis strategy, sensitivity analyses were conducted excluding studies for a dichotomous outcome of interest that had zeros events in all study arms.

4G.1: Continuous outcomes

A summary of the number of studies by duration of treatment period (4-10 weeks, 12-20 weeks, 24-32 weeks, 48-54 weeks, 76 to 208 weeks), for each continuous outcome of interest, is provided in Table 4G.1.

Table 4G.1: Number of studies by duration of treatment for continuous outcomes in the network meta-analysis

Outcome	NMA Model Likelihood/Link	4-10 weeks	12-20 weeks	24-32 weeks	48-54 weeks	76-208 weeks	Total	Section
HbA1c	Normal/Identity	4	32	44	16	14	110	4.3.4.1
Body mass index	Normal/Identity	0	6	7	5	0	18	4.3.4.4a
Weight	Normal/Identity	2	27	34	14	13	90	4.3.4.4b
Systolic blood pressure	Normal/Identity	0	13	17	8	5	43	4.3.4.5a
Diastolic Blood Pressure	Normal/Identity	0	12	11	7	6	36	4.3.4.5b
Total Cholesterol	Normal/Identity	0	13	13	3	4	33	4.3.4.6b
LDL Cholesterol	Normal/Identity	0	13	13	12	3	41	4.3.4.6a
HDL Cholesterol	Normal/Identity	0	16	15	14	3	48	4.3.4.6c

Two approaches were considered for the sensitivity analysis. First, the trend of the effect estimates over the duration of treatment periods was evaluated. For this analysis, the outcome HbA1c was considered since it was available for analysis in more trials than any of the other outcomes, and for a robust trend analysis there must be a sufficient number of trials for each category of duration.

The results of this analysis are provided in Table 4G.2. For the reduced models by duration of treatment period (4-10 weeks, 12-20 weeks, 24-32 weeks, 48-54 weeks, 76 to 208 weeks):

- For the treatment period 76-208 weeks (k=14), the model did not converge.

- For the treatment period 4-10 weeks, the model converged but with few studies (k=4); consequently, only a reduced number of treatment comparisons were possible and results were not significant even in cases where the results for other treatment period models were significant but in all cases (except one) the direction of the effect estimate (mean difference) was in the same as the other models.
- For the treatment period 48-54 weeks, the model converged with a reasonable number of studies involved (k=16); however, some treatment comparison were not possible. Agreement on significance of the results with those of the overall model was found except for 5 cases (likely due to smaller number of studies). Only in 3 cases was the direction of the MD different and even for these cases the results were close to MD=0.
- For the treatment period 12-20 weeks (k=32), 24-32 weeks (k=44) and 48-54 weeks (k=16) the models converged and are in general agreement with the overall model (k=110) 48-54 weeks Subgroup 12-20 weeks, 24-32 weeks, 48-52 weeks:
    - Agreed on the statistical significance for 6 comparisons of an antihyperglycemic agent plus metformin versus metformin monotherapy with similar magnitude and direction of the effect
    - Agreed on the non-statistical significance for 30 treatment comparisons with similar magnitude and direction of the effect
    - Disagreed on statistical significance for 5 treatment comparisons (1 significant for reduced model and 4 significant for base-case model), but all had similar magnitude and direction of the effect
    - No existence of trends across duration of treatment periods

Table 4G.2: HbA1c - network meta-analysis MA results by duration of study: mean difference and 95% credible intervals

Treatment	Reference	4-10 weeks (k=4)	12-20 weeks (k=32)	24-32 weeks (k=44)	48-54 weeks (k=16)	Overall
MET+SUL	MET	-1.09(-4.76,2.62)	**-0.72(-0.95,-0.52)**	**-0.83(-1.09,-0.58)**	**-0.81(-1.15,-0.44)**	**-0.68(-0.78,-0.57)**
MET+MEG		-0.21(-4.11,3.69)	**-0.40(-0.71,-0.10)**	**-1.09(-1.91,-0.26)**	**-0.65(-1.21,-0.08)**	**-0.51(-0.77,-0.26)**
MET+DPP-4		-0.15(-4.16,3.84)	**-0.59(-0.75,-0.44)**	**-0.59(-0.74,-0.44)**	**-0.76(-1.07,-0.40)**	**-0.58(-0.66,-0.49)**
MET+SGLT-2		-0.74(-3.58,1.99)	**-0.61(-0.86,-0.37)**	**-0.59(-0.84,-0.34)**	**-0.73(-1.13,-0.30)**	**-0.65(-0.76,-0.53)**
MET+GLP-1			**-0.68(-0.93,-0.43)**	**-0.81(-1.09,-0.52)**	**-0.73(-1.07,-0.39)**	**-0.85(-0.98,-0.72)**
MET+AGI			-0.16(-0.65,0.31)	**-0.72(-1.18,-0.27)**		**-0.50(-0.80,-0.21)**
MET+TZD			**-0.59(-0.81,-0.36)**	**-0.91(-1.18,-0.66)**	**-0.90(-1.33,-0.49)**	**-0.70(-0.83,-0.58)**
MET+INS-BA			-0.51(-1.21,0.16)	**-1.01(-1.38,-0.63)**		**-0.86(-1.10,-0.61)**
MET+INS-BI			-0.55(-2.23,1.33)	**-1.08(-1.62,-0.56)**		**-0.92(-1.35,-0.49)**
MET+MEG	MET+SUL	0.88(-4.49,6.19)	0.32(-0.04,0.70)	-0.26(-1.13,0.61)	0.16(-0.28,0.59)	0.16(-0.10,0.43)
MET+DPP-4		0.94(-4.47,6.34)	0.13(-0.06,0.34)	**0.24(0.01,0.48)**	0.05(-0.11,0.23)	**0.10(0.01,0.20)**
MET+SGLT-2		0.34(-3.39,3.93)	0.11(-0.20,0.43)	0.24(-0.11,0.59)	0.09(-0.16,0.33)	0.03(-0.10,0.16)
MET+GLP-1			0.04(-0.26,0.37)	0.02(-0.32,0.36)	0.08(-0.29,0.41)	**-0.17(-0.31,-0.03)**
MET+AGI			0.56(0.10,1.01)	0.11(-0.39,0.59)		0.18(-0.12,0.47)
MET+TZD			0.13(-0.08,0.37)	-0.09(-0.32,0.15)	-0.09(-0.37,0.15)	-0.03(-0.14,0.09)
MET+INS-BA			0.21(-0.50,0.91)	-0.18(-0.58,0.23)		-0.18(-0.43,0.08)
MET+INS-BI			0.18(-1.53,2.07)	-0.25(-0.76,0.24)		-0.24(-0.67,0.18)

MET+DPP-4	MET+MEG	0.05(-5.59,5.66)	-0.19(-0.53,0.15)	0.50(-0.34,1.34)	-0.11(-0.56,0.37)	-0.06(-0.32,0.20)
MET+SGLT-2		-0.53(-5.35,4.22)	-0.21(-0.60,0.17)	0.50(-0.36,1.36)	-0.07(-0.56,0.42)	-0.13(-0.41,0.14)
MET+GLP-1			-0.27(-0.67,0.12)	0.27(-0.59,1.15)	-0.08(-0.65,0.47)	-0.33(-0.62,-0.05)
MET+AGI			0.24(-0.33,0.80)	0.36(-0.57,1.31)		0.01(-0.38,0.41)
MET+TZD			-0.19(-0.56,0.20)	0.17(-0.69,1.04)	-0.25(-0.76,0.23)	-0.19(-0.47,0.09)
MET+INS-BA			-0.11(-0.87,0.63)	0.08(-0.83,0.99)		-0.34(-0.70,0.01)
MET+INS-BI			-0.15(-1.86,1.75)	0.00(-0.98,1.00)		-0.41(-0.91,0.09)
MET+SGLT-2	MET+DPP-4	-0.59(-5.45,4.25)	-0.02(-0.29,0.25)	0.00(-0.28,0.28)	0.03(-0.24,0.29)	-0.07(-0.20,0.05)
MET+GLP-1			-0.08(-0.36,0.19)	-0.22(-0.48,0.05)	0.03(-0.35,0.36)	**-0.27(-0.40, -0.15)**
MET+AGI			0.43(-0.05,0.90)	-0.13(-0.57,0.30)		0.08(-0.22,0.37)
MET+TZD			0.00(-0.18,0.19)	-0.33(-0.60,-0.07)	-0.14(-0.44,0.10)	**-0.13(-0.24, -0.01)**
MET+INS-BA			0.08(-0.63,0.77)	**-0.42(-0.77,-0.07)**		**-0.28(-0.53, -0.04)**
MET+INS-BI			0.04(-1.64,1.92)	-0.49(-1.02,0.02)		-0.35(-0.77,0.08)
MET+GLP-1	MET+SGLT-2		-0.06(-0.41,0.28)	-0.22(-0.56,0.12)	-0.01(-0.44,0.40)	**-0.20(-0.36, -0.04)**
MET+AGI			0.45(-0.09,0.98)	-0.13(-0.65,0.37)		0.15(-0.16,0.46)
MET+TZD			0.02(-0.29,0.35)	-0.33(-0.69,0.03)	-0.17(-0.54,0.15)	-0.06(-0.21,0.10)
MET+INS-BA			0.10(-0.64,0.82)	-0.42(-0.85,0.01)		-0.21(-0.47,0.06)
MET+INS-BI			0.06(-1.62,1.97)	-0.49(-1.08,0.08)		-0.27(-0.71,0.16)
MET+AGI	MET+GLP-1		**0.51(0.03,0.98)**	0.09(-0.42,0.58)		**0.35(0.04,0.65)**
MET+TZD			0.09(-0.23,0.41)	-0.10(-0.47,0.25)	-0.17(-0.59,0.25)	0.14(-0.02,0.30)
MET+INS-BA			0.16(-0.49,0.79)	-0.20(-0.54,0.15)		-0.01(-0.24,0.23)
MET+INS-BI			0.13(-1.54,1.97)	-0.27(-0.83,0.26)		-0.07(-0.51,0.35)
MET+TZD	MET+AGI		-0.43(-0.91,0.07)	-0.20(-0.69,0.32)		-0.20(-0.51,0.11)
MET+INS-BA			-0.35(-1.16,0.43)	-0.29(-0.83,0.27)		-0.36(-0.73,0.02)
MET+INS-BI			-0.39(-2.14,1.51)	-0.36(-1.03,0.31)		-0.42(-0.93,0.08)
MET+INS-BA	MET+TZD		0.08(-0.64,0.78)	-0.09(-0.51,0.33)		-0.15(-0.41,0.11)
MET+INS-BI			0.04(-1.65,1.93)	-0.17(-0.71,0.37)		-0.22(-0.65,0.21)
MET+INS-BI	MET+INS-BA		-0.04(-1.56,1.69)	-0.07(-0.60,0.44)		-0.07(-0.49,0.36)
RE-model	Res Dev	9 vs 8,841 pts	57.98 vs 66 pts	80 vs 84 pts	33.11 vs 32 pts	226.4 vs. 238 pts
	DIC	-15	-44.34	-90	-46.60	-256.688

This trend analyses with subgroups was conducted for other outcomes for which there was a sufficient number of studies in the different subgroups for NMA to be possible and the models would converge. Similar results to that for HbA1c were found.

The second approach to the sensitify analysis was considered since for many outcomes there was an insufficient number of studies at the various duration times for a robust analysis. Second, since most of the 204 studies had treatment periods between 3 months and 12 months, as illustrated in Figure 4G.1, a sensitivity analysis for all continuous outcomes of interest was conducted restricting studies in the analysis to those with treatment periods between 3 to 12 months. The results for this reduced model and the base case model for each of the 8 continuous outcomes are provided in Tables 4G.3 to 4G.9.

1. Hemoglobin A1c

A summary of the NMA results for HbA1c are provided in Table 4G.3. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 15 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 25 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 5 treatment comparisons (4 significant for reduced model and 1 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.3: HbA1c - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	**-0.74(-0.86,-0.62)**	**-0.68(-0.78,-0.57)**
MET+MEG		**-0.53(-0.78,-0.28)**	**-0.51(-0.77,-0.26)**
MET+DPP-4		**-0.61(-0.70,-0.52)**	**-0.58(-0.66,-0.49)**
MET+SGLT-2		**-0.63(-0.76,-0.50)**	**-0.65(-0.76,-0.53)**
MET+GLP-1		**-0.85(-1.00,-0.69)**	**-0.85(-0.98,-0.72)**
MET+AGI		**-0.53(-0.83,-0.23)**	**-0.50(-0.80,-0.21)**
MET+TZD		**-0.74(-0.87,-0.61)**	**-0.70(-0.83,-0.58)**
MET+INS-BA		**-0.99(-1.25,-0.72)**	**-0.86(-1.10,-0.61)**
MET+INS-BI		**-1.02(-1.44,-0.60)**	**-0.92(-1.35,-0.49)**
MET+MEG	MET+SUL	0.21(-0.05,0.47)	0.16(-0.10,0.43)
MET+DPP-4		**0.13(0.03,0.24)**	**0.10(0.01,0.20)**
MET+SGLT-2		0.11(-0.04,0.27)	0.03(-0.10,0.16)
MET+GLP-1		-0.10(-0.27,0.07)	**-0.17(-0.31,-0.03)**
MET+AGI		0.21(-0.08,0.51)	0.18(-0.12,0.47)
MET+TZD		0.00(-0.12,0.12)	-0.03(-0.14,0.09)
MET+INS-BA		-0.25(-0.51,0.03)	-0.18(-0.43,0.08)
MET+INS-BI		-0.28(-0.69,0.14)	-0.24(-0.67,0.18)
MET+DPP-4	MET+MEG	-0.08(-0.34,0.18)	-0.06(-0.32,0.20)
MET+SGLT-2		-0.10(-0.38,0.18)	-0.13(-0.41,0.14)
MET+GLP-1		**-0.32(-0.61,-0.03)**	**-0.33(-0.62,-0.05)**
MET+AGI		0.00(-0.38,0.38)	0.01(-0.38,0.41)
MET+TZD		-0.21(-0.49,0.06)	-0.19(-0.47,0.09)
MET+INS-BA		**-0.46(-0.81,-0.09)**	-0.34(-0.70,0.01)
MET+INS-BI		**-0.49(-0.97,0.00)**	-0.41(-0.91,0.09)
MET+SGLT-2	MET+DPP-4	-0.02(-0.16,0.12)	-0.07(-0.20,0.05)
MET+GLP-1		**-0.24(-0.39,-0.09)**	**-0.27(-0.40,-0.15)**
MET+AGI		0.08(-0.21,0.37)	0.08(-0.22,0.37)
MET+TZD		**-0.13(-0.25,-0.02)**	**-0.13(-0.24,-0.01)**
MET+INS-BA		**-0.38(-0.64,-0.12)**	**-0.28(-0.53,-0.04)**
MET+INS-BI		-0.41(-0.83,0.01)	-0.35(-0.77,0.08)

