

Improving Medication Adherence Post-ST-Elevation Myocardial Infarction

Running Title: DERLA-STEMI

Jon-David Schwalm¹

Thesis Supervisor

Dr. Jeremy Grimshaw²

Thesis Committee

Dr. Monica Taljaard²

Dr. Madhu Natarajan³

¹University of Ottawa and McMaster University/Hamilton Health Sciences/Population Health Research Institute

²Clinical Epidemiology Program, Ottawa Hospital Research Institute and University of Ottawa, Ottawa, Ontario

³McMaster University/Hamilton Health Sciences/Population Health Research Institute, Hamilton, Ontario

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**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

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Synopsis:

ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute myocardial infarction, constituting approximately 30% of all cases. Based on the highest level of evidence for improvement in both morbidity and mortality in these patients, clinical guidelines from around the world support the prolonged use of secondary preventative medications (e.g., acetylsalicylic acid, second antiplatelet [clopidogrel, prasugrel, and ticagrelor], statin, beta-blocker, and angiotensin blocker). While in-hospital and discharge prescription rates for these essential life-saving medications is excellent, adherence is known to decline within weeks of hospital discharge. This decline in evidence-based medication use was confirmed in a population of patients with coronary artery disease in Ontario (Chapter 3). Furthermore, it was demonstrated that this decline was consistent across all medication classes and subgroups of patients. We developed a protocol (Chapter 4) for a cluster-randomized controlled trial evaluating the impact of repeated reminders sent by mail to the family physician and the patient, starting one month after the STEMI. The fifth chapter highlights the results of the cluster-randomized controlled trial, which demonstrates suboptimal persistence to all 4 of 4 cardiac medication classes at 12-months. There was no significant difference compared to usual care in the use of guideline-recommended medications post-STEMI when participants (and their family physicians) receive repeated postal reminders.

Acknowledgements:

I would like to express my sincere gratitude to my primary supervisor, Dr. Jeremy Grimshaw, for his mentorship, support, and scientific guidance throughout this thesis project. I would also like to thank my co-supervisor, Dr. Monica Taljaard, for sharing her statistical expertise to guide analyses of this thesis. I would like to thank Dr. Madhu Natarajan, for his continued mentorship and support in both my clinical and research careers. I would like to acknowledge Dr. Noah Ivers, a friend and colleague, who has been a partner in this project since conception. I would also like to acknowledge Kori Kingsbury at the Cardiac Care Network (CCN) of Ontario and Dr. Jack Tu at the Institute for Clinical and Evaluative Sciences (ICES) for their support and collaboration on our baseline population study published in the Canadian Journal of Cardiology. Finally, I would like to acknowledge the support and contributions of the interventional cardiologists at Hamilton Health Sciences, Sarah Knox, Renu Pal, and the staff of the Interventional Cardiology Research Group at Hamilton Health Sciences for their commitment of time and expertise to the completion of the thesis.

Author Contributions:

The very idea of this research program and the questions addressed in this thesis arose following initial discussions between me and Dr. Noah Ivers at the Knowledge Translation (KT) Canada Summer Institute in 2010. Following this initial meeting, we have developed a productive collaboration. We share interests in KT research and both have Dr. Jeremy Grimshaw as a research supervisor.

Manuscript One (Chapter 3):

Dr J-D Schwalm and Dr Ivers are the principal authors of the published manuscript and Dr. Natarajan (thesis committee) is the senior author on this paper. Dr Schwalm was the nominated-PI for this project and secured a research grant from the Cardiac Care Network (CCN) of Ontario (held in J-D Schwalm's name at Hamilton Health Sciences). Helen Guo, Jack Tu and Cynthia Jackevicius work at ICES and contributed to the analysis and drafting of the manuscript.

Manuscript Two (Chapter 4):

Dr. Schwalm and Dr. Ivers are the co-principal authors of this design paper. Dr. Schwalm had secured all required funding for this study from the Hamilton Health Sciences New Investigator Fund (NIF-11274), was coordinating operations at Hamilton Health Sciences and was first author on the final manuscript. The final drafting of this protocol was a joint venture between Dr. Ivers and Dr. Schwalm, as well as the other co-authors identified, but the bulk of the paper was derived from the funding proposal and research ethics board submissions in which Dr. Schwalm was the first author and principal investigator. All other authors provided input into the design and final drafts of the published protocol.

Manuscript Three (Chapter 5):

J-D Schwalm was the nominated PI for this RCT. Dr. Schwalm has secured all required funding for this study from the Hamilton Health Sciences New Investigator Fund (NIF-11274), coordinated all

operations at Hamilton Health Sciences, was involved in all stages of the data collection, cleaning and analysis and was first author on the final manuscript. Research Ethics Board approval was obtained by Dr. Schwalm through Hamilton Health Sciences/McMaster University (REB 11-191). Dr. Schwalm was identified as the principal investigator and he was the first author on any related presentations (Appendix 1-1 and 1-2). Dr. Ivers was the co-PI. Purnima RaoMelacini coordinated the data and analysis locally at PHRI and Dr. Monica aljaard helped develop and supervised the statistical analysis. Dr. Natarajan provided local supervision and the infrastructure of the SMART AMI program in which the DERLA STEMI trial could be conducted. Dr. Grimshaw supervised all stages of the study, from start to completion and provided invaluable input and support into the design, analysis, and discussion relating to this final manuscript. All other authors provided input into the design and final drafts of the final manuscript.

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Glossary:

1. ACC.....	American College of Cardiology
2. ACEI.....	ACE Inhibitors
3. AMI.....	Acute Myocardial Infarction
4. ARB.....	Angiotensin Receptor Blockers
5. BB.....	Beta Blockers
6. CABG.....	Coronary artery bypass graft
7. CAD.....	Coronary artery disease
8. CCN.....	Cardiac Care Network of Ontario
9. CCS.....	Canadian Cardiovascular Society
10. cRCT.....	Cluster Randomized Controlled Trial
11. CV.....	Cardiovascular
12. CVD.....	Cardiovascular Disease
13. DES.....	Drug Eluting Stent
14. FP.....	Family Physician
15. GEE.....	Generalized Estimating Equations
16. ICC.....	Intra-cluster Correlation Coefficient
17. ICES.....	Institute for Clinical Evaluative Sciences
18. KT.....	Knowledge Translation
19. KTA.....	Knowledge to Action
20. LHIN.....	Local Integrated health Network
21. LV.....	Left ventricular
22. LVEF.....	Left ventricular Ejection Fraction
23. MI.....	Myocardial Infarction
24. MMAS.....	Morisky Medication Adherence Score
25. MPR.....	Medication Possession Ratio
26. NNT.....	Numbers needed to treat
27. PCI.....	Percutaneous coronary intervention
28. PDC.....	Proportion of Days Covered
29. PI.....	Principal Investigator
30. RCT.....	Randomized Controlled Trial
31. REB.....	Research Ethics Board
32. STEMI.....	ST-Elevation Myocardial Infarction

Chapter 1: Thesis Introduction and Overview

Jon-David Schwalm¹

¹University of Ottawa and McMaster University/Hamilton Health Sciences/Population Health Research
Institute

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

Problem:

ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute myocardial infarction (AMI), constituting approximately 30% of all cases [1, 2]. Based on the highest level of evidence for improvement in both morbidity and mortality in these patients, clinical guidelines from around the world support the prolonged use of secondary preventative medications (e.g. acetylsalicylic acid, second antiplatelet [clopidogrel, prasugrel, or ticagrelor], statin, beta-blocker, and angiotensin blocker) [3, 4]. While in-hospital and discharge prescription rates for these essential life-saving medications is excellent, adherence is known to decline within weeks of hospital discharge, and this decreased adherence to guideline recommended medications is associated with increased mortality [5-9].

Purpose and Rationale:

There is an important need for research to better understand the determinants of medication non-adherence and to evaluate interventions to address this. We undertook a study to determine the decay in medication adherence in patients with coronary artery disease (CAD) and to identify potential opportunities to improve long-term medication use. A Cochrane review demonstrated that patient reminders were the best way to improve adherence to statin therapy, and recommended testing delayed reminders as opposed to immediate reminders that are given to the patients just after discharge or post-event [10]. Given medication adherence decreases with time, delayed and repeated reminders are likely to achieve a greater effect size. Therefore, the overarching purpose of this thesis was to improve the morbidity and mortality of STEMI patients through the use of repeated and delayed reminders that promote the long-term use of guideline-recommended medications.

Objectives:

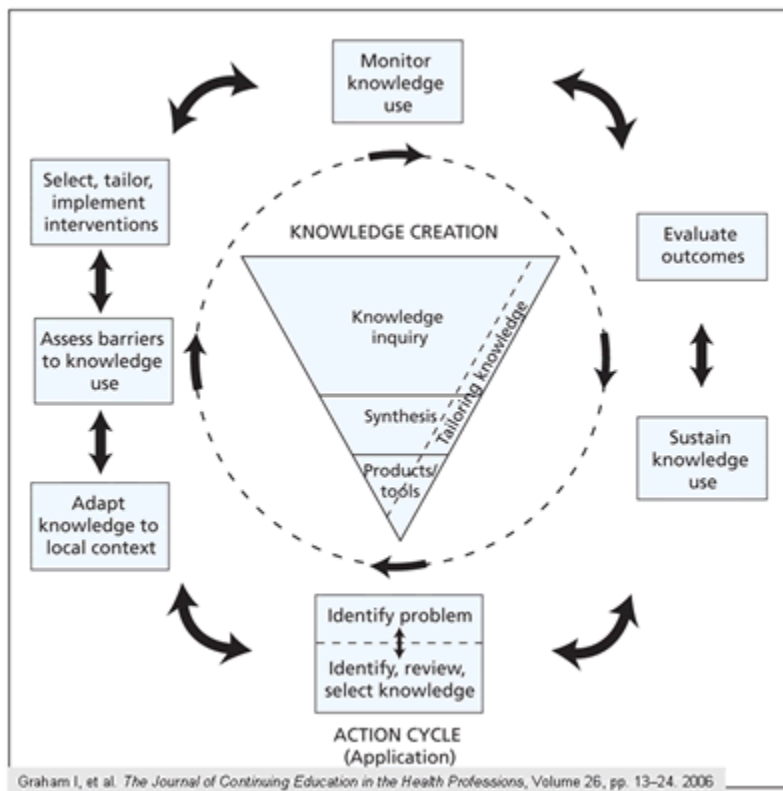
There are two specific objectives of this study which will be explored in three, separate, but related manuscripts in Chapters 3, 4, and 5.

1. The first objective of this thesis was to identify the current Ontario trends in adherence to cardiac medications and factors associated with adherence to cardiac secondary prevention medications in patients in whom CAD was evident during angiography (Chapter 3).
2. The second objective of this thesis was to assess if repeated mailing of educational reminders to the family physician (FP) and the patient will decrease the proportion of patients who discontinue evidence-based secondary prevention medications at 12 months post-STEMI. This objective will be explored in Chapter 4 and Chapter 5.

Overview of Submitted Thesis and Manuscripts:

The Knowledge to Action (KTA) framework, as described by Graham et al. [11] (Figure 1), is a conceptual framework that outlines the movement of knowledge into action, while integrating knowledge creation and application. We adopted this practical process for KT research to guide the development of my thesis. Outlined below are the steps in the KTA process, coupled with the relevant chapters, highlighting the stages of research in this thesis.

Figure 1-1: Knowledge to action process [11]



As outlined in the KTA cycle, the Knowledge Creation funnel (Figure 1) and crux of KT research requires a solid foundation of evidence. “Chapter 2-Knowledge Creation-The Evidence”, provides the background information required by the reader, to better understand the burden of CAD and STEMI. This chapter summarizes the evidence supporting long-term medication use for secondary prevention in CAD.

Chapter 3-“Problem identification, knowledge contextualization and barrier assessment”, begins with a review of evidence-practice gaps in secondary prevention for CAD and reviews the barriers to evidence-based medication use for secondary prevention identified in the literature. This chapter also includes a paragraph summarizing the published paper, “Length of Initial Prescription at Hospital Discharge and Long-term Medication Adherence for Elderly Patients with Coronary Artery Disease: A Population-Level Study” [12]. References will be made to supporting appendices. The manuscript in this chapter highlights the evidence-practice gap that currently exists in Ontario with respect to the long-

term persistence of evidence-based cardiac medication use in patients with identified CAD and suggests some barriers to optimal care.

Chapter 4-“Select, tailor, and implement intervention”, reviews mechanisms to promote long-term medication adherence. This chapter integrates the evidence, identified problem, and established mechanisms to promote medication adherence, and adapts the KTA framework to the local context in one health region in Ontario. These stages of the KTA process provide the foundation for the published study protocol entitled, “Delayed educational reminders for long-term medication adherence in ST-elevation myocardial infarction (DERLA-STEMI): Protocol for a pragmatic, cluster-randomized controlled trial” [13], that is included in Chapter 4. Additional appendices are included.

Chapter 5-“Evaluate Outcomes”, includes a paragraph summarizing the DERLA STEMI cRCT and results. The trial manuscript being submitted for publication is included.

Chapter 6-“Discussion and Sustain Knowledge Use”, summarizes the thesis, reviews novel concepts presented herein, limitations and provides an overall direction and next steps in this program of research.

Chapter 2: “Knowledge Creation-The Evidence”

Jon-David Schwalm¹

¹University of Ottawa and McMaster University/Hamilton Health Sciences/Population Health Research
Institute

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

Introduction:

As described in Chapter 1, the KTA framework for KT research is built on the assumption that a solid foundation of evidence exists before knowledge is moved into action (Knowledge Creation funnel- Figure 1). Without such evidence, the implementation of diagnostic or therapeutic strategies could lead to systematic inefficiencies or even harm [14]. This chapter highlights the burden of CAD and the evidence supporting the use of long-term secondary prevention medications.

Epidemiology: The burden of cardiac disease

Despite important advances in the management of cardiovascular (CV) risk factors, CAD is responsible for about one-third of the mortality in individuals over age 35 [15-17]. Almost half of all middle-aged men and a third of middle-aged women in high-income countries develop clinical manifestations of underlying obstructive CAD, such as an acute coronary syndrome (ACS) in their lifetime [18]. Half of ACS and 70% of CV deaths occur in patients with a history of CAD [19]. Fortunately, CV morbidity and mortality has decreased in the last decade thanks in part to evidence-based medications [16, 20]. Post-ACS guidelines strongly recommend the indefinite use of anti-platelets, beta-blockers, angiotensin blockers, and statins for *all* patients [21-23]. Adherence to guideline-recommended medications reduces mortality by a remarkable 65%-75% [20, 24]. However, sub-optimal adherence to cardiac medications is associated with increased mortality and higher health costs [6, 8, 9, 25-27].

Evidence supporting long-term medication use for secondary prevention in CAD

In conjunction with lifestyle modifications, unless contraindicated, The American College of Cardiology (ACC) and Canadian Cardiovascular Society (CCS) both support the initiation and

maintenance of pharmacotherapy including anti-platelets, cholesterol lowering therapies and blood pressure lowering therapies post-STEMI with Class I support (conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective) and Grade A or B evidence (data derived from multiple randomized clinical trials or meta-analyses and data derived from a single randomized trial, or nonrandomized studies, respectively) (Table 1) [3, 23, 28].

Table 2-1: Guideline Recommended Secondary Prevention Medication [3, 23, 28]

Medication	Duration	Recommendation (Evidence)	Comment:
Acetylsalicylic Acid (ASA)	Indefinitely	Class 1 (Level A)	All ACS patients ¹
2 nd Antiplatelet (clopidogrel/ticagrelor)	12 months	Class 1 (Level A)	All ACS patients ¹
Statin	Indefinitely	Class 1 (level A)	All ACS patients ²
Angiotensin Blocker (ACEI/ARB)	Indefinitely	Class 1 (Level A)	Hypertension, Diabetes, and/or Left Ventricular Ejection Fraction $\leq 40\%$ ³
		Class 2A (Level B)	All other ACS patients ³
Beta-Blocker (BB)	Min 3 years	Class 1 (Level A)	ACS Patients with Left Ventricular Ejection Fraction $<40\%$ ³
	Min 3 Years	Class 1 (Level B)	All ACS patients ³
	> 3 years	Class 2A (Level B)	All ACS patients ³

Summary:

Unlike, many other conditions in medicine, in which the evidence for or against a particular treatment, can be considered a grey zone, it is clear that the majority of CAD patients benefit from the use of secondary prevention medications.

Chapter 3: “Problem identification, knowledge contextualization and barrier assessment”

This chapter incorporates the manuscript, “*Canadian Journal of Cardiology* 2013; 1-7”.

Noah M. Ivers^{1,2}, J.-D. Schwalm^{3,4}, Cynthia A. Jackevicius, PharmD⁵⁻⁹, Helen Guo⁹, Jack V. Tu^{9,10}, Madhu Natarajan^{3,4,11}

¹Family Practice Health Centre, Women’s College Hospital, Toronto, Ontario, Canada

²Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

³Heart Investigation Unit, Hamilton General Hospital, Hamilton, Ontario, Canada

⁴Population Health Research Unit, McMaster University, Hamilton, Ontario, Canada

⁵College of Pharmacy, Western University of Health Sciences, Pomona, California, USA

⁶Department of Pharmacy, Veterans Affairs Greater Los Angeles Health Care System, Los Angeles, California, USA

⁷Department of Pharmacy, University Health Network, Toronto, Ontario, Canada

⁸Institute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

⁹Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada

¹⁰Sunnybrook Schulich Heart Centre, University of Toronto, Toronto, Ontario, Canada