MET+GLP-1	MET+SGLT-2	**-0.22(-0.41,-0.03)**	**-0.20(-0.36,-0.04)**
MET+AGI		0.10(-0.22,0.42)	0.15(-0.16,0.46)
MET+TZD		-0.11(-0.28,0.06)	-0.06(-0.21,0.10)
MET+INS-BA		**-0.36(-0.64,-0.07)**	-0.21(-0.47,0.06)
MET+INS-BI		-0.39(-0.82,0.04)	-0.27(-0.71,0.16)
MET+AGI	MET+GLP-1	0.32(0.00,0.63)	**0.35(0.04,0.65)**
MET+TZD		0.10(-0.07,0.28)	0.14(-0.02,0.30)
MET+INS-BA		-0.14(-0.39,0.11)	-0.01(-0.24,0.23)
MET+INS-BI		-0.17(-0.60,0.25)	-0.07(-0.51,0.35)
MET+TZD	MET+AGI	-0.21(-0.52,0.09)	-0.20(-0.51,0.11)
MET+INS-BA		**-0.46(-0.84,-0.07)**	-0.36(-0.73,0.02)
MET+INS-BI		-0.48(-0.99,0.01)	-0.42(-0.93,0.08)
MET+INS-BA	MET+TZD	-0.25(-0.52,0.04)	-0.15(-0.41,0.11)
MET+INS-BI		-0.28(-0.70,0.14)	-0.22(-0.65,0.21)
MET+INS-BI	MET+INS-BA	-0.03(-0.46,0.38)	-0.07(-0.49,0.36)
Random-effect model	Residual Deviance	180.6 vs 194 data points	226.4 vs. 238 data points
	Deviance information criteria	-184.244	-256.688

2. Body mass index (BMI)

All studies involving BMI had treatment periods between 3 months and 12 months, thus the reduced model and the base case model are identical:

3. Weight

A summary of the NMA results for weight are provided in Table 4G.4. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 17 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 12 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 6 treatment comparisons (0 significant for reduced model and 6 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.4: Weight - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	Reference	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	1.39(0.59,2.19)	**1.90(1.22,2.58)**
MET+MEG		0.63(-0.07,1.34)	0.77(0.08,1.47)
MET+DPP-4		-0.43(-0.98,0.13)	-0.25(-0.76,0.26)
MET+SGLT-2		**-1.75(-2.51,-0.98)**	**-1.73(-2.40,-1.08)**
MET+GLP-1		**-1.45(-2.46,-0.47)**	**-1.39(-2.24,-0.54)**
MET+TZD		**2.35(1.54,3.19)**	**2.72(1.95,3.50)**
MET+ INS-BA		1.53(-0.56,3.68)	**2.79(1.22,4.39)**
MET+ INS-BI		1.74(-1.38,4.87)	3.03(0.19,5.89)
MET+MEG	MET+SUL	-0.77(-1.65,0.15)	**-1.13(-1.98,-0.28)**
MET+DPP-4		**-1.81(-2.51,-1.12)**	**-2.15(-2.73,-1.57)**
MET+SGLT-2		**-3.14(-4.16,-2.10)**	**-3.63(-4.50,-2.78)**
MET+GLP-1		**-2.84(-3.91,-1.77)**	**-3.28(-4.22,-2.36)**
MET+TZD		0.96(0.13,1.82)	0.82(0.02,1.63)
MET+ INS-BA		0.13(-2.02,2.36)	0.90(-0.72,2.55)
MET+ INS-BI		0.36(-2.82,3.53)	1.12(-1.71,4.03)
MET+DPP-4	MET+MEG	**-1.05(-1.82,-0.29)**	**-1.02(-1.79,-0.27)**
MET+SGLT-2		**-2.38(-3.35,-1.40)**	**-2.50(-3.42,-1.60)**
MET+GLP-1		**-2.08(-3.17,-1.00)**	**-2.16(-3.15,-1.19)**
MET+TZD		1.73(0.84,2.61)	**1.94(1.09,2.82)**
MET+ INS-BA		0.90(-1.27,3.11)	**2.02(0.35,3.72)**
MET+ INS-BI		1.11(-2.05,4.34)	2.25(-0.64,5.16)
MET+SGLT-2	MET+DPP-4	**-1.33(-2.15,-0.50)**	**-1.48(-2.23,-0.75)**
MET+GLP-1		**-1.03(-2.02,-0.05)**	**-1.14(-1.99,-0.28)**
MET+TZD		**2.78(1.99,3.56)**	**2.97(2.21,3.74)**
MET+ INS-BA		1.95(-0.09,4.05)	**3.04(1.50,4.64)**
MET+ INS-BI		2.16(-0.94,5.31)	3.27(0.48,6.13)
MET+GLP-1	MET+SGLT-2	0.30(-0.93,1.49)	0.35(-0.68,1.36)
MET+TZD		**4.10(3.05,5.14)**	**4.45(3.50,5.42)**
MET+ INS-BA		**3.27(1.16,5.43)**	**4.53(2.90,6.20)**
MET+ INS-BI		**3.49(0.35,6.67)**	**4.76(1.91,7.66)**
MET+TZD	MET+GLP-1	**3.81(2.68,4.93)**	**4.10(3.09,5.13)**
MET+ INS-BA		**2.97(0.72,5.29)**	**4.19(2.63,5.78)**
MET+ INS-BI		3.19(-0.08,6.49)	**4.40(1.62,7.26)**
MET+ INS-BA	MET+TZD	-0.83(-3.01,1.42)	0.08(-1.59,1.80)
MET+ INS-BI		-0.61(-3.80,2.62)	0.31(-2.57,3.25)
MET+ INS-BI	MET+ INS-BA	0.21(-2.12,2.53)	0.24(-2.06,2.58)

Random-effects model	Residual deviance	147.8 vs 163 data points	182.7 vs. 197 data points
	Deviance information criteria	328.543	384.955

4. Systolic blood pressure (SBP)

A summary of the NMA results for SBP are provided in Table 4G.5. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 10 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 16 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 2 treatment comparisons (0 significant for reduced model and 2 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.5: Systolic blood pressure - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	0.24(-1.70,2.16)	0.56(-0.86,1.95)
MET+DPP-4		-1.22(-2.65,0.10)	**-1.41(-2.58,-0.34)**
MET+SGLT-2		**-3.79(-5.07,-2.60)**	**-3.89(-4.94,-2.89)**
MET+GLP-1		**-3.52(-5.22,-1.91)**	**-3.27(-4.66,-1.92)**
MET+AGI		-4.94(-12.14,1.97)	-4.79(-11.77,2.17)
MET+TZD		**-2.01(-4.06,-0.04)**	**-1.80(-3.53,-0.14)**
MET+INS-BA		-0.77(-3.68,2.07)	-0.69(-3.33,1.94)
MET+DPP-4	MET+SUL	-1.46(-3.48,0.48)	**-1.97(-3.40,-0.57)**
MET+SGLT-2		**-4.04(-5.89,-2.24)**	**-4.45(-5.66,-3.22)**
MET+GLP-1		**-3.77(-6.00,-1.61)**	**-3.83(-5.52,-2.12)**
MET+AGI		-5.16(-12.50,1.92)	-5.35(-12.40,1.69)
MET+TZD		**-2.25(-3.86,-0.71)**	**-2.36(-3.83,-0.91)**
MET+INS-BA		-1.01(-4.24,2.17)	-1.25(-3.99,1.58)
MET+SGLT-2	MET+DPP-4	**-2.57(-3.82,-1.28)**	**-2.48(-3.57,-1.37)**
MET+GLP-1		**-2.29(-3.89,-0.72)**	**-1.86(-3.19,-0.52)**

MET+AGI		-3.72(-10.88,3.27)	-3.39(-10.34,3.63)
MET+TZD		-0.78(-2.78,1.22)	-0.38(-2.10,1.30)
MET+INS-BA		0.45(-2.20,3.20)	0.73(-1.79,3.28)
MET+GLP-1	MET+SGLT-2	0.26(-1.34,1.86)	0.62(-0.77,2.00)
MET+AGI		-1.15(-8.28,5.83)	-0.90(-7.84,6.09)
MET+TZD		1.79(-0.19,3.74)	2.09(0.40,3.71)
MET+INS-BA		**3.02(0.20,5.86)**	**3.21(0.60,5.84)**
MET+AGI	MET+GLP-1	-1.39(-8.38,5.32)	-1.53(-8.36,5.30)
MET+TZD		1.52(-0.67,3.70)	1.47(-0.47,3.36)
MET+INS-BA		**2.76(0.19,5.32)**	**2.59(0.18,5.01)**
MET+TZD	MET+AGI	2.90(-4.17,10.24)	3.01(-4.15,10.04)
MET+INS-BA		4.18(-3.02,11.52)	4.12(-3.08,11.36)
MET+INS-BA	MET+TZD	1.24(-1.96,4.45)	1.11(-1.76,4.08)
Random-effect model	Residual deviance	68.93 vs 72 data points	84.99 vs. 90 data points
	Deviance information criteria	239.59	295.496

5. Diastolic blood pressure (DBP)

A summary of the NMA results for DBP are provided in Table 4G.6. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 29 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 3 treatment comparisons (0 significant for reduced model and 3 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.6: Diastolic blood pressure - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months	Overall –base case
		MD (95% CrI)	MD (95% CrI)
MET+SUL	MET	-0.56(-1.69,0.70)	-0.09(-0.93,0.78)
MET+DPP-4		-0.81(-1.61,0.05)	**-0.81(-1.44,-0.15)**
MET+SGLT-2		**-2.28(-2.97,-1.58)**	**-2.25(-2.83,-1.64)**
MET+GLP-1		-0.76(-1.84,0.45)	-0.68(-1.53,0.23)

MET+AGI		0.17(-4.07,4.47)	0.23(-3.95,4.38)
MET+TZD		-1.28(-2.52,0.05)	-0.91(-1.95,0.15)
MET+INS-BA		-0.60(-6.14,4.92)	-0.65(-5.90,4.56)
MET+INS-BI		-0.60(-6.33,5.36)	-0.59(-6.03,5.05)
MET+DPP-4	MET+SUL	-0.25(-1.41,0.84)	-0.72(-1.56,0.13)
MET+SGLT-2		**-1.72(-2.94,-0.62)**	**-2.16(-2.95,-1.38)**
MET+GLP-1		-0.20(-1.60,1.18)	-0.58(-1.64,0.50)
MET+AGI		0.72(-3.58,5.08)	0.32(-3.93,4.51)
MET+TZD		-0.72(-1.66,0.16)	**-0.82(-1.65,-0.02)**
MET+INS-BA		-0.08(-5.59,5.61)	-0.55(-5.77,4.72)
MET+INS-BI		-0.02(-5.86,6.00)	-0.50(-5.95,5.15)
MET+SGLT-2	MET+DPP-4	**-1.48(-2.32,-0.66)**	**-1.44(-2.13,-0.76)**
MET+GLP-1		0.05(-0.97,1.15)	0.13(-0.69,0.99)
MET+AGI		0.98(-3.25,5.28)	1.03(-3.17,5.18)
MET+TZD		-0.48(-1.63,0.74)	-0.10(-1.11,0.90)
MET+INS-BA		0.21(-5.27,5.72)	0.16(-5.03,5.37)
MET+INS-BI		0.24(-5.51,6.07)	0.22(-5.19,5.88)
MET+GLP-1	MET+SGLT-2	**1.53(0.37,2.79)**	**1.58(0.64,2.56)**
MET+AGI		2.46(-1.81,6.78)	2.48(-1.75,6.64)
MET+TZD		1.01(-0.21,2.32)	**1.34(0.32,2.36)**
MET+INS-BA		1.69(-3.86,7.22)	1.60(-3.58,6.83)
MET+INS-BI		1.73(-4.06,7.64)	1.66(-3.78,7.30)
MET+AGI	MET+GLP-1	0.92(-3.20,5.05)	0.90(-3.21,4.98)
MET+TZD		-0.52(-1.92,0.87)	-0.24(-1.43,0.92)
MET+INS-BA		0.13(-5.30,5.63)	0.02(-5.10,5.20)
MET+INS-BI		0.15(-5.46,5.98)	0.10(-5.26,5.64)
MET+TZD	MET+AGI	-1.43(-5.82,2.88)	-1.14(-5.36,3.16)
MET+INS-BA		-0.89(-7.59,6.18)	-0.84(-7.66,5.80)
MET+INS-BI		-0.85(-7.79,6.51)	-0.74(-7.74,6.07)
MET+INS-BA	MET+TZD	0.65(-4.87,6.31)	0.26(-5.01,5.52)
MET+INS-BI		0.73(-5.08,6.72)	0.32(-5.15,6.03)
MET+INS-BI	MET+INS-BA	0.06(-1.75,1.89)	0.09(-1.64,1.80)
Random-effect model	Residual deviance	64.9 vs 64 data points	78.63 vs. 80 data points
	Deviance information criteria	179.115	222.414

6. LDL cholesterol

A summary of the NMA results for LDL cholesterol are provided in Table 4G.7. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit

- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 29 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 3 treatment comparisons (0 significant for reduced model and 3 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.7: LDL cholesterol - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	0.04(-0.18,0.25)	0.06(-0.07,0.19)
MET+MEG		0.06(-0.26,0.37)	0.06(-0.22,0.34)
MET+DPP-4		-0.01(-0.13,0.10)	-0.01(-0.11,0.07)
MET+SGLT-2		0.15(-0.01,0.31)	**0.15(0.04,0.26)**
MET+GLP-1		-0.05(-0.23,0.11)	0.03(-0.13,0.18)
MET+AGI		-0.14(-0.73,0.46)	-0.06(-0.61,0.47)
MET+TZD		**0.22(0.08,0.36)**	**0.22(0.12,0.33)**
MET+INS-BA		-0.01(-0.31,0.30)	-0.05(-0.29,0.19)
MET+MEG	MET+SUL	0.02(-0.36,0.40)	0.00(-0.31,0.30)
MET+DPP-4		-0.05(-0.27,0.16)	-0.08(-0.20,0.04)
MET+SGLT-2		0.11(-0.14,0.37)	0.09(-0.05,0.23)
MET+GLP-1		-0.09(-0.34,0.16)	-0.03(-0.22,0.15)
MET+AGI		-0.17(-0.80,0.45)	-0.13(-0.68,0.42)
MET+TZD		**0.19(0.03,0.35)**	**0.16(0.05,0.28)**
MET+INS-BA		-0.04(-0.39,0.32)	-0.11(-0.36,0.14)
MET+DPP-4	MET+MEG	-0.07(-0.41,0.27)	-0.08(-0.37,0.21)
MET+SGLT-2		0.09(-0.26,0.45)	0.09(-0.21,0.39)
MET+GLP-1		-0.11(-0.47,0.25)	-0.03(-0.35,0.28)
MET+AGI		-0.19(-0.86,0.47)	-0.13(-0.74,0.48)
MET+TZD		0.16(-0.17,0.51)	0.16(-0.13,0.46)
MET+INS-BA		-0.07(-0.49,0.38)	-0.12(-0.47,0.25)
MET+SGLT-2	MET+DPP-4	0.16(0.00,0.33)	**0.17(0.05,0.29)**
MET+GLP-1		-0.04(-0.21,0.12)	0.04(-0.11,0.20)
MET+AGI		-0.13(-0.72,0.47)	-0.05(-0.59,0.49)
MET+TZD		**0.23(0.09,0.39)**	**0.24(0.13,0.35)**
MET+INS-BA		0.00(-0.28,0.30)	-0.04(-0.26,0.19)

MET+GLP-1	MET+SGLT-2	-0.20(-0.43,0.01)	-0.12(-0.30,0.06)
MET+AGI		-0.29(-0.91,0.32)	-0.21(-0.77,0.33)
MET+TZD		0.07(-0.13,0.28)	0.07(-0.06,0.21)
MET+INS-BA		-0.16(-0.48,0.18)	-0.20(-0.45,0.05)
MET+AGI	MET+GLP-1	-0.08(-0.65,0.49)	-0.09(-0.61,0.43)
MET+TZD		**0.28(0.09,0.48)**	**0.19(0.03,0.36)**
MET+INS-BA		0.05(-0.25,0.36)	-0.08(-0.31,0.16)
MET+TZD	MET+AGI	0.36(-0.24,0.97)	0.29(-0.25,0.84)
MET+INS-BA		0.13(-0.50,0.78)	0.01(-0.56,0.59)
MET+INS-BA	MET+TZD	-0.23(-0.55,0.10)	**-0.28(-0.52,-0.03)**
Random-effects model	Residual deviance	86.48 vs 76 data points	98.57 vs 84 data points
	Deviance information criteria	-35.37	-51.474