¹¹Cardiac Care Network of Ontario, Toronto, Ontario, Canada

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

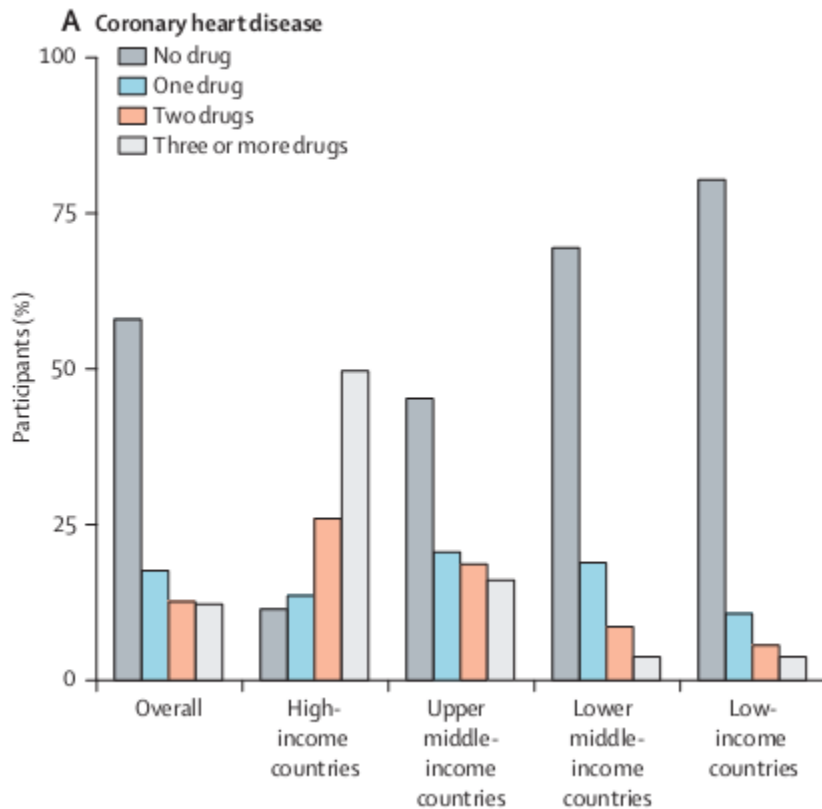
Introduction:

A strong foundation of evidence that supports guideline recommendations is the required first component of the Knowledge to Action framework, as described by Graham et al (Figure 1) [11]. As outlined in Chapter 2, there exist national and international guidelines that support the use of long-term secondary prevention medications in patients with established CAD. Prior to intervening with a knowledge translation (KT) intervention, an evidence-practice gap must first be identified. Following identification of this gap, in order to plan an intervention to improve adherence to secondary prevention medications in CAD, it is necessary to learn more about the factors that predict poor adherence in patients with known CAD. This chapter highlights the existing evidence-practice gaps for the secondary prevention of CAD and barriers to care, both in the literature and in a contemporary, population-based study of over 18000 CAD patients in Ontario (Manuscript included in this chapter).

Evidence-practice gaps in secondary prevention for CAD:

There remains a large gap between ideal and actual provision of care with respect to the use of proven secondary prevention treatments post-ACS. Persistence to medications post-ACS begins falling by thirty days and drops as low as 50% six months post-discharge [5, 7, 29-31]. In the PURE study, the use of secondary prevention medication in patients with established CAD is abysmal, with rates as low as 5% in low-income countries versus 50% for the use of 3 cardiac medications (ASA, statin and anti-hypertensive agent) in high-income countries (Figure 2) [32].

Figure 3-1: Number of individual cardiac medications taken by CAD patients [32]



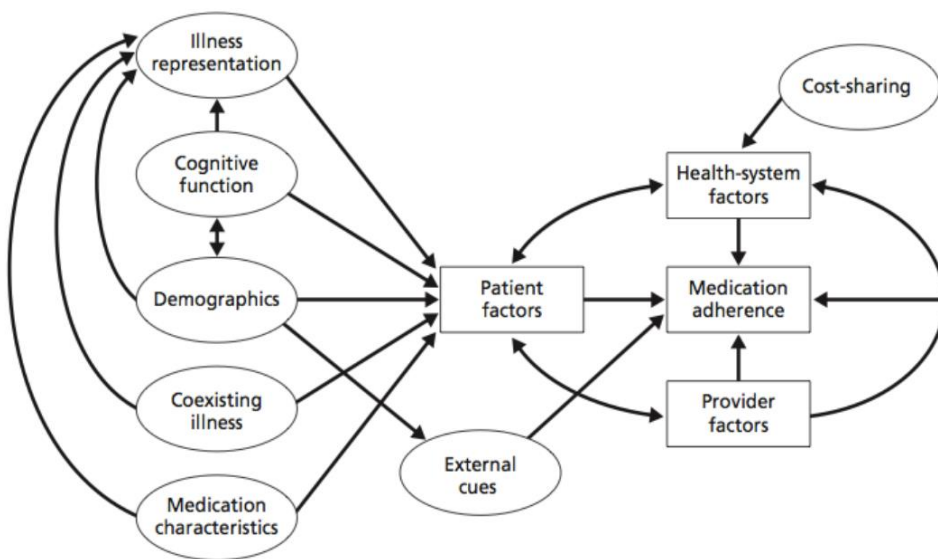
Barriers to adherence to secondary prevention:

Reasons for non-adherence may be categorized as system-level (e.g. access to care, coordination of care, etc.), patient-level (e.g. beliefs, finances, etc.), and provider-level (e.g. motivation, time, knowledge, etc.) as illustrated in Figure 3 [33, 34]. At the system level, poor adherence may be frequently due to fragmented systems of care or communication problems between secondary and primary care [35, 36]. Transitions of care increase risk for inadvertent discontinuation of cardiac medications [37]. At the provider-level, having a cardiologist involved in the care post-MI may increase rates of appropriate medication adherence in the elderly. In one study of community cardiologists, it was determined that inaccurate estimation of future risk was a common reason for not prescribing secondary prevention medications [38, 39]. In addition, physician communication skills are predictive of adherence, yet adherence is infrequently discussed [40, 41]. At the patient level,

socioeconomic factors and side-effects are known to play a role in medication adherence post-AMI, however, side effects are infrequently the primary reason for discontinuation (Table 2) [39, 42, 43].

Patient factors that may be readily modifiable, including beliefs about their illness and treatment, play a key role. Post-MI, those stopping statins tend to feel well (low perceived susceptibility) and believe their cholesterol is controlled (low perceived benefit) [44]. In those who are intentionally non-adherent, concerns about treatment may outweigh perceived necessity [45]. To address unintentional non-adherence, it has been suggested that interventions should include prompts to aid memory and coping plans, so that recommended treatments can be fit into normal routines and foreseeable challenges managed [46].

Figure 3-2: Conceptual Framework of Factors influencing adherence [34]



From: Gellad, Walid F., Jerry Grenard and Elizabeth A. McGlynn. *A Review of Barriers to Medication Adherence: A Framework for Driving Policy Options*. Santa Monica, CA: RAND Corporation, 2009. http://www.rand.org/pubs/technical_reports/TR765.

Table 3-1: Side-effects of Guideline-recommended Secondary Prevention Medications

Medication or Class	Side-Effects leading to Discontinuation (%) in RCTs	Absolute Contraindications
Statins [47-50]	No Difference compared to placebo	Hypersensitivity to med or active liver disease,
Aspirin [50]	Major or minor bleeding < 3%	Hypersensitivity to med or active pathological bleeding
Clopidogrel [50]	Major or minor bleeding < 5%	Hypersensitivity to med or active pathological bleeding
ACEI/ARB [50]	Increased cough (10%) and renal dysfunction (less than 3%)	Hypersensitivity to med (prior angioedema)
Beta-Blocker [50]	Dyspnea and bronchospasm < 3%	Hypersensitivity to med

The DERLA Baseline Study:

While there is evidence in the literature, as highlighted above, that demonstrates: (1) the existing evidence –practice gaps in secondary prevention of CAD and (2) identified factors associated with poor adherence, understanding the knowledge of local gaps and contextual barriers are important when considering KT interventions as outlined in the KTA framework [11]. Therefore, using administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) and the Cardiac Care Network of Ontario (CCN), we conducted a population-based project in approximately 18000 patients in Ontario, over the age of 65 years old. This study was designed to help inform the design of an intervention to promote secondary prevention medication use as outlined in Chapter 4 and 5.

The specific objectives of the DERLA baseline study were to: (1) identify current evidence-practice gaps by assessing adherence rates and time to discontinuation of cardiac medications (clopidogrel, ACEI/ARB, BB, statin) for 18 months following an angiography that confirmed the presence of CAD (ASA use could not be captured in the administrative databases); and (2) assess predictors of medication adherence.

This study had four significant findings. First, in a contemporary Ontario population, non-adherence is a significant issue in cardiac patients, even when medication costs is not an issue (all patients were > 65 years old and thus covered by Ontario Drug Benefits).

Second, non-adherence was found to be a problem across all subgroups, thus supporting the need for global interventions in all secondary prevention patients (Appendix 3-1). These findings were not described in detail in the attached manuscript. However, the DERLA baseline study was also designed to help identify vulnerable subgroups of patients that could be targeted by interventions to promote ongoing adherence to cardiac secondary prevention medications. For instance, if it were identified that low income populations were much more non-adherent than higher income populations, then the intervention would be tailored to this subgroup of patients. However, as outlined in Appendix 3-1, no clinically significant differences in the numerous subgroups were identified among the demographics captured in the administrative databases. For example, patients in the highest income quintile were more adherent to ACEI/ARBs at 18 months follow-up (73.6% versus 68.9%, $p=0.0002$). However, there was no statistically significant difference in beta blocker use between the lowest and highest income quintiles (66.9% versus 64%, respectively, $p=0.1547$). Targeting a subgroup with a 4.7% absolute difference in rates of adherence of one indicated medication but not another, was not felt to be efficient, as both subgroups had suboptimal adherence overall and would thus both benefit from an intervention to improve medication use. This was the case for the other identified subgroups in this study. Therefore an intervention that targeted the entire population of patients with identified CAD was considered to be most appropriate.