7. Total cholesterol

A summary of the NMA results for total cholesterol are provided in Table 4G.8. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 8 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 24 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 3 treatment comparisons (0 significant for reduced model and 3 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.8: Total cholesterol - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	-0.04(-0.23,0.17)	0.00(-0.13,0.12)
MET+DPP-4		-0.02(-0.15,0.11)	-0.03(-0.12,0.07)
MET+ SGLT-2		0.22(-0.01,0.46)	**0.19(0.05,0.34)**
MET+ GLP-1		-0.03(-0.23,0.16)	-0.04(-0.21,0.11)
MET+ AGI		-0.20(-0.52,0.12)	-0.21(-0.48,0.06)
MET+ TZD		**0.29(0.14,0.45)**	**0.29(0.17,0.42)**
MET+ INS-BA		-0.17(-0.53,0.18)	-0.15(-0.43,0.15)
MET+ MEG		0.00(-0.31,0.31)	0.00(-0.28,0.28)

MET+DPP-4	MET+SUL	0.02(-0.19,0.21)	-0.03(-0.15,0.10)
MET+ SGLT-2		0.25(-0.04,0.55)	**0.20(0.04,0.36)**
MET+ GLP-1		0.00(-0.25,0.25)	-0.04(-0.23,0.14)
MET+ AGI		-0.17(-0.52,0.19)	-0.21(-0.49,0.08)
MET+ TZD		**0.33(0.16,0.49)**	**0.30(0.17,0.42)**
MET+ INS-BA		-0.14(-0.52,0.25)	-0.15(-0.44,0.16)
MET+ MEG		0.04(-0.34,0.40)	0.00(-0.30,0.31)
MET+ SGLT-2	MET+DPP-4	**0.24(0.01,0.47)**	**0.22(0.07,0.37)**
MET+ GLP-1		-0.01(-0.20,0.17)	-0.01(-0.18,0.13)
MET+ AGI		-0.18(-0.48,0.12)	-0.18(-0.43,0.07)
MET+ TZD		**0.31(0.15,0.48)**	**0.32(0.20,0.45)**
MET+ INS-BA		-0.15(-0.48,0.18)	-0.12(-0.38,0.16)
MET+ MEG		0.02(-0.31,0.36)	0.03(-0.26,0.33)
MET+ GLP-1	MET+ SGLT-2	-0.25(-0.55,0.03)	**-0.24(-0.45,-0.04)**
MET+ AGI		**-0.42(-0.79,-0.05)**	**-0.40(-0.70,-0.11)**
MET+ TZD		0.07(-0.19,0.34)	0.10(-0.07,0.28)
MET+ INS-BA		-0.39(-0.79,0.01)	**-0.34(-0.65,-0.02)**
MET+ MEG		-0.22(-0.61,0.16)	-0.19(-0.51,0.13)
MET+ AGI	MET+ GLP-1	-0.17(-0.49,0.16)	-0.17(-0.45,0.12)
MET+ TZD		**0.32(0.12,0.54)**	**0.34(0.17,0.52)**
MET+ INS-BA		-0.14(-0.51,0.24)	-0.11(-0.40,0.22)
MET+ MEG		0.03(-0.33,0.40)	0.04(-0.27,0.37)
MET+ TZD	MET+ AGI	**0.49(0.16,0.82)**	**0.50(0.23,0.79)**
MET+ INS-BA		0.03(-0.41,0.47)	0.06(-0.30,0.44)
MET+ MEG		0.20(-0.24,0.64)	0.21(-0.17,0.60)
MET+ INS-BA	MET+ TZD	**-0.46(-0.84,-0.10)**	**-0.44(-0.74,-0.14)**
MET+ MEG		-0.29(-0.64,0.05)	-0.29(-0.60,0.01)
MET+ MEG	MET+ INS-BA	0.17(-0.30,0.65)	0.15(-0.26,0.55)
Random-effects model	Residual deviance	64 vs 83.74 data points	77 vs.97.51 data points
	Deviance information criteria	2.225	-23.122

8. HDL cholesterol

A summary of the NMA results for HDL cholesterol are provided in Table 4G.9. Compared to the base case, the reduced model:

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 12treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 32 treatment comparisons with similar magnitude and direction of the effect

- Disagreed on statistical significance for 1 treatment comparisons (0 significant for reduced model and 1 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.9: HDL cholesterol - network meta-analysis results for studies of duration 3 to 12 months: mean difference and 95% credible intervals

Treatment	Reference	Duration 3 to12 months	Overall –base case
		MD (95% Crl)	MD (95% Crl)
MET+SUL	MET	-0.02(-0.06,0.02)	-0.03(-0.05,0.00)
MET+MEG		0.00(-0.06,0.05)	0.00(-0.06,0.05)
MET+DPP-4		0.00(-0.03,0.03)	-0.01(-0.03,0.02)
MET+SGLT-2		**0.07(0.03,0.11)**	**0.07(0.04,0.09)**
MET+GLP-1		-0.02(-0.07,0.02)	-0.02(-0.06,0.02)
MET+AGI		-0.03(-0.12,0.05)	-0.03(-0.11,0.04)
MET+TZD		**0.10(0.07,0.14)**	**0.10(0.07,0.13)**
MET+INS-BA		0.04(-0.04,0.12)	0.01(-0.06,0.08)
MET+INS-BI		0.03(-0.06,0.12)	0.02(-0.05,0.10)
MET+MEG	MET+SUL	0.01(-0.06,0.09)	0.02(-0.04,0.08)
MET+DPP-4		0.02(-0.03,0.07)	0.02(-0.01,0.05)
MET+SGLT-2		**0.09(0.04,0.15)**	**0.09(0.06,0.13)**
MET+GLP-1		-0.01(-0.06,0.05)	0.01(-0.04,0.05)
MET+AGI		-0.01(-0.10,0.08)	-0.01(-0.08,0.07)
MET+TZD		**0.12(0.09,0.16)**	**0.13(0.10,0.15)**
MET+INS-BA		0.06(-0.03,0.15)	0.04(-0.03,0.11)
MET+INS-BI		0.05(-0.03,0.13)	0.05(-0.02,0.12)
MET+DPP-4	MET+MEG	0.00(-0.06,0.07)	0.00(-0.06,0.06)
MET+SGLT-2		**0.08(0.01,0.15)**	**0.07(0.01,0.13)**
MET+GLP-1		-0.02(-0.09,0.06)	-0.02(-0.08,0.05)
MET+AGI		-0.03(-0.13,0.08)	-0.03(-0.12,0.06)
MET+TZD		**0.11(0.04,0.18)**	**0.10(0.05,0.16)**
MET+INS-BA		0.04(-0.05,0.15)	0.01(-0.07,0.10)
MET+INS-BI		0.04(-0.08,0.15)	0.03(-0.07,0.12)
MET+SGLT-2	MET+DPP-4	**0.07(0.03,0.11)**	**0.07(0.04,0.10)**
MET+GLP-1		-0.02(-0.07,0.02)	-0.02(-0.05,0.02)
MET+AGI		-0.03(-0.11,0.05)	-0.03(-0.10,0.04)
MET+TZD		**0.11(0.07,0.14)**	**0.11(0.08,0.13)**
MET+INS-BA		0.04(-0.03,0.11)	0.01(-0.05,0.08)

MET+INS-BI		0.03(-0.07,0.13)	0.03(-0.05,0.11)
MET+GLP-1	MET+SGLT-2	**-0.09(-0.15,-0.04)**	**-0.09(-0.13,-0.04)**
MET+AGI		**-0.10(-0.19,-0.01)**	**-0.10(-0.18,-0.02)**
MET+TZD		0.03(-0.01,0.08)	**0.03(0.00,0.07)**
MET+INS-BA		-0.03(-0.11,0.05)	-0.06(-0.13,0.01)
MET+INS-BI		-0.04(-0.14,0.06)	-0.04(-0.13,0.04)
MET+AGI	MET+GLP-1	-0.01(-0.09,0.08)	-0.01(-0.09,0.06)
MET+TZD		**0.13(0.08,0.18)**	**0.12(0.08,0.16)**
MET+INS-BA		0.06(-0.01,0.14)	0.03(-0.04,0.10)
MET+INS-BI		0.06(-0.05,0.16)	0.04(-0.04,0.13)
MET+TZD	MET+AGI	**0.14(0.05,0.22)**	**0.13(0.06,0.21)**
MET+INS-BA		0.07(-0.04,0.18)	0.04(-0.05,0.14)
MET+INS-BI		0.06(-0.06,0.18)	0.06(-0.05,0.16)
MET+INS-BA	MET+TZD	-0.07(-0.14,0.02)	-0.09(-0.16,-0.02)
MET+INS-BI		-0.07(-0.16,0.02)	-0.08(-0.15,0.00)
MET+INS-BI	MET+INS-BA	-0.01(-0.13,0.11)	0.02(-0.09,0.12)
Random-effect model	Residual deviance	157.7 vs 85 data points	182.4 vs. 103 data points
	Deviance information criteria	-173.124	-245.107

4G.2: Dichotomous outcomes

For dichotomous outcomes, zero event counts can lead to problems in the analysis. In particular, if all treatment arms have zero events; we label this situation of all zero counts as 'zero case'. In the base case analysis, the zero case is handled by adjustment of the zeros with a factor (0 to 1) that is proportional to the number of patients allocated to that arm.

Two approaches were considered for the sensitivity analysis. First, the duration of the study treatment period was considered. Since most of the 204 studies had treatment periods between 3 months and 12 months, as illustrated in Figure 4G.1, a sensitivity analysis was conducted restricting studies in the analysis to those with treatment periods between 3 to 12 months. Second, as part of the sensitivity analysis, zero case studies were removed.

Table 4G.10 for the dichotomous outcomes.

Table 4G.10: Number of studies by duration of treatment and zero cases for binary outcomes in the network meta-analysis

Outcome	NMA Model Likelihood/Link	4-10 weeks	12-20 weeks	24-32 weeks	48-54 weeks	76-208 weeks	Zero case	Section
Non-severe hypoglycemia	Binomial/Logit	4	21	28	15	4	8/72	4.3.4.3
Severe hypoglycemia	Binomial/Logit	1	18	21	12	13	37/65	4.3.4.2
Total Adverse Events	Binomial/Logit	0	20	31	16	9	1/76	4.3.4.7a
Serious Adverse Events	Binomial/Logit	3	22	36	17	12	10/90	4.3.4.7b
Withdrawals due to Adverse Events	Binomial/Logit	2	29	36	23	12	9/102	4.3.4.7c
Urogenital Adverse Events	Binomial/Logit	1	7	13	9	5	0/35	4.3.4.8
Renal Adverse Events	Binomial/Logit	1	5	9	1	8	4/24	4.3.4.9
Unstable Angina	Binomial/Logit	0	2	6	7	5	0/17	4.3.4.18a
Heart Failure	Binomial/Logit	0	2	5	5	6	3/18	4.3.4.12
Transient Ischemic Attack	Binomial/Logit	0	3	4	5	6	2/15	4.3.4.14
Fractures	Binomial/Logit	0	5	6	6	3	5/20	4.3.4.10
All-Cause Mortality	Binomial/Logit	3	15	21	13	10	27/61	4.3.4.11a
Cardiovascular Mortality	Binomial/Logit	2	7	14	8	6	21/37	4.3.4.11b
Fatal Stroke	Binomial/Logit	1	7	12	8	2	23/30	4.3.4.13a
Pancreatitis	Binomial/Logit	1	5	10	5	5	14/26	4.3.4.15

In the following tables (Table 4G.11 to Table 4G.25), the NMA results for the binary outcomes for which a NMA was conducted are presented for the three possible sensitivity analyses and the original base case analysis, namely:

- Duration 3 to 12 months, exclude zero cases
- Duration 3 to 12 months, include zero cases
- Duration no restriction, exclude zero cases
- Duration no restriction, include zero cases (base case)

1. All-cause mortality

A summary of the NMA results for all-cause mortality are provided in Table 4G.11.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- No model possible for zero cases excluded for restricted duration

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- No model possible for zero cases excluded for restricted duration

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.11: All-cause mortality - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET		1.15(0.17,7.25)	1.73(0.75,4.16)	1.35(0.72,2.61)
MET+DPP-4			0.84(0.14,4.92)	1.35(0.56,3.50)	1.01(0.52,1.99)
MET+SGLT-2			1.43(0.23,10.53)	1.49(0.54,3.82)	1.13(0.57,2.47)
MET+GLP-1			0.49(0.04,5.90)	0.77(0.15,3.11)	0.81(0.29,2.08)
MET+TZD			0.91(0.13,5.93)	1.44(0.65,3.17)	1.17(0.62,2.25)
MET+DPP-4	MET+SUL		0.73(0.32,1.67)	0.78(0.45,1.30)	0.75(0.44,1.17)
MET+SGLT-2			1.26(0.24,9.08)	0.85(0.44,1.62)	0.85(0.47,1.52)
MET+GLP-1			0.42(0.05,3.67)	0.44(0.09,1.68)	0.60(0.18,1.62)
MET+TZD			0.79(0.41,1.48)	0.83(0.50,1.33)	0.87(0.56,1.36)
MET+SGLT-2	MET+DPP-4		1.72(0.35,12.79)	1.11(0.49,2.37)	1.15(0.59,2.36)
MET+GLP-1			0.57(0.08,4.65)	0.56(0.12,2.44)	0.80(0.27,2.25)
MET+TZD			1.09(0.38,2.88)	1.07(0.53,2.17)	1.16(0.66,2.19)
MET+GLP-1	MET+SGLT-2		0.33(0.03,2.96)	0.50(0.11,2.29)	0.71(0.20,1.94)
MET+TZD			0.63(0.08,3.48)	0.98(0.44,2.19)	1.01(0.53,2.03)
MET+TZD	MET+GLP-1		1.88(0.21,15.19)	1.88(0.48,9.13)	1.44(0.52,4.83)
Random-effect model	Residual deviance		34.01 vs 43 data points	48.7 vs 63 data points	72.5 vs.127 data points
	Deviance information criteria		158	244.41	400.082

2. Heart failure

A summary of the NMA results for heart failure are provided in Table 4G.12.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 7 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 3 treatment comparison (0 significant for reduced model and 3 significant for base-case model), but all had similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 3 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for all 5 treatment comparisons with similar magnitude and direction
- Disagreed on statistical significance for 1 treatment comparison (1 significant for reduced model and 0 significant for base-case model), but all had similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- Agreed on the non-statistical significance for 9 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 2 treatment comparison (2 significant for reduced model and 0 significant for base-case model), but all had similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- Agreed on the statistical significance for 1 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 6 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 3 treatment comparison (0 significant for reduced model and 3 significant for base-case model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.12: Heart failure - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95%Crl)	OR (95%Crl)	OR (95%Crl)	OR (95%Crl)
MET+SUL	MET	8.93(0.21,1223.00)	4.00(0.69,32.75)	1.12(0.29,5.83)	1.14(0.36,4.05)
MET+DPP-4		2.02(0.09,215.80)	0.99(0.16,6.64)	0.81(0.18,4.64)	0.74(0.24,2.55)
MET+SGLT-2		1.95(0.00,763.30)	0.95(0.17,7.45)	1.10(0.10,12.93)	0.99(0.18,5.16)
MET+TZD		22.53(0.41,3730.00)	**9.72(1.87,78.81)**	2.72(0.87,9.97)	**3.31(1.44,9.02)**
MET+DPP-4	MET+SUL	0.27(0.03,1.33)	**0.24(0.05,0.90)**	0.70(0.28,1.72)	0.65(0.28,1.44)
MET+SGLT-2		0.22(0.00,7.03)	0.23(0.03,1.81)	1.00(0.14,7.23)	0.84(0.20,3.56)
MET+TZD		2.45(0.68,11.16)	**2.43(0.83,8.46)**	2.34(0.71,7.92)	**2.82(1.10,9.19)**
MET+SGLT-2	MET+DPP-4	0.83(0.00,57.01)	0.95(0.13,6.32)	1.40(0.16,12.11)	1.29(0.29,6.33)
MET+TZD		**9.39(1.25,136.40)**	**9.84(2.58,61.68)**	3.35(0.81,13.37)	**4.30(1.55,14.14)**
MET+TZD	MET+SGLT-2	11.35(0.25,7107.00)	**10.99(1.40,109.80)**	2.38(0.22,24.96)	3.41(0.63,17.97)
Random-effect model	Residual deviance	10.1 vs 14 data points	15.7 vs 26 data points	18.7 vs 25 data points	25.25 vs.37 data points
	Deviance information criteria	55.892	88.013	98.345	132.088

3. Fatal stroke

A summary of the NMA results for fatal stroke are provided in Table 4G.13.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- No model possible for zero cases excluded for reduced model

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction of the effect for 11 comparisons

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- No model possible for zero cases excluded for restricted and unrestricted duration

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- No model possible for zero cases excluded for restricted duration

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.13: Fatal stroke - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		no results	OR (95%Crl)	no results	OR (95%Crl)
MET+SUL	MET		0.75(0.13,4.72)		0.64(0.13,4.06)
MET+DPP-4			0.66(0.18,2.43)		0.63(0.23,1.85)
MET+SGLT-2			1.04(0.27,5.89)		1.00(0.26,4.69)
MET+GLP			0.59(0.07,3.95)		0.72(0.11,3.38)
MET+TZD			0.88(0.10,6.53)		0.88(0.12,6.65)
MET+DPP-4	MET+SUL		0.88(0.20,3.74)		0.97(0.21,4.61)
MET+SGLT-2			1.46(0.24,9.59)		1.61(0.21,9.22)
MET+GLP			0.76(0.07,9.66)		1.15(0.11,8.31)
MET+TZD			1.21(0.21,6.38)		1.29(0.16,11.14)
MET+SGLT-2	MET+DPP-4		1.66(0.37,8.78)		1.60(0.37,6.59)
MET+GLP			0.89(0.11,7.28)		1.12(0.18,5.54)
MET+TZD			1.41(0.17,8.78)		1.33(0.21,10.47)
MET+TZD	MET+SGLT-2		0.55(0.04,5.26)		0.72(0.09,4.29)
MET+GLP			0.86(0.08,6.74)		0.90(0.08,8.81)
MET+TZD	MET+GLP		1.57(0.12,14.81)		1.26(0.12,14.77)
Random-effect model	Residual deviance		22.82 vs 54 data points		25.6 vs. 61 data points
	Deviance information criteria		147.337		164.934

4. Cardiovascular mortality

A summary of the NMA results for cardiovascular mortality are provided in Table 4G.14.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.14: Cardiovascular mortality - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95%Crl)	OR (95%Crl)	OR (95%Crl)	OR (95%Crl)
MET+SUL	MET	0.85(0.10,6.25)	0.89(0.20,4.47)	0.88(0.10,8.65)	1.04(0.34,3.06)
MET+DPP-4		0.58(0.09,3.21)	0.52(0.18,1.54)	0.54(0.07,3.36)	0.66(0.27,1.72)
MET+SGLT-2		6.74(0.16,722.50)	1.04(0.16,6.47)	6.69(0.13,2859.00)	1.16(0.29,4.86)
MET+GLP-1		0.21(0.01,2.30)	0.28(0.04,1.65)	0.21(0.01,2.89)	0.51(0.12,1.87)
MET+TZD		1.20(0.04,34.21)	0.91(0.22,3.90)	1.13(0.05,31.20)	1.09(0.21,5.16)
MET+DPP-4	MET+SUL	0.66(0.20,2.24)	0.58(0.14,2.01)	0.59(0.22,1.57)	0.64(0.27,1.48)
MET+SGLT-2		7.06(0.34,772.80)	1.17(0.14,8.85)	7.24(0.32,2947.00)	1.18(0.22,6.21)
MET+GLP-1		0.25(0.03,1.28)	0.30(0.04,2.73)	0.24(0.03,1.11)	0.48(0.13,1.75)
MET+TZD		1.42(0.10,17.92)	1.01(0.22,5.00)	1.33(0.14,15.41)	1.04(0.24,4.71)
MET+SGLT-2	MET+DPP-4	11.34(0.48,1170.00)	2.02(0.27,15.69)	11.83(0.46,5576.00)	1.82(0.36,8.22)
MET+GLP-1		0.39(0.05,1.94)	0.52(0.09,3.13)	0.41(0.05,2.19)	0.79(0.20,2.43)
MET+TZD		2.13(0.12,41.36)	1.79(0.42,6.71)	2.17(0.20,29.03)	1.62(0.39,7.92)
MET+GLP-1	MET+SGLT-2	0.03(0.00,1.13)	0.27(0.02,2.98)	0.03(0.00,1.15)	0.43(0.05,3.16)
MET+TZD		0.18(0.00,12.24)	0.87(0.09,10.02)	0.17(0.00,11.18)	0.94(0.12,6.55)
MET+TZD	MET+GLP-1	5.55(0.23,153.20)	3.36(0.39,26.66)	5.39(0.36,119.90)	2.23(0.38,14.27)
Random-effect model	Residual deviance	18.52 vs 24 data points	29.95 vs 58 data points	19.68 vs 26 data points	40.89 vs. 75 data points
	Deviance information criteria	88.863	166.309	97.052	220.929

5. Transient ischemic attack

A summary of the NMA results for transient ischemic attack are provided in Table 4G.15.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.15: Transient ischemic attack - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95%Crl)	OR (95%Crl)	OR (95%Crl)	OR (95%Crl)
MET+SUL	MET	0.24(0.01,4.53)	0.33(0.02,4.24)	1.05(0.13,6.76)	0.78(0.16,4.39)
MET+DPP-4		0.24(0.01,3.30)	0.31(0.02,2.35)	0.71(0.09,4.48)	0.54(0.12,2.81)
MET+SGLT-2		0.22(0.01,3.35)	0.31(0.03,2.43)	0.73(0.09,3.97)	0.55(0.11,2.95)
MET+TZD		0.22(0.00,4.54)	0.29(0.02,4.29)	0.88(0.09,7.54)	0.66(0.10,4.97)

MET+DPP-4	MET+SUL	0.94(0.17,4.80)	0.95(0.19,4.82)	0.67(0.25,2.01)	0.71(0.25,1.90)
MET+SGLT-2		0.94(0.10,9.03)	0.98(0.10,8.12)	0.67(0.23,2.04)	0.70(0.25,2.08)
MET+TZD		0.89(0.32,2.71)	0.89(0.32,2.75)	0.84(0.31,2.53)	0.86(0.31,2.35)
MET+SGLT-2	MET+DPP-4	0.99(0.11,9.29)	1.01(0.15,7.65)	1.01(0.25,3.68)	1.01(0.28,3.47)
MET+TZD		0.95(0.17,6.04)	0.92(0.17,5.94)	1.24(0.32,5.12)	1.21(0.31,4.83)
MET+TZD	MET+SGLT-2	0.96(0.09,10.54)	0.91(0.09,9.96)	1.25(0.30,5.59)	1.21(0.28,5.19)
Random-effect model	Residual deviance	12.82 vs 16 data points	13.24 vs 19 data points	23.21 vs 26 data points	24.54 vs.32 data points
	Deviance information criteria	62.118	68.318	102.856	115.993

6. Unstable angina

A summary of the NMA results for unstable angina are provided in Table 4G.16.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the non-statistical significance for all 6 treatment comparisons with similar magnitude and direction
- No model possible for restricted duration for 4 treatments

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- Agreed on the non-statistical significance for all 6 treatment comparisons with similar magnitude and direction
- No model possible for zero cases for 4 treatments

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.16: Unstable angina - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration 3 to12 months	
		Zero cases excluded	Zero cases excluded	Zero cases excluded	Overall – base case Zero cases included
		OR (95%CrI)	OR (95%CrI)	OR (95%CrI)	OR (95%CrI)
MET+SUL	MET	1.70(0.09,36.49)	1.56(0.20,16.56)	0.75(0.15,3.99)	0.90(0.25,3.93)
MET+DPP-4		1.23(0.20,7.80)	1.64(0.40,8.53)	0.77(0.18,3.26)	1.05(0.33,3.50)
MET+SGLT-2		1.29(0.05,35.93)	0.56(0.03,15.58)	0.93(0.14,6.09)	0.86(0.20,3.74)
EMT+TZD			1.17(0.14,13.06)	0.59(0.08,4.31)	0.71(0.15,3.55)
MET+DPP-4	MET+SUL	0.73(0.07,6.92)	1.04(0.20,5.96)	1.03(0.34,2.84)	1.14(0.46,2.90)
MET+SGLT-2		0.77(0.24,2.51)	0.38(0.02,6.61)	1.21(0.29,5.44)	0.93(0.29,3.24)
MET+TZD			0.76(0.28,1.92)	0.78(0.28,2.20)	0.77(0.33,1.81)
MET+SGLT-2	MET+DPP-4	1.06(0.08,15.62)	0.37(0.02,5.14)	1.18(0.23,6.26)	0.81(0.21,3.16)
MET+TZD			0.72(0.11,4.06)	0.77(0.18,3.39)	0.68(0.19,2.15)
MET+TZD	MET+SGLT-2		2.00(0.10,49.63)	0.66(0.11,3.60)	0.82(0.19,3.48)
Random-effect model	Residual deviance	11.56 vs 12 data points	14.99 vs 20 data points	20.49 vs 23 data points	23.65 vs.31 data points
	Deviance information criteria	50.55	72.671	92.7	112.765

7. Urogenital adverse event

A summary of the NMA results for urogenital adverse events are provided in Table 4G.17.

Compared to the base case, the reduced model with zero cases excluded was identical (Column 5 vs 6):

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction
- Agreed on the non-statistical significance for all 11 treatment comparisons with similar magnitude and direction
- No model possible for zero cases excluded with restricted duration for 6 treatments

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide

- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction
- Agreed on the non-statistical significance for all 11 treatment comparisons with similar magnitude and direction
- No model possible for zero cases excluded with restricted duration for 6 treatments

Compared to the reduced model with restricted duration for zero cases included vs excluded was identical (Column 3 vs 4)

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.17: Urogenital adverse event - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	0.91(0.53,1.53)	0.91(0.53,1.53)	0.89(0.60,1.31)	0.89(0.60,1.31)
MET+DPP-4		1.22(0.82,1.77)	1.22(0.82,1.77)	1.05(0.76,1.48)	1.05(0.76,1.48)
MET+SGLT-2		**2.13(1.29,3.50)**	**2.13(1.29,3.50)**	**1.67(1.17,2.46)**	**1.67(1.17,2.46)**
MET+GLP-1		1.17(0.59,2.33)	1.17(0.59,2.33)	0.92(0.55,1.58)	0.92(0.55,1.58)
MET+TZD		0.65(0.18,1.90)	0.65(0.18,1.90)	0.53(0.16,1.58)	0.53(0.16,1.58)
MET+INS-BA				0.63(0.05,5.03)	0.63(0.05,5.03)
MET+DPP-4	MET+SUL	1.34(0.87,2.08)	1.34(0.87,2.08)	1.19(0.86,1.66)	1.19(0.86,1.66)
MET+SGLT-2		**2.33(1.56,3.75)**	**2.33(1.56,3.75)**	**1.88(1.41,2.55)**	**1.88(1.41,2.55)**
MET+GLP-1		1.29(0.64,2.66)	1.29(0.64,2.66)	1.04(0.59,1.83)	1.04(0.59,1.83)
MET+TZD		0.71(0.19,2.18)	0.71(0.19,2.18)	0.59(0.18,1.77)	0.59(0.18,1.77)
MET+INS-BA				0.71(0.06,5.63)	0.71(0.06,5.63)
MET+SGLT-2	MET+DPP-4	1.75(1.14,2.78)	1.75(1.14,2.78)	1.59(1.11,2.27)	1.59(1.11,2.27)
MET+GLP-1		0.96(0.50,1.86)	0.96(0.50,1.86)	0.87(0.51,1.49)	0.87(0.51,1.49)
MET+TZD		0.53(0.15,1.49)	0.53(0.15,1.49)	0.50(0.15,1.45)	0.50(0.15,1.45)
MET+INS-BA				0.60(0.05,4.78)	0.60(0.05,4.78)
MET+GLP-1	MET+SGLT-2	**0.55(0.28,1.05)**	**0.55(0.28,1.05)**	**0.55(0.32,0.94)**	**0.55(0.32,0.94)**
MET+TZD		**0.30(0.08,0.89)**	**0.30(0.08,0.89)**	**0.32(0.09,0.94)**	**0.32(0.09,0.94)**
MET+INS-BA				0.38(0.03,2.97)	0.38(0.03,2.97)
MET+TZD	MET+GLP-1	0.55(0.16,1.56)	0.55(0.16,1.56)	0.57(0.17,1.70)	0.57(0.17,1.70)
MET+INS-BA				0.69(0.06,4.98)	0.69(0.06,4.98)
MET+INS-BA	MET+TZD			1.19(0.09,12.63)	1.19(0.09,12.63)

Random-effects model	Residual deviance	49.61 vs 52 data points	49.61 vs 52 data points	70.22 vs. 74 data points	70.22 vs. 74 data points
	Deviance information criteria	265.563	265.563	410.453	410.453

8. Withdrawals due to adverse events

A summary of the NMA results for withdrawals due to adverse events are provided in Table 4G.18.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 5 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 40 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 5 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 39 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 1 treatment comparison (0 significant for restricted model and 1 significant for base-case model), but all had similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 6 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 39 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 5 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 39 treatment comparisons with similar magnitude and direction of the effect