Third, vulnerable periods of time appear to be consistent with prescription refills (30, 60, 90, and 120 days post index angiogram) (Figure 2 in manuscript 1). This finding helped inform the timing of the intervention delivery as outlined in Chapter 4 and 5.

Finally, we learned that the duration of the initial prescription was the biggest predictor of long-term adherence to guideline recommended therapies. Unfortunately, this aspect could not be incorporated into the DERLA STEMI trial but the duration of initial prescription will be discussed further in the final chapter as it relates to next steps in this program of research.

Limitations of the DERLA Baseline Study:

The DERLA Baseline study has 5 limitations. First, the study is limited to patients > 65 years and older. This limits the generalizability of the findings, as we cannot assume the same results apply to patients less than 65 years old. Furthermore, this study population had their medications fully covered by the Ontario Drug Benefits plan, thus medication costs are likely another barrier in patients < 65 years old. Second, the database did not capture medications that are purchased over the counter (i.e. ASA). Third, while the measure of proportion of days covered is valid, it is a surrogate of true medication adherence. Fourth, the subgroup analyses were limited by the variables captured in the administrative databases housed at ICES and CCN. Finally, this was an observational study and the findings related to the length of prescription need to be confirmed in a randomized controlled trial.

Manuscript One:**Length of initial prescription at hospital discharge and long-term medication adherence for elderly patients with coronary artery disease: a population-level study.**

Noah M Ivers MD^{1,2}, J-D Schwalm MD^{3,4}, Cynthia A. Jackevicius PharmD, MSc^{5,6,7,8,9}, Helen Guo MSc⁹, Jack V. Tu MD, PhD^{9,10}, Madhu Natarajan MD, MSc^{3,4,11}

Affiliations

1. Family Practice Health Centre, Women's College Hospital
2. Department of Family and Community Medicine, University of Toronto
3. Heart Investigation Unit, Hamilton General Hospital
4. Population Health Research Unit, McMaster University
5. College of Pharmacy, Western University of Health Sciences
6. Department of Pharmacy, Veterans Affairs Greater Los Angeles Health Care System
7. Department of Pharmacy, University Health Network
8. Institute of Health Policy Management and Evaluation, University of Toronto
9. Institute for Clinical Evaluative Sciences
10. Sunnybrook Schulich Heart Centre, University of Toronto
11. Cardiac Care Network of Ontario

Word count: 2527

Short title: Length of prescription and long-term adherence

Brief summary

Cardiac medication non-adherence has been shown to be associated with mortality. This was a population-level, retrospective cohort study examining the role of a modifiable factor, length of initial prescription for cardiac medications post-angiography, on long-term medication adherence. We found that length of initial prescriptions for cardiac secondary prevention medications upon hospital discharge seem to represent a modifiable factor for long-term adherence in patients with coronary artery disease, possibly by reducing the patient's refill burden.

ABSTRACT

Background

Adherence to cardiac secondary prevention medications declines over time. We examined whether the length of the initial prescription post-hospital discharge after coronary angiography would be associated with long-term adherence.

Methods

We conducted a population-level cohort study to examine adherence to cardiac medications for 18 months following a coronary angiography in elderly patients with coronary artery disease. We identified patients with clinical indications for angiotensin converting enzyme-inhibitors or angiotensin receptor blockers (ACE-I/ARB), beta-blockers (BB), and/or statins. In each medication class cohort, we defined high adherence as proportion of days covered > 80%. The length of the initial prescription was defined as 0 to 30 days, 31 to 60 days, and greater than 60 days. We controlled for patient socio-demographic factors, previous adherence, and comorbidities.

Results

The ACE-I/ARB cohort included 13,305 patients, the BB cohort included 5,792 patients, and the statin cohort included 16,134 patients. Using less than 30 days as the reference, initial prescriptions covering at least 60 days were more likely to result in high long-term adherence for ACE-I/ARB (adjusted odds ratio (aOR) = 4.1, 95% confidence interval (CI) 3.6, 4.7), BB (aOR = 2.4, 95% CI 1.9, 3.1), and for statins (aOR = 3.0, 95% CI 2.6, 3.4). Over 80% of patients had outpatient follow up with a primary care provider within 30 days and this did not vary based on length of initial prescription.

Conclusion

Longer prescriptions for cardiac secondary prevention medications upon hospital discharge seem to increase the likelihood of high long-term adherence in elderly patients.

Background

Patients with documented coronary artery disease (CAD) have an increased risk of subsequent cardiovascular events, including myocardial infarction, heart failure, and death [19]. Guidelines stress that the initiation and long-term maintenance of evidence-based secondary prevention medications such as antiplatelets, angiotensin converting enzyme-inhibitor or angiotensin receptor blockers (ACE-I/ARB), beta-blockers (BB), and statins are essential for reducing cardiovascular outcomes [3, 23].

Unfortunately, adherence to cardiac secondary prevention medications declines over time and this decreased adherence is associated with increased mortality [31, 5-9].

The purpose of this study was to identify factors associated with adherence to cardiac secondary prevention medications in patients who had CAD evident during angiography. In particular, we assessed whether the length of the initial prescription post-angiography was associated with long-term adherence, based on our clinical observation that many patients were offered brief prescriptions to encourage early outpatient follow-up.

Methods

We conducted a retrospective cohort study to examine adherence to cardiac secondary prevention medication 18 months after coronary angiography. The Research Ethics Board at Sunnybrook Health Sciences Centre approved this study.

Databases

We used population-based administrative records linked through a unique identifier at the Institute for Clinical Evaluative Sciences (ICES). Data were compiled from the following databases: (a) the Ontario Drug Benefits (ODB) database, covering all medications prescribed to persons in Ontario over 65 years of age [51, 52]; (b) the Canadian Institute for Health Information Discharge Abstract Database covering hospital discharge diagnoses [53] using International Classification of Disease (ICD) codes, permitting the calculation of the Charlson comorbidity score [54]; (c) the Ontario Health Insurance Plan (OHIP)

database, covering physician billings for procedures and consultations [55]; (d) the Registered Persons Database covering demographic information including date of death; and (e) the Cardiac Care Network of Ontario (CCN) cardiac registry, with clinical variables collected at the time of angiography. The CCN cardiac registry has recently been used as a reference standard to validate other databases [56].

Patient Cohorts

We examined patients with CAD identified during coronary angiography occurring between October 1, 2008 and September 30, 2009. The included cohort had at least 70% blockage in at least one vessel or at least 50% blockage in the left main. Medication data in the ODB is captured for all patients over 65. Therefore, restricting to patients aged 65 plus 120 days allowed us to account for prescriptions started prior to the date of the angiography.

From the entire cohort of patients with CAD, we created three medication-class cohorts to identify patients who had a clinical indication for long-term use of ACE-I/ARB, BB, and/or statin based on Class 1A evidence from recent guidelines [23]: the ACEI/ARB cohort included patients with diabetes, *or* hypertension, *or* decreased left ventricular ejection fraction (<50%); the BB cohort included patients with decreased left ventricular ejection fraction (<50%) *and* NYHA class 2-4, *or* a history of myocardial infarction prior to or as indication for the angiography; the statin cohort was not limited as guidelines recommend long-term use of statins in all patients with evidence of CAD [3]. We did not assess antiplatelets because clopidogrel is not indicated for the long-term in many patients and because ASA is usually purchased over-the-counter, without a prescription in Ontario. We limited analyses to patients who survived for 18 months post-angiography.

Outcome: Assessment of adherence

In each medication-class cohort, we assessed adherence using the proportion of days covered (PDC) technique, in which the days supplied during each interval is divided by the number of days in the interval. The PDC was calculated 540 days (i.e., 18 months) post-angiography. Patients not prescribed any medication in a class would have PDC equal to zero. When patients were dispensed a prescription

renewal prior to the end of their previous prescription period, the excess supply was carried over to the next period, but the maximum PDC for the interval was equal to one. We dichotomized patients based on their PDC into high and not-high adherence, with high-adherence defined as PDC >80% [8]

Exposure: Length of initial prescription post-angiography.

We examined the number of days supplied in the initial prescription fill for each medication class [51, 52]. Prescriptions covered by the ODB plan are dispensed for a maximum of 100 days. Therefore, we categorized the initial days supplied of the initial prescription as follows: a) <1 month (0 - 30 days); b) 1-2 months (31 - 60 days); and c) >2 months (>60 days). For those who did not have any leftover pills from a previous prescription and who did not fill a new prescription within 30 days of their angiography, the length of initial prescription was set at zero.

Covariates

We controlled for confounding factors that might influence prescription adherence, including sex, rural location, and socioeconomic status. For the latter, we used median neighborhood income quintile using postal code linkage to census data from Statistics Canada [57]. We also adjusted for comorbid disease burden [58, 59] using the number of distinct medications dispensed in the year prior to cohort entry [60, 61] as well as by Charlson Score [62]. In addition, we accounted for the severity of the presentation leading to the angiography (ST-elevation MI, non-ST-elevation MI, unstable angina, elective), findings during angiography (number of vessels affected), subsequent treatment (medical management or percutaneous coronary intervention or coronary artery bypass within 90 days), and presence of heart failure (left ventricular function and NYHA class), angina (CCS class), chronic obstructive pulmonary disease, diabetes, hypertension, dyslipidemia, peripheral vascular disease, cerebrovascular disease, plus smoking status and history of coronary bypass and/or myocardial infarction. These clinical variables are recorded in the CCN cardiac registry at the time of angiography. We also adjusted for history of mental health care given the potential association with adherence [58-60]. This was assessed using a validated algorithm for identifying patients with a relevant OHIP billing code (ICD-9 295-304, 306, 309, 311,

897-902, 904-906, 909) representing an outpatient family physician assessment for mental health [63] or any hospitalization for mental health (ICD-10 F00-F99) or any billing by a psychiatrist in the previous year. Using data from ODB, we also adjusted for past medication adherence for those who were prescribed the medication of interest in the year prior to the angiography as well as concurrent cardiovascular medications. Finally, we used OHIP to determine the number of outpatient appointments with a specialist (cardiologist or internist) or with a primary care provider (family physician or general practitioner).