- Disagreed on statistical significance for 1 treatment comparison (1 significant for excluded model and 0 significant for included model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.18: Withdrawals due to adverse events - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% CrL)	OR (95% CrL)	OR (95% CrL)	OR (95% CrL)
MET+SUL	MET	0.71(0.50,1.02)	0.83(0.59,1.17)	0.74(0.54,1.02)	0.74(0.54,1.02)
MET+MEG		0.44(0.02,6.53)	0.78(0.25,2.33)	0.74(0.23,2.44)	0.75(0.24,2.43)
MET+DPP-4		0.72(0.54,0.99)	0.98(0.74,1.32)	0.77(0.58,1.02)	0.77(0.58,1.02)
MET+SGLT-2		0.90(0.61,1.35)	1.17(0.78,1.73)	0.95(0.67,1.38)	0.95(0.67,1.35)
MET+GLP-1		**1.77(1.17,2.71)**	**2.49(1.54,4.01)**	**1.67(1.13,2.53)**	**1.68(1.14,2.50)**
MET+AGI		0.36(0.03,3.73)	0.44(0.04,4.18)	0.39(0.03,3.95)	0.38(0.03,3.50)
MET+TZD		0.85(0.54,1.37)	1.06(0.74,1.57)	0.96(0.65,1.43)	0.95(0.65,1.41)
MET+INS-BA		0.28(0.05,1.19)	0.66(0.11,3.37)	0.33(0.07,1.27)	0.36(0.08,1.32)
MET+INS-BI		0.93(0.02,310.40)	2.99(0.47,26.75)	2.79(0.38,39.39)	1.88(0.30,15.98)
MET+MEG	MET+SUL	0.63(0.02,9.24)	0.94(0.29,2.88)	1.00(0.30,3.36)	1.03(0.31,3.32)
MET+DPP-4		1.02(0.78,1.36)	1.19(0.91,1.57)	1.04(0.80,1.36)	1.04(0.80,1.35)
MET+SGLT-2		1.27(0.88,1.84)	1.41(0.93,2.12)	1.29(0.92,1.84)	1.28(0.91,1.81)
MET+GLP-1		**2.50(1.59,3.97)**	**3.00(1.86,4.81)**	**2.27(1.49,3.49)**	**2.28(1.50,3.48)**
MET+AGI		0.50(0.04,4.99)	0.53(0.04,4.85)	0.53(0.03,5.27)	0.52(0.04,4.82)
MET+TZD		1.20(0.80,1.84)	1.28(0.95,1.78)	1.29(0.92,1.84)	1.28(0.92,1.82)
MET+INS-BA		0.40(0.08,1.68)	0.80(0.13,4.01)	0.45(0.09,1.73)	0.49(0.11,1.79)
MET+INS-BI		1.32(0.02,435.30)	3.59(0.58,31.12)	3.77(0.51,53.18)	2.54(0.42,21.09)
MET+DPP-4	MET+MEG	1.63(0.11,46.78)	1.27(0.41,4.03)	1.04(0.31,3.53)	1.01(0.31,3.30)
MET+SGLT-2		2.02(0.14,60.01)	1.50(0.46,4.88)	1.29(0.38,4.47)	1.25(0.38,4.19)
MET+GLP-1		3.98(0.26,114.70)	3.20(0.97,10.75)	2.27(0.65,7.98)	2.23(0.66,7.57)
MET+AGI		0.81(0.02,47.82)	0.57(0.04,6.81)	0.52(0.03,6.46)	0.50(0.03,6.46)
MET+TZD		1.92(0.13,55.60)	1.36(0.44,4.51)	1.29(0.38,4.56)	1.25(0.37,4.20)
MET+INS-BA		0.63(0.03,25.05)	0.85(0.11,6.28)	0.45(0.06,2.65)	0.47(0.08,2.71)
MET+INS-BI		2.40(0.01,1647.00)	3.86(0.46,45.72)	3.86(0.35,64.89)	2.54(0.28,28.28)
MET+SGLT-2	MET+DPP-4	1.25(0.83,1.84)	1.19(0.79,1.77)	1.25(0.87,1.80)	1.24(0.86,1.76)
MET+GLP-1		**2.45(1.60,3.74)**	**2.53(1.61,3.99)**	**2.19(1.47,3.30)**	**2.20(1.46,3.26)**
MET+AGI		0.49(0.04,4.88)	0.45(0.04,4.12)	0.51(0.03,5.07)	0.50(0.04,4.57)

MET+TZD		1.18(0.79,1.77)	1.08(0.79,1.51)	1.25(0.88,1.79)	1.23(0.88,1.76)
MET+INS-BA		0.39(0.07,1.61)	0.67(0.11,3.37)	0.43(0.09,1.65)	0.47(0.11,1.69)
MET+INS-BI		1.28(0.02,425.80)	3.06(0.49,26.56)	3.64(0.49,50.60)	2.45(0.40,20.49)
MET+GLP-1	MET+SGLT-2	**1.97(1.19,3.27)**	**2.14(1.22,3.64)**	**1.76(1.08,2.83)**	**1.78(1.12,2.83)**
MET+AGI		0.39(0.03,4.10)	0.37(0.03,3.59)	0.41(0.03,4.19)	0.40(0.03,3.78)
MET+TZD		0.95(0.57,1.60)	0.91(0.57,1.47)	1.00(0.65,1.57)	1.00(0.64,1.56)
MET+INS-BA		0.31(0.06,1.33)	0.57(0.09,2.98)	0.35(0.07,1.38)	0.38(0.09,1.43)
MET+INS-BI		1.03(0.02,355.30)	2.59(0.40,23.36)	2.92(0.38,41.63)	1.99(0.31,16.55)
MET+AGI	MET+GLP-1	0.20(0.02,2.06)	0.18(0.01,1.71)	0.23(0.01,2.42)	0.23(0.02,2.13)
MET+TZD		**0.48(0.28,0.83)**	**0.43(0.26,0.73)**	**0.57(0.35,0.93)**	**0.56(0.35,0.92)**
MET+INS-BA		**0.16(0.03,0.66)**	0.27(0.04,1.45)	**0.20(0.04,0.76)**	**0.21(0.05,0.78)**
MET+INS-BI		0.53(0.01,174.00)	1.21(0.19,10.91)	1.67(0.22,23.10)	1.12(0.18,9.56)
MET+TZD	MET+AGI	2.39(0.23,32.55)	2.43(0.26,30.34)	2.48(0.25,38.09)	2.48(0.26,35.08)
MET+INS-BA		0.79(0.05,14.66)	1.49(0.09,30.64)	0.83(0.05,18.15)	0.94(0.07,17.29)
MET+INS-BI		2.73(0.02,1907.00)	7.03(0.37,198.80)	7.49(0.35,314.50)	5.11(0.28,168.10)
MET+INS-BA	MET+TZD	0.33(0.06,1.44)	0.63(0.10,3.12)	0.35(0.07,1.36)	0.38(0.09,1.41)
MET+INS-BI		1.09(0.02,363.40)	2.82(0.44,24.64)	2.90(0.38,41.14)	1.99(0.31,16.79)
MET+INS-BI	MET+INS-BA	3.23(0.07,954.30)	4.62(0.88,37.41)	8.50(1.27,123.70)	5.37(0.99,42.86)
Random-effect model	residual Deviance	156.7 vs 167 data points	179 vs 182 data points	201 vs 203 data points	211.1 vs. 219 data points
	Deviance information criteria	858.938	849.877	1026.16	1067.56

9. Total adverse events

A summary of the NMA results for total adverse events are provided in Table 4G.19.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 16 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 29 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 26 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 5 treatment comparison (3 significant for restricted model and 2 significant for base case model), but all had similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 26 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 5 treatment comparison (3 significant for reduced model and 2 significant for unrestricted model), but all had similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 17 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 28 treatment comparisons with similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.19: Total adverse events - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95%Crl)	OR (95%Crl)	OR (95%Crl)	OR (95%Crl)
MET+SUL	MET	1.14(0.99,1.31)	1.13(0.98,1.31)	1.10(0.96,1.24)	1.10(0.97,1.25)
MET+MEG		1.09(0.71,1.64)	1.10(0.72,1.67)	1.11(0.73,1.70)	1.10(0.72,1.70)
MET+DPP-4		0.97(0.87,1.07)	0.97(0.87,1.07)	0.95(0.85,1.04)	0.94(0.85,1.04)
MET+SGLT-2		1.09(0.96,1.25)	1.09(0.96,1.25)	1.07(0.95,1.21)	1.07(0.95,1.21)
MET+GLP-1		**1.63(1.33,1.99)**	**1.62(1.33,2.01)**	**1.52(1.29,1.82)**	**1.52(1.28,1.81)**
MET+AGI		**1.72(1.09,2.75)**	**1.71(1.10,2.70)**	**1.68(1.05,2.66)**	**1.66(1.05,2.64)**
MET+TZD		0.98(0.84,1.16)	0.98(0.84,1.16)	0.96(0.82,1.15)	0.97(0.82,1.15)
MET+INS-BA		**1.66(1.08,2.47)**	**1.65(1.07,2.48)**	1.52(0.99,2.28)	1.51(0.99,2.24)
MET+INS-BI		**1.72(1.01,2.96)**	**1.73(1.01,2.98)**	**1.82(1.10,2.98)**	**1.83(1.12,3.04)**

MET+MEG	MET+SUL	0.96(0.61,1.48)	0.97(0.62,1.50)	1.01(0.65,1.58)	1.00(0.65,1.58)
MET+DPP-4		**0.85(0.76,0.96)**	**0.85(0.75,0.96)**	**0.86(0.78,0.96)**	**0.86(0.78,0.95)**
MET+SGLT-2		0.96(0.83,1.13)	0.97(0.83,1.13)	0.98(0.86,1.11)	0.98(0.86,1.11)
MET+GLP-1		**1.43(1.15,1.80)**	**1.43(1.14,1.81)**	**1.39(1.16,1.69)**	**1.39(1.15,1.68)**
MET+AGI		1.51(0.96,2.42)	1.51(0.97,2.39)	1.53(0.97,2.42)	1.51(0.96,2.41)
MET+TZD		0.87(0.74,1.02)	0.87(0.74,1.02)	0.88(0.75,1.04)	0.88(0.76,1.04)
MET+INS-BA		1.46(0.95,2.18)	1.46(0.94,2.17)	1.39(0.91,2.06)	1.38(0.90,2.05)
MET+INS-BI		1.52(0.90,2.60)	1.53(0.91,2.59)	1.66(1.02,2.69)	1.67(1.03,2.73)
MET+DPP-4	MET+MEG	0.89(0.58,1.37)	0.88(0.57,1.35)	0.85(0.55,1.32)	0.86(0.55,1.32)
MET+SGLT-2		1.00(0.65,1.57)	0.99(0.64,1.54)	0.97(0.62,1.51)	0.98(0.62,1.51)
MET+GLP-1		1.49(0.95,2.40)	1.47(0.93,2.37)	1.38(0.87,2.19)	1.38(0.86,2.18)
MET+AGI		1.58(0.85,2.98)	1.56(0.85,2.84)	1.51(0.82,2.84)	1.51(0.81,2.82)
MET+TZD		0.91(0.58,1.43)	0.89(0.57,1.42)	0.87(0.55,1.37)	0.88(0.55,1.38)
MET+INS-BA		1.53(0.83,2.77)	1.50(0.83,2.63)	1.37(0.75,2.44)	1.38(0.75,2.45)
MET+INS-BI		1.58(0.81,3.22)	1.57(0.81,3.11)	1.64(0.86,3.15)	1.67(0.86,3.22)
MET+SGLT-2	MET+DPP-4	1.13(0.99,1.29)	1.13(0.99,1.30)	**1.13(1.00,1.29)**	**1.14(1.00,1.29)**
MET+GLP-1		**1.68(1.38,2.06)**	**1.68(1.38,2.07)**	**1.62(1.36,1.92)**	**1.61(1.36,1.92)**
MET+AGI		**1.78(1.14,2.81)**	**1.77(1.15,2.77)**	**1.78(1.13,2.78)**	**1.76(1.12,2.77)**
MET+TZD		1.02(0.88,1.19)	1.02(0.88,1.19)	1.02(0.88,1.20)	1.02(0.88,1.20)
MET+INS-BA		**1.72(1.14,2.53)**	**1.71(1.12,2.52)**	**1.61(1.07,2.37)**	**1.60(1.06,2.35)**
MET+INS-BI		**1.78(1.06,3.05)**	**1.80(1.07,3.06)**	**1.93(1.17,3.11)**	**1.94(1.19,3.18)**
MET+GLP-1	MET+SGLT-2	**1.49(1.20,1.87)**	**1.48(1.19,1.86)**	**1.42(1.18,1.73)**	**1.42(1.18,1.73)**
MET+AGI		1.57(0.99,2.52)	1.56(0.99,2.48)	1.57(0.98,2.49)	1.55(0.97,2.48)
MET+TZD		0.90(0.75,1.09)	0.90(0.75,1.09)	0.90(0.75,1.09)	0.90(0.75,1.08)
MET+INS-BA		1.52(0.98,2.27)	1.51(0.97,2.27)	1.42(0.92,2.13)	1.41(0.92,2.11)
MET+INS-BI		1.58(0.92,2.73)	1.59(0.92,2.71)	**1.70(1.03,2.78)**	**1.71(1.04,2.81)**
MET+AGI	MET+GLP-1	1.06(0.65,1.74)	1.06(0.65,1.71)	1.10(0.68,1.77)	1.09(0.68,1.77)
MET+TZD		**0.60(0.48,0.77)**	**0.61(0.48,0.77)**	**0.63(0.51,0.79)**	**0.64(0.51,0.79)**
MET+INS-BA		1.02(0.64,1.57)	1.02(0.63,1.58)	1.00(0.64,1.51)	0.99(0.63,1.51)
MET+INS-BI		1.06(0.60,1.88)	1.07(0.61,1.88)	1.19(0.71,1.98)	1.20(0.72,2.03)
MET+TZD	MET+AGI	**0.57(0.36,0.92)**	**0.57(0.36,0.91)**	**0.57(0.36,0.93)**	**0.58(0.36,0.94)**
MET+INS-BA		0.97(0.51,1.73)	0.97(0.52,1.69)	0.91(0.49,1.64)	0.91(0.49,1.63)
MET+INS-BI		1.01(0.50,2.03)	1.01(0.52,2.01)	1.09(0.56,2.10)	1.11(0.57,2.20)
MET+INS-BA	MET+TZD	**1.69(1.07,2.55)**	**1.69(1.07,2.56)**	**1.58(1.01,2.39)**	**1.57(1.00,2.36)**
MET+INS-BI		**1.76(1.02,3.03)**	**1.77(1.02,3.06)**	**1.89(1.12,3.12)**	**1.90(1.13,3.14)**
MET+INS-BI	MET+INS-BA	1.05(0.60,1.84)	1.05(0.61,1.85)	1.20(0.75,1.90)	1.22(0.78,1.91)
Random-effect model	Residual deviance	156.5 vs 129 data points	157.4 vs 131 data points	191.9 vs 159 data points	192.1 vs. 161 data points
	Deviance information criteria	930.324	934.84	1148.38	1152.78

10. Severe hypoglycemia

A summary of the NMA results for severe hypoglycemia are provided in Table 4G.20.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 17 treatment comparisons with similar magnitude and direction of the effect
- No model possible for zero cases excluded for 7 treatments

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 24 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 17 treatment comparisons with similar magnitude and direction of the effect
- No model possible for restricted and unrestricted duration for 7 treatments

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Credible intervals wide
- Agreed on the statistical significance for 4 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 17 treatment comparisons with similar magnitude and direction of the effect
- No model possible for zero cases excluded for 7 treatments