Statistical Analysis

We conducted multivariable logistic regression to examine the effects of initial prescription and follow-up characteristics on adherence, adjusting for potential confounding variables. The strength of the association between exposure and adherence is expressed as an adjusted odds ratio (aOR). A separate model was conducted for each medication-class. All models included patient age and sex, as well as indication for the angiography; other covariates were included in the model if their P-values were less than 0.05, using a backward selection process. [64]

We conducted additional, *post-hoc* analyses to further examine the findings. First, we repeated the main analysis after excluding patients with an initial prescription length of less than seven days under the assumption that the physician in such cases was uncertain if the patient required or could tolerate the medication. Second, we explored timing of outpatient follow-up to see if this could explain the relationship between adherence and prescription length. Finally, we examined medication discontinuation post-angiography for each medication-class. We defined discontinuation as occurring when the prescription is inactive for at least 20% of the length of time of the previous medication. [37] To measure discontinuation, we included only patients who were initially taking the medication-class of interest by limiting to those who had leftover pills in a medication-class from a prescription prior to the angiography or those who filled a new prescription for that class within 30 days after the angiography. All analyses were conducted using SAS 9.2.

Results

The ACE-I/ARB cohort included 13,305 patients, the BB cohort included 5,792 patients, and the statin cohort included 16,134 patients (Figure 1). Demographic and clinical characteristics for each medication-class cohort are described in Table S1, along with the proportion of patients achieving high adherence over 540 days. Some patient characteristics were associated with increased long-term adherence in specific medication classes, but not across all medication classes. For instance, significantly more women had high-adherence to BB than men ($p < 0.001$) and there was a trend suggesting more women had high-adherence to ACE-I/ARB than men ($p = 0.07$), while significantly more men had high-adherence to statin than women ($p < 0.001$).

Of all initial prescriptions 19.5% for ACE-I/ARB, 11.0% for BB, and 20.6% for statins covered more than 60 days. The association between length of initial prescription post-angiography and likelihood of high adherence at 540 days is described in Table 1. Using less than 30 days as the reference, initial prescriptions > 60 days were more likely to result in high long-term adherence for ACE-I/ARB (adjusted odds ratio (aOR) = 4.1, 95% confidence interval (CI) 3.6, 4.7), BB (aOR = 2.4, 95% CI 1.9, 3.1), and statins (aOR = 3.0, 95% CI 2.6, 3.4). Age and sex were significant covariates in each model. Each 10-year increase in age was associated with a reduction in long-term adherence for ACE-I/ARB (aOR = 0.8, 95% CI 0.8, 0.9), BB (aOR = 0.9, 95% CI 0.8, 0.9) and statins (aOR = 0.89, 95% CI 0.83, 0.95). Males were less likely to have high long-term adherence to ACE-ARB (aOR = 0.88, 95% CI 0.80, 0.96) and BB (aOR = 0.78, 95% CI 0.69, 0.88), but more likely to have high long-term adherence to statins (aOR = 1.18, 95% CI 1.09, 1.29).

Of all prescriptions covering less than 31 days, 3292 (50.3%) for ACE-I/ARB, 715 (23.3%) for BB, and 3789 (42.3%) for statins were prescribed for less than 7 days. After removing these cases, patients receiving initial prescriptions longer than 60 days still had greater long-term adherence for ACE-I/ARB (aOR = 1.3, 95% CI 1.1, 1.6) and a trend toward high long-term adherence for BB (aOR = 1.0, 95% CI 0.9, 1.1).

1.2, 95% CI 0.9, 1.5) and statins (aOR = 1.2, 95% CI 1.0, 1.4). As seen in Figure 1, while medication persistence fell gradually over time, higher rates of discontinuation were apparent at 30 and 90 days. This coincides with the common length of initial prescriptions, marking the time when refills would be necessary.

The vast majority of patients had follow up in primary care within 30 days post-angiography (Table S2). The proportion with outpatient follow-up in primary care within 30 days was nearly equivalent for the different initial prescription-lengths. However, those receiving initial prescriptions for less than one month were slightly more likely to have an outpatient follow-up with a specialist within 30 days.

Discussion

This study identifies an easily modifiable factor within the control of providers and/or systems to improve adherence. The length of initial prescription was associated with long-term adherence and the strength of the association was consistent for each cardiac secondary prevention medication even after adjusting for relevant clinical factors and socio-demographic factors. We found that the majority of prescriptions at discharge cover less than one month. This may be based on a clinical assumption that short prescriptions encourage patients to attend early outpatient follow-up. While early follow up is essential to assess the patient and to address medication side effects, the vast majority did have follow-up within one month, regardless of prescription length. Therefore, shorter prescriptions may create an unnecessary inconvenience (i.e., a refill burden) for elderly patients and the subsequent risk of reduced adherence may outweigh other potential benefits.

Two previous small studies examined the association between length of prescriptions and long-term adherence to cardiac medications [65, 66]. The first included 290 patients and found that those with at least 90-day supplies of digoxin less likely to run out of tablets over 9 to 14 months. The other study included 3386 patients and found that those receiving mostly 60 day prescriptions for statins were more likely to have high adherence than those receiving mostly 30 day prescriptions (adjusted risk ratio 1.40;

95% CI 1.27–1.55). We agree with the conclusion of both studies that longer prescriptions may partially address a major reason for (unintentional) non-adherence: forgetfulness [67]. Our findings focus specifically on the length of the first prescription post-angiography rather than considering the average fill-size and build upon these studies by considering a population-level sample and by extending the findings to multiple cardiac medications.

The same databases as those used in our study have previously been used to reveal improvements between 1992 and 2005 in the proportion of cardiac patients dispensed secondary prevention medications at discharge [68]. However, we found similar proportions of patients with high long-term adherence to statins and BB as a study using the same databases between 1999 and 2003 [8], suggesting that quality improvement efforts that have successfully improved rates of prescriptions at discharge should now be directed to support long-term adherence [13].

The World Health Organization found that patient-level, provider-level, and system-level factors each may play a role in sub-optimal adherence [69]. Less than 4% of patients report side effects as the primary reason for discontinuation of cardiac medications post-STEMI [43, 70], suggesting that many cases of cardiac medication non-adherence are unintentional or attributable to system-level and provider-level factors [71]. Qualitative studies have found that poor adherence to cardiac medications is often due to sub-optimal organization of care [35, 36]. In particular, transitions between specialty and primary care represent an important risk factor for unintentional discontinuation of cardiac medications [37, 72]. Guidelines recommend outpatient follow-up post MI within 2-6 weeks [73], though a previous study has shown lower rates of evidence-based cardiac medication use at 6 months in MI patients without an outpatient assessment within 30 days [74]. We found that over 80% of patients had outpatient follow up with a primary care provider within 30 days of an angiography finding significant CAD. However, in the context of poor continuity of information between providers [75], the hand-off in responsibility for repeat prescriptions may not be transparent. It is also possible that short prescriptions

inadvertently indicate to both patients and primary care providers that long-term adherence is unnecessary.

Some methodological limitations also warrant consideration. Administrative databases evaluate prescription fills rather than swallowing of pills and cannot account for intentional discontinuation, assess medications that are not covered by the ODB plan, or evaluate those younger than 65. The design of the study cannot fully exclude clinical differences between those receiving longer and shorter prescriptions. However, the consistency in findings across medication classes reduces the likelihood that the results are biased by unobserved patient-level factors.

In summary, long-term adherence to cardiac secondary prevention medications remains suboptimal and forcing elderly patients to frequently visit outpatient providers to renew prescriptions may exacerbate this problem. Thus, although dosage adjustments may occasionally be necessary, the length of prescription provided for cardiac medications post-angiography may represent a novel modifiable factor for long-term adherence [76]. A trial would be necessary to provide conclusive evidence, but our findings suggest that the advantages of a general approach of providing cardiac medication prescriptions for a longer interval post-discharge may outweigh the potential harms resulting from over-supply.