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.20: Severe hypoglycemia - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	**4.90(1.48,18.19)**	**5.64(2.36,13.03)**	**8.32(2.98,24.06)**	**7.70(3.37,15.91)**
MET+DPP-4		0.64(0.19,2.88)	0.91(0.41,2.27)	0.89(0.31,2.73)	1.01(0.44,2.13)
MET+SGLT-2		0.42(0.12,1.42)	0.54(0.23,1.23)	0.69(0.24,2.01)	0.74(0.32,1.59)
MET+GLP-1		0.75(0.11,4.51)	0.96(0.29,3.08)	1.83(0.59,6.95)	1.49(0.60,4.26)
MET+TZD		3.51(0.09,413.80)	1.38(0.25,10.13)	4.39(0.38,759.60)	2.49(0.58,15.17)
MET+INS-BA		2.55(0.19,82.77)	3.05(0.48,40.64)	3.43(0.29,59.06)	2.97(0.63,15.41)
MET+INS-BI			2.22(0.17,168.40)		2.77(0.25,57.32)
MET+DPP-4	MET+SUL	**0.14(0.05,0.30)**	**0.16(0.08,0.33)**	**0.11(0.05,0.20)**	**0.13(0.07,0.24)**
MET+SGLT-2		**0.08(0.05,0.16)**	**0.09(0.05,0.17)**	**0.08(0.05,0.15)**	**0.10(0.06,0.17)**
MET+GLP-1		**0.15(0.03,0.73)**	**0.17(0.05,0.50)**	**0.22(0.07,0.94)**	**0.19(0.07,0.63)**
MET+TZD		0.64(0.02,120.40)	0.25(0.04,1.94)	0.51(0.05,85.24)	0.33(0.08,2.41)
MET+INS-BA		0.50(0.05,13.53)	0.57(0.08,6.18)	0.40(0.04,5.95)	0.39(0.09,2.02)
MET+INS-BI			0.41(0.02,27.70)		0.37(0.03,7.17)
MET+SGLT-2	MET+DPP-4	0.62(0.24,1.81)	0.58(0.25,1.33)	0.76(0.34,1.86)	0.72(0.36,1.52)
MET+GLP-1		1.09(0.23,6.03)	1.05(0.33,2.97)	2.02(0.62,9.03)	1.47(0.58,4.36)
MET+TZD		4.76(0.16,763.00)	1.52(0.30,9.27)	4.84(0.51,777.90)	2.48(0.66,14.68)
MET+INS-BA		3.69(0.39,90.96)	3.43(0.54,37.01)	3.74(0.45,51.09)	2.98(0.74,16.36)
MET+INS-BI			2.65(0.19,136.30)		2.78(0.27,67.14)
MET+GLP-1	MET+SGLT-2	1.76(0.31,9.31)	1.82(0.51,5.78)	2.69(0.74,11.69)	1.98(0.69,7.20)
MET+TZD		7.92(0.22,1384.00)	2.56(0.44,23.08)	6.16(0.60,1031.00)	3.38(0.79,25.27)
MET+INS-BA		5.78(0.54,175.90)	5.86(0.82,74.19)	4.90(0.47,72.64)	3.95(0.88,20.34)
MET+INS-BI			4.19(0.28,296.60)		3.86(0.33,76.17)
MET+TZD	MET+GLP-1	4.80(0.09,773.00)	1.54(0.28,8.79)	2.33(0.19,354.30)	1.75(0.32,11.05)
MET+INS-BA		3.55(0.24,90.46)	3.25(0.45,40.29)	1.85(0.15,30.42)	2.04(0.48,10.75)
MET+INS-BI			2.38(0.19,241.20)		1.88(0.19,45.04)
MET+INS-BA	MET+TZD	0.74(0.00,94.54)	2.11(0.19,35.89)	0.76(0.00,24.26)	1.19(0.10,9.15)
MET+INS-BI			1.74(0.08,110.90)		1.10(0.06,30.33)
MET+INS-BI	MET+INS-BA		0.80(0.08,23.27)		0.94(0.10,11.97)
Random-effect model	Residual Deviance	30.42 vs 40 data points	59.31 vs 107 data points	41.61 vs 54 data points	79.45 vs. 136 data points
	Deviance information criteria	157.539	320.584	211.762	416.066

11. Non-severe hypoglycemia

A summary of the NMA results for non-severe hypoglycemia are provided in Table 4G.21.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 22 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 22 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 22 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 22 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 14 treatment comparisons with similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.21: Non-severe hypoglycemia - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	**10.13(6.31,17.14)**	**10.11(6.32,16.73)**	**9.96(6.46,16.15)**	**8.75(5.96,13.31)**
MET+MEG		**8.16(3.75,18.30)**	**8.19(3.86,18.30)**	**7.87(3.89,17.05)**	**7.81(3.44,18.55)**
MET+DPP-4		0.93(0.62,1.43)	0.93(0.63,1.39)	0.90(0.63,1.33)	0.85(0.60,1.23)
MET+SGLT-2		1.06(0.57,1.96)	1.05(0.57,1.92)	0.99(0.58,1.72)	0.87(0.55,1.40)
MET+GLP-1		0.75(0.39,1.46)	0.76(0.42,1.42)	0.79(0.44,1.52)	0.75(0.45,1.25)
MET+TZD		0.75(0.36,1.60)	0.76(0.37,1.50)	0.87(0.43,1.76)	0.66(0.37,1.23)
MET+INS-BA		**4.18(2.02,9.03)**	**4.25(2.06,8.66)**	**4.29(2.22,8.56)**	**3.37(1.76,6.41)**
MET+INS-BI		**9.19(4.09,21.10)**	**9.29(4.14,20.35)**	**8.47(4.13,18.20)**	**7.42(3.37,16.51)**
MET+MEG	MET+SUL	0.81(0.36,1.75)	0.81(0.38,1.75)	0.79(0.38,1.65)	0.89(0.38,2.10)
MET+DPP-4		**0.09(0.06,0.14)**	**0.09(0.06,0.14)**	**0.09(0.06,0.13)**	**0.10(0.07,0.13)**
MET+SGLT-2		**0.11(0.05,0.21)**	**0.10(0.05,0.21)**	**0.10(0.05,0.18)**	**0.10(0.06,0.16)**
MET+GLP-1		**0.07(0.04,0.14)**	**0.08(0.04,0.14)**	**0.08(0.04,0.15)**	**0.08(0.05,0.14)**
MET+TZD		**0.07(0.04,0.15)**	**0.08(0.04,0.14)**	**0.09(0.04,0.17)**	**0.08(0.04,0.14)**
MET+INS-BA		**0.42(0.22,0.79)**	**0.42(0.22,0.77)**	**0.43(0.24,0.77)**	**0.38(0.21,0.70)**
MET+INS-BI		0.91(0.44,1.81)	0.92(0.45,1.80)	0.85(0.44,1.59)	0.85(0.40,1.76)
MET+DPP-4	MET+MEG	**0.11(0.05,0.26)**	**0.11(0.05,0.25)**	**0.11(0.05,0.24)**	**0.11(0.05,0.26)**
MET+SGLT-2		**0.13(0.05,0.34)**	**0.13(0.05,0.32)**	**0.13(0.05,0.29)**	**0.11(0.04,0.28)**
MET+GLP-1		**0.09(0.03,0.24)**	**0.09(0.04,0.24)**	**0.10(0.04,0.25)**	**0.10(0.04,0.24)**
MET+TZD		**0.09(0.03,0.25)**	**0.09(0.03,0.24)**	**0.11(0.04,0.28)**	**0.09(0.03,0.23)**
MET+INS-BA		0.52(0.19,1.37)	0.51(0.20,1.32)	0.54(0.22,1.36)	0.43(0.15,1.16)
MET+INS-BI		1.13(0.39,3.15)	1.13(0.40,3.08)	1.07(0.41,2.76)	0.95(0.31,2.85)
MET+SGLT-2	MET+DPP-4	1.15(0.60,2.10)	1.14(0.61,2.06)	1.10(0.62,1.88)	1.03(0.63,1.66)
MET+GLP-1		0.81(0.44,1.46)	0.82(0.45,1.45)	0.88(0.50,1.57)	0.88(0.55,1.42)
MET+TZD		0.80(0.40,1.63)	0.82(0.41,1.57)	0.96(0.48,1.89)	0.78(0.42,1.46)
MET+INS-BA		**4.53(2.34,8.63)**	**4.57(2.38,8.48)**	**4.76(2.62,8.65)**	**3.98(2.14,7.18)**
MET+INS-BI		**9.90(4.64,20.54)**	**9.97(4.65,20.26)**	**9.42(4.81,18.25)**	**8.80(4.05,18.58)**
MET+GLP-1	MET+SGLT-2	0.71(0.31,1.63)	0.72(0.32,1.65)	0.81(0.38,1.73)	0.86(0.46,1.60)
MET+TZD		0.70(0.29,1.77)	0.72(0.31,1.69)	0.88(0.38,2.06)	0.77(0.37,1.58)
MET+INS-BA		**3.94(1.69,9.75)**	**4.01(1.72,9.75)**	**4.33(2.04,9.85)**	**3.86(1.85,7.92)**
MET+INS-BI		**8.66(3.40,22.67)**	**8.76(3.49,22.60)**	**8.54(3.82,20.41)**	**8.52(3.62,20.02)**
MET+TZD	MET+GLP-1	0.99(0.42,2.39)	1.00(0.44,2.24)	1.09(0.46,2.54)	0.89(0.43,1.84)
MET+INS-BA		**5.59(2.36,13.26)**	**5.54(2.43,12.57)**	**5.41(2.42,12.11)**	**4.51(2.40,8.36)**
MET+INS-BI		**12.21(4.77,30.47)**	**12.10(4.86,28.91)**	**10.65(4.64,24.62)**	**9.98(4.47,21.89)**
MET+INS-BA	MET+TZD	**5.65(2.26,13.68)**	**5.54(2.33,13.46)**	**5.00(2.07,11.89)**	**5.06(2.23,11.35)**
MET+INS-BI		**12.35(4.61,31.32)**	**12.09(4.71,30.90)**	**9.83(3.85,24.85)**	**11.18(4.37,28.23)**
MET+INS-BI	MET+INS-BA	**2.19(1.23,3.77)**	**2.19(1.26,3.75)**	**1.98(1.24,3.14)**	**2.21(1.20,4.13)**
Random-effect model	Residual deviance	105 vs 105.8 data points	111.6 vs 117 data points	122 vs 132 data points	136.4 vs. 151 data points
	Deviance information criteria	508.279	538.066	591.672	728.193

12. Serious adverse events

A summary of the NMA results for serious adverse events are provided in Table 4G.22.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 2 treatment comparisons with similar magnitude and direction of the effect

- Agreed on the non-statistical significance for 34 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 1 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 34 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 1 treatment comparison (0 significant for restricted model and 1 significant for base case model), but all had similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 2 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 34 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Agreed on the statistical significance for 1 treatment comparisons with similar magnitude and direction of the effect
- Agreed on the non-statistical significance for 34 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 1 treatment comparison (1 significant for excluded model and 0 significant for included model), but all had similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.22: Serious adverse events - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included

		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	0.92(0.66,1.28)	0.91(0.67,1.21)	0.89(0.71,1.10)	0.88(0.71,1.10)
MET+DPP-4		0.91(0.70,1.20)	0.90(0.69,1.17)	0.86(0.70,1.06)	0.86(0.69,1.06)
MET+SGLT-2		1.10(0.76,1.60)	1.08(0.77,1.51)	1.01(0.80,1.28)	1.00(0.79,1.27)
MET+GLP-1		0.94(0.63,1.45)	0.91(0.58,1.45)	0.99(0.74,1.38)	1.02(0.74,1.42)
MET+AGI		0.33(0.04,1.81)	0.32(0.04,1.71)	0.29(0.03,1.44)	0.32(0.03,1.83)
MET+TZD		1.20(0.86,1.72)	1.17(0.85,1.65)	1.10(0.85,1.44)	1.08(0.85,1.43)
MET+INS-BA		1.96(0.76,5.43)	1.89(0.72,6.12)	1.42(0.60,3.49)	1.42(0.64,3.19)
MET+INS-BI		2.11(0.40,9.73)	2.08(0.40,10.97)	1.44(0.32,7.44)	1.47(0.39,7.41)
MET+DPP-4	MET+SUL	0.99(0.81,1.24)	0.99(0.82,1.23)	0.97(0.85,1.13)	0.97(0.85,1.12)
MET+SGLT-2		1.19(0.86,1.66)	1.19(0.87,1.63)	1.14(0.95,1.37)	1.13(0.95,1.36)
MET+GLP-1		1.02(0.67,1.59)	1.01(0.64,1.61)	1.12(0.81,1.60)	1.15(0.82,1.64)
MET+AGI		0.36(0.04,1.95)	0.35(0.05,1.93)	0.33(0.03,1.63)	0.36(0.03,2.04)
MET+TZD		**1.29(1.01,1.79)**	**1.28(1.01,1.74)**	**1.23(1.00,1.58)**	**1.22(1.00,1.57)**
MET+INS-BA		2.13(0.83,5.91)	2.10(0.79,6.68)	1.60(0.69,3.88)	1.60(0.74,3.60)
MET+INS-BI		2.28(0.45,10.74)	2.31(0.44,12.18)	1.63(0.36,8.67)	1.66(0.44,7.97)
MET+SGLT-2	MET+DPP-4	1.21(0.85,1.70)	1.20(0.88,1.64)	1.17(0.95,1.44)	1.17(0.95,1.43)
MET+GLP-1		1.03(0.71,1.55)	1.02(0.66,1.58)	1.16(0.84,1.61)	1.19(0.86,1.66)
MET+AGI		0.36(0.04,1.97)	0.36(0.05,1.89)	0.34(0.03,1.66)	0.38(0.03,2.05)
MET+TZD		**1.31(1.01,1.77)**	1.30(0.99,1.74)	**1.27(1.02,1.61)**	**1.26(1.03,1.61)**
MET+INS-BA		2.15(0.86,5.85)	2.09(0.82,6.63)	1.64(0.72,3.94)	1.65(0.77,3.64)
MET+INS-BI		2.30(0.46,10.85)	2.34(0.45,12.19)	1.67(0.37,8.88)	1.71(0.46,8.28)
MET+GLP-1	MET+SGLT-2	0.86(0.53,1.39)	0.85(0.52,1.38)	0.99(0.69,1.42)	1.01(0.71,1.46)
MET+AGI		0.30(0.03,1.69)	0.30(0.04,1.59)	0.29(0.03,1.42)	0.32(0.03,1.81)
MET+TZD		1.09(0.75,1.68)	1.08(0.74,1.62)	1.09(0.84,1.46)	1.08(0.84,1.44)
MET+INS-BA		1.79(0.67,5.13)	1.75(0.66,5.76)	1.40(0.60,3.44)	1.41(0.65,3.20)
MET+INS-BI		1.91(0.36,9.28)	1.92(0.36,10.24)	1.43(0.31,7.58)	1.47(0.39,7.08)
MET+AGI	MET+GLP-1	0.35(0.04,1.99)	0.35(0.05,1.96)	0.29(0.03,1.49)	0.32(0.03,1.81)
MET+TZD		1.27(0.79,2.01)	1.28(0.79,2.09)	1.10(0.76,1.58)	1.07(0.74,1.56)
MET+INS-BA		2.08(0.75,6.04)	2.09(0.73,6.83)	1.43(0.59,3.51)	1.39(0.62,3.23)
MET+INS-BI		2.19(0.42,11.06)	2.29(0.41,12.45)	1.45(0.32,7.66)	1.44(0.39,7.25)
MET+TZD	MET+AGI	3.62(0.63,34.48)	3.70(0.69,27.01)	3.76(0.77,38.24)	3.37(0.59,40.45)
MET+INS-BA		6.09(0.93,61.74)	6.00(0.93,63.42)	4.98(0.84,53.88)	4.44(0.71,58.74)
MET+INS-BI		6.62(0.68,78.54)	6.56(0.73,105.50)	5.38(0.56,60.58)	4.75(0.55,60.84)
MET+INS-BA	MET+TZD	1.64(0.62,4.54)	1.61(0.60,5.23)	1.29(0.54,3.16)	1.31(0.58,3.02)
MET+INS-BI		1.75(0.34,8.48)	1.77(0.35,9.51)	1.31(0.29,7.04)	1.35(0.35,6.70)
MET+INS-BI	MET+INS-BA	1.05(0.29,3.59)	1.08(0.32,3.72)	1.02(0.30,4.08)	1.05(0.34,3.81)
Random-effect model	Residual Deviance	124.7 vs. 134 datapoints	134 vs. 150 data points	157.8 vs. 165 data points	169.4 vs 186 data points
	Deviance Information Criteria	684.37	708.15	867.793	919.422

13. Renal adverse events

A summary of the NMA results for renal adverse events are provided in Table 4G.23.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 14 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 1 treatment comparison (1 significant for excluded model and 0 significant for base case model), but all had similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for 15 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 14 treatment comparisons with similar magnitude and direction of the effect
- Disagreed on statistical significance for 1 treatment comparison (1 significant for unrestricted model and 0 significant for restricted model), but all had similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 15 treatment comparisons with similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.23: Renal adverse events - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	**Reference**	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% CrI)	OR (95% CrI)	OR (95% CrI)	OR (95% CrI)
MET+SUL	MET	1.51(0.07,41.33)	1.50(0.33,9.06)	1.10(0.45,2.76)	1.16(0.52,2.64)