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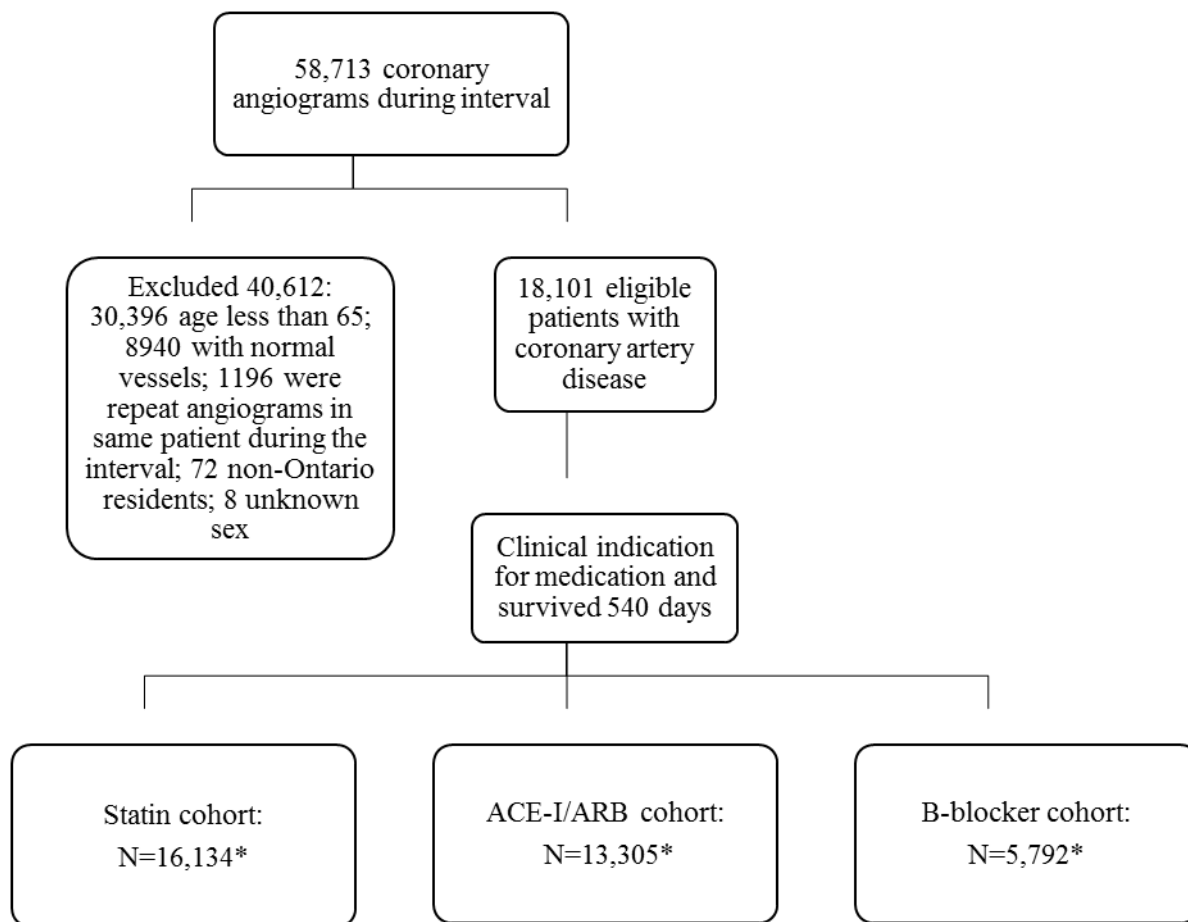
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Integration Networks and service providers and is dedicated to improving quality, efficiency, access and equity in the delivery of the continuum of adult cardiac services in Ontario. The opinions, results and conclusions reported in this paper are those of the authors and are independent from the funding sources.

No endorsement by CCN, ICES or the Ontario MOHLTC is intended or should be inferred.

Disclosures: None.

Figure 1: Patient flow diagram of study population



* Assessment of adherence over 540 days includes all patients with a clinical indication for that class of medication. Assessment of persistence is limited to those who had leftover pills in a medication-class from a prescription prior to the angiography or those who filled a new prescription for that class within 30 days after the angiography.

Figure 2. Persistence with secondary prevention medications post angiography

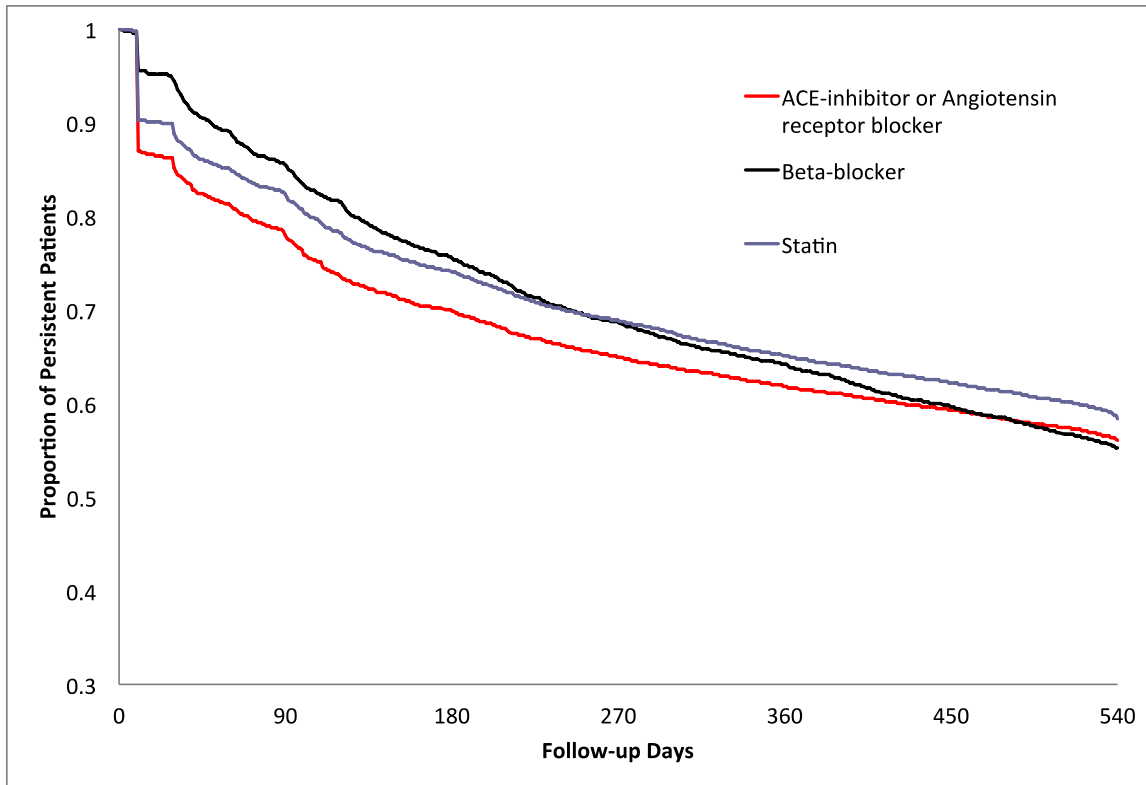


Table 1: Association between days supplied with initial prescription and long-term adherence for each drug class

Drug cohort	Initial prescription length post-angiography					
	< 31 days		31 to 60 days		> 60 days	
	High PDC N (%)	OR*	High PDC N (%)	OR* (95% CI)	High PDC N (%)	OR* (95% CI)
ACE-I/ARB N=13305	6550 (65.8%)	1	640 (84.4%)	2.6 (2.1, 3.2)	2,314 (89.1%)	4.1 (3.6, 4.7)
BB N=5792	3074 (62.9%)	1	224 (80.9%)	1.8 (1.3, 2.5)	529 (84.8%)	2.4 (1.9, 3.1)
Statin N=16134	8962 (76.1%)	1	887 (87.0%)	2.0 (1.7, 2.4)	3,019 (90.5%)	3.0 (2.6, 3.4)

OR = Odds ratios; ACE-I/ARB = ACE-inhibitors or angiotensin receptor blockers; BB = beta blockers; PDC = proportion of days covered

*Odds ratios for high adherence at 540 days are adjusted for significant covariates and use initial prescription length < 31 days as the reference. Since the adherence value for prescriptions < 31 days in length was used as the reference for the other groups receiving longer prescriptions, by definition the value for the odds ratio for those receiving prescriptions < 31 days is equal to 1.

*Reprint of Manuscript One (Supplement A)

Chapter 4: “Select, tailor, and implement intervention”

This chapter incorporates the manuscript, “*Implementation Science 2012,7:54*”

Noah M Ivers^{1,2}, Jon-David Schwalm^{3,4,5}, Jeremy M Grimshaw^{5,6}, Holly Witteman⁷,
Monica Taljaard^{5,6}, Merrick Zwarenstein⁸, and Madhu K Natarajan^{3,4}

¹Family Practice Health Centre, Women ’ s College Hospital, Toronto, Ontario, Canada

²Department of Family and Community Medicine, University of Toronto, Toronto,
Ontario, Canada

³Heart Investigation Unit, Hamilton General Hospital, Hamilton, Ontario, Canada

⁴Population Health Research Unit, McMaster University, Hamilton, Ontario, Canada

⁵University Of Ottawa, Ottawa Ontario, Canada

⁶Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital

⁷Department of Family and Emergency Medicine, University of Laval, Quebec City,
Quebec

⁸Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

Introduction:

Chapter 2 highlighted the strong foundation of evidence supporting the use of secondary prevention medications in CAD patients. Next, Chapter 3 and the DERLA baseline publication, outlined barriers to evidence-based secondary prevention medications and confirmed a contemporary evidence-practice gap with respect to secondary prevention medication use for patients with established CAD in Ontario [31]. Furthermore, this study demonstrated these gaps exist across all sub-groups of cardiac patients, thus calling for a generalizable intervention to promote the persistence of cardiac medications. The DERLA baseline study also identified vulnerable periods post-discharge, when prescriptions needed to be refilled and could result in premature discontinuation of cardiac medications. The identified barriers to care in Chapter 3 and the findings in the DERLA baseline study, coupled with evidence in the literature supporting mechanisms to promote medication adherence as outlined below, contribute to the next step in the KTA framework; the intervention development for the DERLA STEMI cRCT. This chapter will finish with the published protocol of the DERLA STEMI cRCT.