MET+DPP-4		3.63(0.39,76.47)	1.87(0.63,8.31)	1.33(0.51,3.84)	1.27(0.56,2.93)
MET+SGLT-2		0.34(0.11,1.90)	1.07(0.41,2.81)	0.92(0.44,2.04)	0.97(0.49,1.99)
MET+GLP-1		1.47(0.27,13.08)	1.83(0.45,8.93)	1.66(0.54,5.50)	1.70(0.61,5.20)
MET+TDZ		0.84(0.04,27.94)	0.81(0.18,4.91)	0.54(0.17,1.66)	0.63(0.23,1.79)
MET+DPP-4	MET+SUL	2.42(0.32,25.83)	1.24(0.33,5.22)	1.22(0.63,2.40)	1.09(0.57,2.06)
MET+SGLT-2		0.23(0.01,7.24)	0.68(0.11,4.31)	0.84(0.45,1.58)	0.83(0.45,1.55)
MET+GLP-1		1.01(0.04,21.39)	1.22(0.19,7.99)	1.53(0.45,5.95)	1.48(0.40,5.26)
MET+TDZ		0.54(0.17,2.85)	0.54(0.28,1.27)	**0.48(0.25,0.99)**	0.54(0.29,1.10)
MET+SGLT-2	MET+DPP-4	0.09(0.00,1.43)	0.55(0.13,2.12)	0.69(0.30,1.59)	0.77(0.34,1.67)
MET+GLP-1		0.42(0.02,4.25)	1.00(0.20,4.52)	1.25(0.33,5.50)	1.34(0.41,4.70)
MET+TDZ		0.23(0.02,2.31)	0.44(0.10,1.74)	0.39(0.16,0.99)	0.49(0.21,1.23)
MET+GLP-1	MET+SGLT-2	4.21(0.53,32.00)	1.71(0.42,8.74)	1.80(0.55,6.45)	1.75(0.55,6.03)
MET+TDZ		2.45(0.09,72.19)	0.79(0.13,5.16)	0.58(0.23,1.49)	0.64(0.27,1.66)
MET+TDZ	MET+GLP-1	0.55(0.03,15.52)	0.45(0.07,3.01)	0.32(0.07,1.30)	0.37(0.09,1.54)
Random-effect model	Residual deviance	21.94 vs 22 data points	24.64 vs 37 data points	33.31 vs 38 data points	39.24 vs.54 data points
	Deviance information criteria	97.7	128.792	168.134	205.869

14. Pancreatitis

A summary of the NMA results for pancreatitis are provided in Table 4G.24.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 21 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for 15 treatment comparisons with similar magnitude and direction of the effect
- No model possible for restricted duration for 6 treatments

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 6 treatment comparisons with similar magnitude and direction of the effect
- No model possible for restricted duration for 15 treatments

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 6 treatment comparisons with similar magnitude and direction of the effect
- No model possible for zero cases excluded for 9 treatments

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.24: Pancreatitis - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	0.41(0.01,5.84)	1.02(0.09,10.09)	0.31(0.01,5.80)	0.80(0.16,5.82)
MET+DPP-4		0.24(0.00,48.40)	0.70(0.17,3.06)	0.35(0.01,4.01)	0.75(0.23,4.08)
MET+SGLT-2		2.55(0.20,89.60)	0.50(0.05,5.19)	0.92(0.02,19.71)	0.83(0.10,5.71)
MET+GLP-1			1.09(0.25,6.39)	3.23(0.43,39.16)	1.20(0.37,4.56)
MET+TZD			1.44(0.15,10.15)	0.30(0.00,29.65)	1.35(0.21,8.62)
MET+INS-BA				1.05(0.00,144.40)	0.49(0.00,43.24)
MET+DPP-4	MET+SUL	0.58(0.00,180.20)	0.69(0.09,5.95)	1.00(0.18,5.73)	0.92(0.28,3.07)
MET+SGLT-2		5.89(0.39,479.90)	0.52(0.04,6.40)	2.60(0.21,63.63)	1.02(0.17,5.02)
MET+GLP-1			1.11(0.13,9.19)	10.91(0.63,374.40)	1.50(0.30,6.46)
MET+TZD			1.34(0.16,11.01)	0.95(0.02,33.81)	1.59(0.30,11.48)
MET+INS-BA				3.42(0.00,994.30)	0.59(0.00,41.40)
MET+SGLT-2	MET+DPP-4	9.96(0.28,7461.00)	0.75(0.09,4.93)	2.74(0.15,72.51)	1.06(0.18,6.37)
MET+GLP-1			1.60(0.41,6.24)	10.47(0.80,372.20)	1.57(0.45,5.01)
MET+TZD			2.06(0.32,11.49)	0.99(0.02,46.91)	1.70(0.36,10.64)
MET+INS-BA				3.33(0.00,1012.00)	0.63(0.00,43.31)
MET+GLP-1	MET+SGLT-2		2.05(0.31,22.85)	3.86(0.27,105.50)	1.41(0.26,11.48)
MET+TZD			2.68(0.24,44.53)	0.37(0.00,34.49)	1.54(0.19,17.85)
MET+INS-BA				1.07(0.00,267.30)	0.55(0.00,68.50)
MET+TZD	MET+GLP-1		1.26(0.19,8.37)	0.09(0.00,10.35)	1.08(0.19,7.32)
MET+INS-BA				0.32(0.00,19.09)	0.40(0.00,20.29)
MET+INS-BA	MET+TZD			2.84(0.00,3045.00)	0.36(0.00,23.32)
Random-effect model	Residual deviance	5.89 vs 8 data points	20.45 vs 43 data points	14.79 vs 20 data points	29.57 vs. 60 data points
	Deviance information criteria	30.149	120.969	73.851	172.469

15. Fractures

A summary of the NMA results for fractures are provided in Table 4G.25.

Compared to the base case, the reduced model with zero cases excluded (Column 5 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction of the effect

Compared to the base case, the reduced model with restricted duration (Column 4 vs 6):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for 10 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with zero cases excluded for restricted duration vs unrestricted: duration (Column 3 vs 5):

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction of the effect

Compared to the reduced model with restricted duration for zero cases included vs excluded (Column 3 vs 4)

- DIC indicated a somewhat better fit
- Agreed on the non-statistical significance for all 10 treatment comparisons with similar magnitude and direction of the effect

The conclusion was that the sensitivity analysis confirmed that the base case was acceptable.

Table 4G.25: Fractures - network meta-analysis results for studies of duration 3 to 12 months and overall with zeros out versus in: odds ratios and 95% credible intervals

Treatment	Reference	Duration 3 to12 months		Duration all	
		Zero cases excluded	Zero cases included	Zero cases excluded	Overall – base case Zero cases included
		OR (95% Crl)	OR (95% Crl)	OR (95% Crl)	OR (95% Crl)
MET+SUL	MET	0.64(0.06,7.56)	0.54(0.11,3.40)	1.03(0.22,8.50)	0.76(0.25,3.12)
MET+DPP-4		1.16(0.21,9.16)	1.00(0.28,3.97)	1.48(0.37,10.54)	1.07(0.36,4.21)
MET+SGLT-2		1.35(0.11,17.36)	0.89(0.14,6.04)	1.02(0.19,8.85)	0.77(0.24,3.58)
MET+TZD		1.20(0.09,16.71)	1.02(0.19,6.67)	1.94(0.34,17.70)	1.38(0.39,6.32)
MET+DPP-4	MET+SUL	1.90(0.44,9.01)	1.85(0.52,7.04)	1.44(0.72,3.02)	1.42(0.71,2.88)
MET+SGLT-2		2.03(0.35,12.66)	1.65(0.31,8.24)	0.99(0.52,1.89)	1.02(0.56,1.93)

MET+TZD		1.91(0.73,4.93)	1.87(0.82,4.47)	1.87(0.86,4.31)	1.85(0.85,3.88)
MET+SGLT-2	MET+DPP-4	1.06(0.22,5.60)	0.90(0.18,3.97)	0.69(0.26,1.73)	0.72(0.30,1.79)
MET+TZD		1.02(0.17,5.71)	1.02(0.24,4.32)	1.32(0.46,3.91)	1.29(0.48,3.47)
MET+TZD	MET+SGLT-2	0.93(0.12,7.42)	1.14(0.20,6.95)	1.91(0.68,5.33)	1.81(0.67,4.51)
Random-effect model	Residual deviance	14.52 vs 18 data points	18.2 vs 29 data points	19.38 vs 25 data points	24.85 vs.38 data points
	Deviance information criteria	72.912	99.71	107.701	141.273

Appendix 5A: International patient decision aid standards instrument

IPDASi v3 Dimensions and Items [22]

Dimension	Item
Information	1.The decision support technology describes the health condition or problem (intervention, procedure or investigation) for which the index decision is required
Providing information about options in sufficient detail for making a specific decision	2.The decision support technology describes the decision that needs to be considered (the index decision)
	3.The decision support technology describes the options available for the index decision
	4. The decision support technology describes the natural course of the health condition or problem, if no action is taken.
	5.The decision support technology describes the positive features (benefits or advantages) of each option
	6. The decision aid describes negative features (harms, side effects or disadvantages) of each option.
	7. The decision support technology makes it possible to compare the positive and negative features of the available options.
	8. The decision support technology shows the negative and positive features of options with equal detail (for example using similar fonts, order, and display of statistical information).
Probabilities	1. The decision support technology provides information about outcome probabilities associated with the options (i.e. the likely consequences of decisions)
Presenting outcome probabilities	2. The decision support technology specifies the defined group (reference class) of patients for which the outcome probabilities apply.
	3. The decision support technology specifies the event rates for the outcome probabilities (in natural frequencies).
	4. The decision support technology specifies the time period over which the outcome probabilities apply.
	5. The decision support technology allows the user to compare outcome probabilities across options using the same denominator and time period.
	6. The decision support technology provides information about the levels of uncertainty around event or outcome probabilities (e.g. by giving a range or by using phrases such as “our best estimate is…”)
	7. The decision support technology provides more than one way of viewing the probabilities (e.g. words, numbers, and diagrams).
	8. The decision support technology provides balanced information about event or outcome probabilities to limit framing biases.
Values	1. The decision support technology describes the features of options to help patients imagine what it is like to experience the physical effects.
Clarifying and expressing values	2. The decision support technology describes the features of options to help patients imagine what it is like to experience the psychological effects.
	3. The decision support technology describes the features of options to help patients imagine what it is like to experience the social effects.
	4. The decision support technology asks patients to think about which positive and negative features of the options matter most to them.
Decision Guidance	1. The decision support technology provides a step-by-step way to make a decision.
Structured guidance in deliberation and communication	2. The decision support technology includes tools like worksheets or lists of questions to use when discussing options with a practitioner.
Development	1. The development process included finding out what clients or patients need to prepare them to discuss a specific decision

Dimension	Item
Using a systematic development process	2. The development process included finding out what health professionals need to prepare them to discuss a specific decision with patients
	3. The development process included expert review by clients/patients not involved in producing the decision support technology
	4. The development process included expert review by health professionals not involved in producing the decision aid.
	5. The decision support technology was field tested with patients who were facing the decision.
	6. The decision support technology was field tested with practitioners who counsel patients who face the decision.
Evidence	1. The decision support technology (or associated documentation) provides citations to the studies selected.
Using evidence	2. The decision support technology (or associated documentation) describes how research evidence was selected or synthesized.
	3. The decision support technology (or associated documentation) provides a production or publication date.
	4. The decision support technology (or associated documentation) provides information about the proposed update policy.
	5. The decision support technology (or associated documentation) describes the quality of the research evidence used.
Disclosure	1. The decision support technology (or associated technical documentation) provides information about the funding used for development.
Disclosure and transparency	2. The decision support technology includes author/developer credentials or qualifications.
Plain Language	1. The decision support technology (or associated documentation) reports readability levels (using one or more of the available scales).
Using plain language	
DST Evaluation	1. There is evidence that the decision support technology improves the match between the features that matter most to the informed patient and the option that is chosen
	2. There is evidence that the patient decision support technology helps patients improve their knowledge about options' features
Test (for DSTs that are directed at investigations or screening tests)	1. The decision support technology describes what the test is designed to measure.
	2. The decision support technology includes information about the chances of having a true positive test result.
	3. The decision support technology includes information about the chances of having a true negative test result.
	4. The decision support technology includes information about the chances of having a false positive test result.
	5. The decision support technology includes information about the chances of having a false negative test result.
	6. If the test detects the condition or problem, the decision support technology describes the next steps typically taken.
	7. The decision support technology describes the next steps if the condition or problem is not detected.
	8. The decision support technology describes the chances that the disease is detected with and without the use of the test.
	9. The decision support technology has information about the consequences of detecting the condition or disease that would never have caused problems if screening had not been done (lead time bias).

Appendix 5B: Probability determined in lieu of network meta-analysis

If a network meta-analysis (NMA) could not be conducted for a particular antihyperglycemic agent and outcome, since evidence from randomized controlled trials was not available, the probability considered in the patient decision aid (PDA) prototype were based on information from observational studies and, failing this, expert opinion (in gray). These situations are highlighted in Box 5.B.1.

Box 5.B.1: Probability of efficacy and safety outcomes*

Compared to metformin for metformin plus	HbA1c change >0.3%	Hypoglycemia occurrence	Body weight change >2.3kg	Urinary tract infections and genital infections occurrence	Blood pressure Change** >5 mmHg
Sulfonylureas	↓ 100%	↑ 10.5%	↑ 11.97%	↓ -0.30%	↔ 0%
Meglitinides	↓ 95.02%	↑ 9.35%	↔ 0%	↓-0.30% (1)	↔ 0% (1)
DPP-4 inhibitors	↓ 100%	↔ -0.23%	↔ 0%	↔ 0.13%	↔ 0.10%
Thiazolidinedione	↓ 100%	↔ -0.52%	↑ 86.08%	↓ -1.27%	↓ 3.80%
GLP-1 agonists	↓ 100%	↔ -0.38%	↓1.61%	↔ -0.21%	↓ 9.90%
SGLT-2 inhibitors	↓ 100%	↔ -0.20%	↓ 4.21%	↑ 1.76%	↓ 13.80%
Alpha-glucosidase inhibitors	↓ 91.24%	↔ (2)	↓ (2)	↔ (3)	↓ 48.50%
Basal insulin	↓ 100%	↑ 3.47%	↑ 73.18%	↓-1.00%	↓ 6.20%
Biphasic insulin	↓ 99.8%	↑ 8.86%	↑ 69.58%	↓-1.00% (4)	↓ 6.20% (4)

* ↑ arrow indicates an increase probability; ↓ arrow indicates a decrease probability; and ↔ arrow indicates little or no change in the probability of the efficacy or safety when patients are on an antihyperglycemic medication plus metformin compared to metformin alone

** In the table 4.10 NMA (Chapter 4), three antihyperglycemic classes of sulfonylureas, alpha-glucosidase inhibitors, and insulin were not statistically significant differences in comparison with metformin alone. We only consider those statistically significant classes in the table in the PDA.

The probability determined in lieu of the NMA were determined as follows with the number corresponding to the highlighted cells of the box.

(1) No data available. Meglitinides and sulfonylureas are similar function in lowering glycose level, and consensus of the research team was results would be similar.

(2) Wang JS, Huang CN, Hung YJ, et al. Acarbose/Metformin Fixed-Dose Combination Study Investigators Acarbose plus metformin fixed-dose combination outperforms acarbose monotherapy for type 2 diabetes. Diabetes Res Clin Pract. 2013;102(1):16–24. [PubMed] [Google Scholar]. Results suggested that no hypoglycemia events occurred either in the control arm or in the treatment arm. Combination therapy significantly reduced bodyweight in comparison with monotherapy (1.7 kg vs 1.0 kg, $p<0.01$).

(3) Wu QL, Liu YP, Lu JM, et al. Efficacy and safety of acarbose chewable tablet in patients with type 2 diabetes: a multicentre, randomized, double-blinded, double-dummy positive controlled trial. J Evid Based Med. 2012;5(3):134–138. [PubMed] [Google Scholar]. Results suggested that there were no differences of urine analysis results between the control arm and the treatment arm.

(4) No data available. Consensus of the research team was the result would be similar to basal insulin.

Appendix 5C: Patient decision aid prototype

WHAT IS THE BEST TREATMENT AFTER METFORMIN ALONE FAILS TO ACHIEVE GOOD GLUCOSE CONTROL?

A decision aid to discuss treatment options with your doctor

The decision aid is for you if:

- You are an adult with type 2 diabetes and have been taking metformin alone plus lifestyle modification to control diabetes
- You need to add a medication to metformin because your blood glucose level (blood sugar level) or HbA1c (average blood sugar level over a period of weeks/months) is still high

How can this decision aid help you?

If metformin alone cannot control your blood glucose or sugar at a targeted level (HbA1c), then various medications can be considered to add on to metformin. However, each add on medication has pros and cons. This decision aid provides information on these treatment options in a way that you can understand them, and describes these pros and cons in an objective manner. It also asks you to consider your personal values and preferences when making a decision on treatment.

This decision aid, as a tool, helps you understand more about the treatment options. It is not to replace your doctor's advice.

There are 4 steps in this decision aid that may help you in making these two decisions about your diabetes. Before considering these 4 steps, some background information about your diabetes may be useful.

What is type 2 diabetes?

Type 2 diabetes occurs when there is higher sugar or glucose than normal in your blood. Commonly, blood glucose levels are monitored by measuring the haemoglobin A1c (HbA1c) level. HbA1c levels reflect an average blood glucose level over the past 2 to 3 months.

Taking simple steps in your lifestyle can delay the occurrence of type 2 diabetes and reduce the risk of complications associated with diabetes, such as walking at least 30 minutes per day.

In addition to lifestyle modifications such as exercise and diet, most patients with type 2 diabetes require medications to help control blood glucose over time.

Today, no medications can cure your type 2 diabetes.

What is the risk of high blood glucose to your body?

In the short-term, high glucose in your body can cause symptoms such as increased thirst and frequency of urination, and sometimes unexpected weight loss and fatigue. You can feel uncomfortable and sick.

In the long-term, it can damage multiple organs in your body and result in severe diseases such as problems with eyes (blindness), kidneys (kidney failure with need for dialysis), heart (heart attack) and brain (stroke). These problems can lead you to have a low quality of life.

Blood glucose levels naturally tend to get higher over time when you have type 2 diabetes, and you will need to add more medications to your current treatment, which is likely metformin, to control your blood glucose levels over time (that is, your HbA1c).

What is the risk of lowering your high blood glucose?

The more medications you take, the more likely you will get side effects that are related to the medication, and this may lead to medical costs for treating these side effects.

Currently, there are many medications available that can be added to metformin and each medication added to metformin has pros and cons. We cannot tell you with certainty which one of these medications added on will be best for you. Remember, a medication that works for one person, may not work in the same way for another person. A medication may have a side effect for one person, but may not have the same side effect in another person.

What does research tell us in setting a target level for your blood glucose level or HbA1c?

There is a clear relationship between your level of HbA1c and diabetes associated with damage to your small blood vessels known as microvascular complications. This includes damage to eyes (leading to blindness), to kidneys (leading to renal failure), to nerves (leading to erectile dysfunction in men) and diabetic foot disorders and severe infections (leading to amputation). For example, HbA1c greater than 7% (or 53mmol/mol) is more likely to increase the risk of such complications.

However, there is not a clear relationship between your level of HbA1c and diabetes associated with damage to your large blood vessels known as macrovascular complications. This includes cardiovascular diseases such as heart attacks, and strokes. A HbA1c cut-off value (or a target level) to reduce the risk of such complications depends on your health conditions and your treatment experience as described in the guidelines below, and you will need to discuss this with your doctor.

The 2019 diabetes guidelines in China recommend the following HbA1c levels for patients with type 2 diabetes.

- HbA1c target level <7% (53mmol/mol) is for most patients with type 2 diabetes, which is equal to an average blood sugar level of 8.3 mmol/L (or 150 mg/dl).
- HbA1c target level < 6.5% (48mmol/mol) is for patients with a short duration of type 2 diabetes, long life expectancy, no complications, no significant cardiovascular diseases, without significant hypoglycemia or other adverse effects of treatment.
- HbA1c target level < 8.0% is for patients with a history of severe hypoglycemia, limited life expectancy, advance microvascular or macrovascular complications, extensive comorbid conditions, long-standing diabetes in whom the goal is difficult to achieve despite comprehensive treatment including diabetes self-management education, appropriate glucose monitoring, and effective dose of multiple glucose-lowering agents (including insulin).

What is your health condition?

The following information about you and your health is important and will help prepare you in discussions with your doctor.

- Age
- Height (centimeter)
- Weight (kg)
- Complications
  - Hypertension
  - Dyslipidemia
  - Cardiovascular disease
  - Chronic kidney disease
  - Foot ulcers and amputation risk
  - Neuropathy
  - Retinopathy
  - Sexual dysfunction (e.g., erectile dysfunction in men)
- Years of diabetes
- Experience of hypoglycemia
- Living by yourself

Note. Body Mass Index (BMI) = weight/height^2 (kg/m^2). BMI≥ 24 kg/m^2 is considered overweight, and BMI≥28 kg/m^2 is considered obese in the Chinese population

For more information on your *type 2* diabetes, please click on the links below

- Link to diabetes website in China
- Link to diabetes Chinese website in WHO
- Link to diabetes Chinese website in IDF

Working through the 4 steps of this aid may help you in making two decisions about your diabetes

This patient decision aid helps you to think about two decisions about your diabetes: one is identifying an appropriate HbA1c level; the other is choosing an adjunct medication for you to combine with metformin.

Step 1 Which reason matters most to you in making a decision?

Think about the items in the following table and if they are important to you. You are asked to specify how important each item is to you by checking the box on the scale from 0 (not important) to 5 (very important). For instance, if you strongly wish to avoid weight gain, then you may select a 4 or 5 for the item '*to avoid weight gain*'. If you do not mind taking a medication several times during the day, you may select a 0 or 1, under the item of *'to avoid taking medications many times during the day*'. If you strongly wish to avoid diabetic complications in the long term such as damage to your eyes or kidneys, you may select a 4 or 5, under the item of having long-term benefits.

How important to you is it …	**Scale from 0 (not important) to 5 (very important)**					
	0 (Not important)	1	2	3	4	5 (Very important)
to have a quick reduction in your blood sugar level						
to take a pill and not a shot						
to avoid taking medications many times during the day						

to have the medication covered by medical insurance						
to avoid weight gain						
to avoid Hypoglycemia						
to avoid medication related side effects on liver or kidney						
to control blood sugar for long-term benefits, such as eyes (avoid blindness) and kidneys (avoid kidney failure with need for dialysis).						

Step 2: What medications are available to you as a patient with type 2 diabetes in China?

If your metformin alone cannot meet a targeted glucose level, there are 8 types of medications available in China that you can considered as an addition to be combined with metformin. The key aspects of these 8 types of medications are briefly described in this table.

Types of Medications	Times per day	Cost	Covered by medical insurance	Shot or pill	Frequent blood checks (e.g., testing finger blood)
Metformin	2-3	$	✓		No
Sulfonylureas	1-2	$	✓		Yes
Meglitinides	3	$$	✓		Yes
DPP-4 inhibitors	1	$$$	?		No
Thiazolidinedioznes	1-2	$$	✓		Yes
GLP-1 receptor agonists	1-2	$$$$	?		No
SGLT-2 inhibitors	1	$$$	?		No
Alpha-glucosidase inhibitors	3	$$	✓		No
Basal insulin	2 or more	From $ to $$$$	✓		Yes
Biphasic insulin	2 or more	From $ to $$$$	✓		Yes

✓ Medications are covered by medical insurance.

? Consult your practitioners whether these medications are actually covered by medical insurance or need co-payments in your jurisdiction.

What does research tell you about the benefits and harms of the different types of medications that can be combined with metformin?

The table below lists some benefits and harms of the different types of medications that can be combined with metformin. These benefits and harms are based on a review of the research carried out on these 8 types of medications. You must understand that not everyone taking the same medication will have the same degree of glucose-lowering, and not everyone taking the same medication will experience the same harms.

In the table below, the likelihood of the outcome (named at the top of the column) when the medciation is changed from metformin alone to metformin plus an antihyperglycemic agent (named at the start of the row). The ↑ arrow indicates an increase, the ↓ indicates a decrease and the ↔ indicates no or little change.

The ↑ arrow indicates an increase likelihood of the outcome (named at the top of the column) when the medciation is changed from metformin alone to metformin plus an antihyperglycemic agent (named at the start of the row). The more arrows (e.g., ↑↑) the greater the increase in the likelihood.

The ↓ arrow indicates a decrease likelihood of the outcome (named at the top of the column) when the medciation is changed from metformin alone to metformin plus an antihyperglycemic agent (named at the start of the row). The more arrows (e.g., ↓↓) the greater the decrease in the likelihood.

The ↔ arrow indicates little or no change in the likelihood of the outcome (named at the top of the column) when the medciation is changed from metformin alone to metformin plus an antihyperglycemic agent (named at the start of the row).

Compared to metformin for metformin plus	HbA1c change >0.3%	Hypoglycemia occurrence	Body weight change >2.3kg	Urinary tract infections and genital infections occurrence	Blood pressure Change >5 mmHg
Sulfonylureas	↓↓	↑↑	↑	↓	↔
Meglitinides	↓	↑↑	↔	↓	↔
DPP-4 inhibitors	↓↓	↔	↔	↔	↔
Thiazolidinedione	↓↓	↔	↑↑	↓	↓
GLP-1 agonists	↓↓	↔	↓	↔	↓↓
SGLT-2 inhibitors	↓↓	↔	↓	↑↑	↓↓
Alpha-glucosidase inhibitors	↓	↔	↓	↔	↔
Basal insulin	↓↓	↑	↑↑	↓	↔
Biphasic insulin	↓↓	↑↑	↑↑	↓	↔

Step 3 What else do you need to prepare for decision making?

Find out how well this decision aid helped you learn the key facts

- Do you know enough on the benefits and harms of lowering high blood glucose level?
  - ✓ Yes
  - ✓ No
- Do you know enough on the benefits and harms of each treatment option?
  - ✓ Yes
  - ✓ No
- Are you clear about which benefits and harms matter most to you in setting a target HbA1c level
  - ✓ Yes
  - ✓ No
- Do you have enough support and advice from this patient decision aid to make a choice?
  - ✓ Yes
  - ✓ No

Step 4 What are your next steps?

This patient decision aid helps you to think about two decisions about your diabetes: one is understanding an appropriate HbA1c level setting; the other is choosing an adjunct medication for you to combine with metformin.

Once the two decisions are made, you are encouraged to see your doctors at least every 2-3 months to monitor your HbA1c level and adjust your medications as needed.

Note. Format based on the Ottawa Personal Decision Guide @ 2000, A O'Connor, D Stacey, University of Ottawa, Canada. For more information updated 2020, please visit: https://decisionaid,ohri.ca

Appendix 5D: Acceptability and usability rating questionnaire

A patient decision aid for individuals with type 2 diabetes failure in metformin monotherapy and considering add-on medications in China

Hello,

First of all, thank you so much to agreeing to do this interview.

We are doing this interview just to see if our patient decision aid (or PDA) for individuals with type 2 diabetes is easy to use and could be helpful. This is our first draft PDA and many things will be modified in the future. We would now like to get your feedback on it.

In the first part, we would like to ask you go through the PDA and explain everything you think as you read through it. In the second part, we would like to ask questions on the format and content of the PDA, as well as questions on whether this PDA is helpful for you to make a decision. Also, questions on what information is missing or how to make the PDA better from your view.

All feedback is good feedback. Feel free to make suggestions of things to improve as you go along. This will help us to improve the PDA.

Part 1: Pre-interview

1. Just before we begin, could you tell us the treatments you know of that treat type 2 diabetes?

2. Do you feel sure that you use the best treatment for your diabetes? (Yes/No)

Part 2: going through the patient decision aid (PDA)

Comments:

Part 3: other questions

Now, we would like to ask you a few general questions on the PDA.

Part I: Content and format of the PDA

1. How would you rate the amount of information in the PDA in general? Please check (√) one.

- □ Too much information
- □ Too little information
- □ Just right

2. How would you rate the amount of information given for each treatment? Please check (√) one.

- □ Too much information
- □ Too little information
- □ Just right

3. Do you think we included enough information to help you decide on choosing a medication for diabetes? Please check (√) one.

- □ Yes
- □ No

4. How do you find the length of the PDA? Please check (√) one.

- □ Too long
- □ Too short
- □ Just right

5. How clear is the information in the PDA? Please check (√) one.

- □ Everything is clear

- □ Most things are clear
- □ Some things are unclear (go to question 5a)
- □ Most things are unclear (go to question 5a)

5a. If anything was unclear, what did you find to be unclear?

_____

_____

_____

6. Would you use the PDA in the future to learn how to choose an antidiabetic medication?

- □ I would definitely use it
- □ I would probably use it
- □ I would probably not use it
- □ I would definitely not use it

6a. Why would you use it/ why wouldn't you use it?

_____

_____

_____

These next set of questions will ask about whether the PDA was helpful preparing you to make a decision or would be helpful in future decisions.

Part II: Preparation for Decision making

7. Do you think the PDA would help you recognize that a decision needs to be made to manage your diabetes? Please check (√) one.

- □ Not at all
- □ A little
- □ Somewhat
- □ Quite a bit
- □ A great deal

8. Do you think the PDA would help you learn about new treatment options?

- □ Not at all
- □ A little
- □ Somewhat
- □ Quite a bit
- □ A great deal

9. Do you think the PDA would help you think about the pros and cons of each option?

- □ Not at all
- □ A little
- □ Somewhat
- □ Quite a bit
- □ A great deal

10. Do you think the PDA would help you know that the decision depends on what matters most to you? Please check (√) one.

- □ Not at all
- □ A little
- □ Somewhat
- □ Quite a bit
- □ A great deal

11. Do you think the PDA would help you think about how involved you want to be in the decision? Please check (√) one.

- □ Yes, more involved
- □ Yes, less involved
- □ No, the same

12. Do you think the PDA would prepare you to talk to your doctor about what matters most to you? Please check (√) one.

- □ Not at all
- □ A little
- □ Somewhat
- □ Quite a bit
- □ A great deal

Thanks for answering these questions. We now have a few more questions to ask you to make sure that we haven't missed anything that might help us in making sure that the PDA meets the needs of people

with diabetes. Now we would like to ask you a couple of open questions. Your comments are completely confidential.

1. What do you like about the PDA?

_____
_____
_____
_____
_____
_____
_____
_____

2. What, if any, changes would you make to the PDA?

_____
_____
_____
_____
_____
_____
_____
_____

3. How did you find the discussion after using the PDA? Would you like to discuss the PDA with your doctor? Would you like to use the PDA more in the future?

_____
_____
_____
_____
_____
_____
_____
_____

System Usability Scale

	Strongly Disagree				Strongly Agree
1. I think that I would like to use this PDA frequently					
2. I thought the PDA was easy to use					
3. I would imagine that most people with diabetes would learn to use this PDA very quickly					

This completes the study.

Thank you very much for your participation in this important project.

Your involvement is sincerely appreciated

Note. The Acceptability and Usability Rating Form was modified with permission from Dr. Karine Toupin April's JIA study.