Mechanisms to promote long-term medication adherence:**Addressing determinants of adherence to secondary prevention:**

There is a need for system-level interventions that address patient-level and provider-level determinants of behaviours related to secondary prevention, since interventions tailored to known barriers are more likely to be effective [77]. A possible strategy would be to primarily target the patient with interventions that improve adherence, as they are the ones who must take tablets, organize refills, and participate in rehabilitation. Secondary targets for interventions should include community-based providers (e.g., FPs and pharmacists) as they are the ones responsible for recognizing the risk/indication for treatment and the prescribing and dispensing of cardiac medications.

Interventions to increase adherence to secondary prevention: evidence from systematic reviews:

The 2008 Cochrane systematic review of interventions to improve medication adherence, highlighted the effectiveness of simplified dosing regimens as well as more complex interventions [78]. The latter group targeted more than one patient support systems, including, beliefs, self-efficacy, and/or memory. In a 2012 systematic review of interventions to improve medication adherence in chronic disease, benefit of education and behaviour support via telephone or mail post-ACS was noted, but further study was encouraged [79]. A 2013 systematic review of nurse-led interventions for adherence to medical recommendations found that interventions with multiple interactions over the course of a year seemed promising [80]. The 2010 Cochrane systematic review on adherence to statins also concluded that promising interventions featured multiple reminders to patients [81]. Our team has also conducted a systematic review of post-event patient automated reminder systems for improving adherence to medical recommendations among chronic disease [82]. This review indicates that automated reminder systems can increase adherence rates to medical recommendations, particularly if the following features are employed: (1) the intervention is delivered after hospital contact, (2) the reminders are repeated, (3) primary care physicians are included in the reminders, and (4) the reminders must be specific in reinforcing not only the intended behavior, but also the reasons for taking such action [82].

Reminders to encourage adherence to cardiac secondary prevention therapies:

Based on the systematic reviews described above, we have identified 6 trials that have evaluated post-event postal reminders sent to the family physician and/or patient for adherence to evidenced-based cardiovascular therapies, with one in Alberta, Canada (Table 4-1) [83-88]. These trials found absolute increases in adherence of 0-18%, but were under-powered. Given the proven effectiveness of secondary prevention medications for reducing morbidity and mortality and the huge burden of CAD in the population, it is appropriate to plan a study that is adequately powered to detect clinically important

differences. Based on the findings from the evidence described above, and the fact that these secondary prevention medications are meant to be taken indefinitely and discontinuation rates increase over time, testing repeated and delayed reminders directed at the patient and FP needed to be further evaluated.

Table 4-1: Characteristics of studies that evaluated the effect of post-event reminders on medication adherence in patients with CAD.

Study	Participants	Health Event	Intervention Description	Results
Feder (1999) BMJ [83]	328 Patients Britain	Admitted with ACS	Letter to patient urging importance of medication use Frequency: Multiple FP Co-intervention: No	OR 1.7 (95% CI 0.8-3)
Smith (2008) Arch Intern Med [84]	907 patients Mean age: 64.9 33% female USA	ER Visit (MI)	Letter to patient reminding importance of beta-blocker therapy & risks of non-adherence Frequency: multiple FP Co-intervention: no	RR 1.13 (95% CI 1.01-1.26)
Guthrie (2001) Clin Ther[85]	13,100 patients Mean age: 58 51% female UK	New diagnosis of CAD	Reminder postcards & telephone reminders Frequency: multiple FP co-intervention: no	RR 1.10 (95% CI 1.02-1.18)
Munoz (2007) Int J Cardiol [87]	983 patients Mean age: 63.9 26% female Spain	ER visits Myocardial infarction	Letter advising follow-up with physician Frequency: multiple FP Co-intervention: yes	RR 1.0 (95% CI 0.85-1.19)
McAlister (2009) CMAJ [86]	480 adults from 252 practices Canada	Time of coronary angiography	Evidence summaries sent to the FP of patients with CAD. Frequency: Single Patient co-intervention: No	OR 1.18 (95% CI 0.71-1.94)
Riesen (2008) Swiss Med Wkly [88]	1,128 patients Mean age: 60 35% female Switzerland	New diagnosis Hypercholesterolaemia & elevated CHD risk (> 20%)	Education, reminder newsletters, telephone helpline & website Frequency: multiple FP co-intervention: no	RR 1.01 (95% CI 0.95-1.07)

DERLA STEMI Intervention:

The Hamilton General Hospital/Hamilton Health Sciences has an existing registry for all patients presenting to a Local Health Integrated Network IV (LHIN) healthcare facility with an STEMI. This registry (SMART-AMI) captures baseline demographics, reperfusion details (thrombolysis and percutaneous coronary intervention [PCI]), in-hospital medication use, and three-month follow-up of medications and clinical events. Using this established infrastructure, the protocol for the DERLA STEMI trial was developed and implemented [5]. DERLA STEMI is a pragmatic, cluster-randomized controlled trial that has been designed to evaluate the impact of a low-cost and sustainable intervention to improve the long-term use of secondary preventative medications post-STEMI. All patients from one health region in Ontario, Canada (LHIN IV) who underwent a coronary angiogram during their admission for an STEMI and survived their initial hospitalization were included. The intervention consisted of recurrent, personalized, paper-based educational messages and reminders sent via post on behalf of the interventional cardiologist to the patient, family physician, and tear-outs for the pharmacist, urging long-term adherence to secondary prevention medications. The timing of the delivery of the intervention was based on (1) the Cochrane review suggesting delayed and repeated reminders, (2) the vulnerable periods post-discharge identified in the DERLA baseline study and (3) the experience from previous reminder trials described above [31, 81]. The primary outcome was the proportion of patients who reported, in a phone interview, taking all relevant classes of cardiac medications at twelve months. This cRCT used blinded outcome assessment. Self-reported measures of adherence were validated using administrative data for prescriptions filled. This intervention is designed to be easily generalizable and could be implemented broadly. An embedded process evaluation was also conducted to offer insights regarding how such an intervention could be optimized in the future.

Supporting Documents for Chapter 4;

Included in the Appendix are copies of the intervention letters sent to the patient (postcard, Appendix 4-1 and letter, Appendix 4-2), physician (Appendix 4-3), and tear-out section for the pharmacist (Appendix 4-4). The copyright transfer is highlighted in Appendix 4-5.

Manuscript Two:**Delayed Educational Reminders for Long-term medication Adherence in ST-Elevation Myocardial Infarction (DERLA-STEMI): Protocol for a pragmatic, cluster-randomized controlled trial.**

Noah M. Ivers^{1§}, Jon-David Schwalm², Jeremy M. Grimshaw³, Holly Witteman⁴, Monica Taljaard⁵, Merrick Zwarenstein⁶, Madhu K. Natarajan²

¹Family Practice Health Centre, Women's College Hospital, 76 Grenville Ave Toronto, Ontario, Canada

²Department of Medicine, Division of Cardiology, McMaster University/Hamilton Health Sciences, 237 Barton Street East Hamilton, Ontario, Canada

³Ottawa Hospital - General Campus, Centre for Practice-Changing Research, 501 Smyth Road, Ottawa, Ontario, Canada

⁴Center for Bioethics & Social Sciences in Medicine, Department of Internal Medicine, University of Michigan, 300 North Ingalls Ann Arbor, Michigan, USA

⁵Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital, Civic Campus, 1053 Carling Avenue, Ottawa, Ontario, Canada

⁶Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada

§Corresponding author

Abstract**Background**

Despite evidence-based recommendations supporting long-term use of cardiac medications in patients post ST-elevation myocardial infarction, adherence is known to decline over time. Discontinuation of cardiac medications in such patients is associated with increased mortality.

Methods/design

This is a pragmatic, cluster-randomized controlled trial with blinded outcome assessment and embedded qualitative process evaluation. Patients from one health region in Ontario, Canada who undergo a coronary angiogram during their admission for ST-elevation myocardial infarction and who survive their initial hospitalization will be included. Allocation of eligible patients to intervention or usual care will take place within one week after the angiogram using a computer-generated random sequence. To avoid treatment contamination, patients treated by the same family physician will be allocated to the same study arm. The intervention consists of recurrent, personalized, paper-based educational messages and reminders sent via post on behalf of the interventional cardiologist to the patient, family physician, and pharmacist urging long-term adherence to secondary prevention medications. The primary outcome is the proportion of patients who report in a phone interview taking all relevant classes of cardiac medications at twelve months. Secondary outcomes to be measured at three and twelve months include proportions of patients who report: actively taking each cardiac medication class of interest (item-by-item); stopping medications due to side effects; taking one or two or three medication classes concurrently; a perfect Morisky Medication Adherence Score for cardiac medication compliance; and having a discussion with their family physician about long-term adherence to cardiac medications. Self-reported measures of adherence will be validated using administrative data for prescriptions filled.

Discussion

This intervention is designed to be easily generalizable. If effective, it could be implemented broadly. If it does not change medication utilization, the process evaluation will offer insights regarding how such an intervention could be optimized in future.

Trial registration

Clinicaltrials.gov NCT01325116

Keywords

Randomized trial, medication adherence, reminders

Background**Cardiovascular disease burden and the role for long-term pharmacotherapy**

Worldwide, cardiovascular disease (CVD) is estimated to be the leading cause of death and disability [89]. Approximately 50% of myocardial infarctions (MIs) and 70% of CVD deaths occur in patients who have already documented coronary artery disease (CAD) [19]. Therefore, the prompt identification of modifiable cardiovascular risk factors and initiation of proven secondary preventative medications post-MI are essential to the prevention of subsequent cardiac events [4]. Population-level observational studies provide evidence that the rate of cardiovascular morbidity and mortality has been decreased through the use evidence-based therapies [16, 20].

ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute myocardial infarction (AMI) constituting approximately 30% of all cases [2]. Post-STEMI, patients are at high risk for subsequent cardiac events—18% of men and 35% of women will have a repeat MI within six years and STEMI patients have four to six times the risk of sudden cardiac death compared to the general population [90]. While acute treatment is crucial for STEMI patients, relevant guidelines emphasize that the initiation and long-term maintenance of evidence-based secondary preventative therapies are essential for reducing the overall burden of CVD [4, 21, 91].

Poor long-term adherence to cardiac medications

While there is a significant body of evidence supporting these guidelines (Figure 1), there remains a large gap between ideal and actual care with regard to the long-term management of cardiovascular risk for these patients. Studies show that adherence to evidence-based therapies begins decreasing at 30 days and falls to as low as 50% adherence at six months post-discharge [5, 7, 29, 31, 81]. Unfortunately, discontinuation of evidence-based therapies has repeatedly been shown to be associated with increased mortality in patients with CAD [6, 8, 92-93].

Medication non-adherence is increasingly recognized as a very important issue due to its significant health consequences [94, 95]. Many reasons for non-adherence have been proposed and these can generally be categorized as provider-level (*e.g.*, knowledge, motivation, time), patient-level (*e.g.*, knowledge, motivation, finances [33]), and system-level (*e.g.*, access to care, coordination of care). Furthermore, both ethnicity [96, 97] and socio-economic status [98] seem to be related to quality of care for cardiovascular disease, even in countries with universal healthcare like Canada and the United Kingdom (UK), and non-adherence related to such factors may not be readily impacted with quality improvement interventions.

Fortunately, the evidence suggests that many of the key factors contributing to cardiac medication non-adherence may be amenable to intervention. Discontinuation of evidence-based cardiac medicines post-STEMI is rarely due to an active, informed choice after discussion of risks and benefits between patient and health-care-provider; absolute contraindications are rare and side effects are infrequently reported by patients as the primary reason for discontinuation (less than 4% of patients) [39, 43]. In contrast to situations where informed decisions are made to deviate from standard treatment protocols, qualitative work in primary care has found that poor adherence may be frequently due to fragmented systems of care [35] or communication problems at the interface between secondary and primary care [36]. A recent study in Canada has highlighted the risk related to transitions in care; it appears that hospitalizations increase the risk for inadvertent discontinuation of cardiac medications [37].

The provider also can have an impact; having a cardiologist involved in the patient's care may increase rates of appropriate medication adherence [38]. However, there is undesirable variation among prescription rates by specialists as well. In one study of cardiologists, the most common reason given for not prescribing secondary prevention medications was, 'not high-enough risk' [39]. However, in that study, risk scores of patients not treated for this reason were often higher than those of patients prescribed such treatment. Meanwhile, the same study found that approximately one-third of patients

had stopped their medication without instruction from their doctor. This indicates a potential role for multi-pronged interventions addressing both the provider and the patient.

Previous research aiming to improve adherence

Numerous systematic reviews have been published regarding interventions to improve adherence to medications. An overview of reviews found that no patient-mediated interventions were effective across all diseases, but found that the most promising interventions included self-management, simplified dosing, and involvement of pharmacists [99]. A review focusing on anti-depressants found that patient education alone was ineffective [100], and a review focusing on anti-epileptics found that patient education was inconsistent, while interventions with multiple reminders featuring action planning were more often effective [101]. Recognizing that non-adherence tends to worsen over time, a recent Cochrane review recommended testing a delayed intervention as opposed to the immediate reminders used in similar previous trials [10], as one would expect a larger effect size in a delayed intervention.

One previous trial has shown that brief evidence summaries regarding medications attached to discharge letters sent to primary care providers resulted in improved adherence [102]. Three other trials have evaluated the role of reminder letters to the primary care provider (with or without patient reminders) to improve adherence to evidenced-based cardiovascular therapies: one in the USA, one in the UK, and one in Canada [83, 84, 86]. The American trial focused on beta-blocker use post-MI and found a small increase in compliance (proportion of days covered), with a number needed to treat of 16 for achieving high adherence, but no change in the proportion who discontinued their beta-blocker. The other two trials focused on statin use in patients with known CAD. These trials found absolute increases in adherence of 9% to 10% in statin use, but despite this being a potentially important effect size on a population basis, both were under-powered for effects this size.

Objectives

The overarching goal of this project is to improve long-term use of secondary prevention medications for patients with CAD, and thereby reduce cardiovascular events through the use of an easily generalizable and sustainable intervention. The primary objective of this study is to assess if repeated mailing of an educational message and reminder to the family physician and the patient will decrease the proportion of patients who discontinue evidence-based secondary-prevention medications at twelve months post-STEMI. A secondary objective is to encourage cardiac patients and their primary care providers to discuss the benefits of long-term adherence to cardiac medications.

Methods/design

Study design

DERLA-STEMI is a pragmatic, cluster-randomised controlled trial, with blinded outcome-assessment, and is registered with clinicaltrials.gov (NCT01325116).

Participants and Setting

In Ontario, healthcare is financed through a single-payer (publicly administered) system. There are no co-payments for visits to generalist or specialist physicians or for care provided in hospitals for patients of any age, and almost all licensed prescription medications are covered for patients 65 and over.

Patients younger than 65 years pay for medications out-of-pocket or through private insurance plans, or are covered by the provincial plan if they qualify for social support.

In this study, eligible patients are adult patients (>18 years) with a diagnosis of STEMI, who undergo a coronary angiography procedure (with or without angioplasty), at the Heart Investigation Unit (HIU) in Hamilton, Ontario, and who are alive at hospital discharge. In keeping with the pragmatic approach to study design, no other exclusion criteria will be applied. The HIU is the only catheterization lab in its region, with a catchment population of almost 1.5 million people. More than 700 STEMI patients undergo an angiogram there each year. Studies at the HIU have highlighted excellent rates of prescribing

of evidence-based therapies at discharge post-STEMI, but substantial reduction in use starting three months following discharge [103, 104]. While 78% of STEMI patients leave the HIU taking a statin, an ACE-inhibitor (or ARB), a beta-blocker, and aspirin, by 90 days the proportion still taking all four of these medication classes falls to 63% (unpublished data from the Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction (SMART-AMI) study).

Intervention

The intervention was developed in concert with clinical experts from both primary care and cardiology, as well as experts in knowledge translation and medical decision-making. Personalized letters sent via post to the patient and their family physician at one, five, eight, and eleven months after their angiogram, signed by the interventional cardiologist (see Appendix A for prototype). The letter for the family physician names the patient and provides brief evidence in support of long-term medication use for these patients. This was reviewed with a series of family physicians from a different area of the province.

The patient letter provides a review of the importance and role of each of the cardiac medications and urges short- and long-term adherence (see Appendix B for prototype). This educational aspect is designed to address knowledge and beliefs about medication use as a potential cause of poor adherence. The intervention explicitly encourages discussion of medication adherence with the family physician by asking patients to bring the letter to their family physician. It also asks patients to deliver the final page of their letter to their pharmacist; this page is written to the pharmacist urging them to participate in promoting long-term adherence. The intention is to facilitate recurrent discussions with primary care providers that emphasize long-term adherence and to address coordination of care and continuity of information as barriers to medication persistence. This letter was developed with iterative evaluations of understanding and acceptability amongst a series of cardiology patients at the HIU. The language in the patient letter is simplified to a grade six-level.

The timing of the intervention was specifically chosen based on the preliminary data obtained from the SMART-AMI trial demonstrating suboptimal rates at 90 days. Furthermore, literature (referenced above) demonstrates that adherence starts decreasing by thirty days and continues to decrease in an almost linear fashion. Finally, the common practice in Ontario is for pharmacists to dispense medications for no more than three months at a time (regardless of duration of the prescription ordered by the physician). Therefore, we decided to deliver the intervention at regular intervals (1, 5, 8, and 11 months post-STEMI) corresponding to the likely time periods prior to patients requiring a prescription renewal/refill. In pilot testing the intervention with family physicians and patients, we determined that sending the full letter too frequently would be undesirable and that the physicians in particular did not want to have monthly reminders. At the same time, close examination of data from Ontario indicated large stepwise declines in adherence at 30 and 60 days post-STEMI. To address this, patients will be provided an additional postcard type reminder two months post-STEMI (see Appendix C).

In summary, the unique aspects of the intervention compared to usual care include the following: the letter to the primary care provider is personalized and includes a summary of the evidence in support of long-term adherence and represents a recurrent form of contact between the cardiologist and the primary care provider; the letter to the patient use clear language suitable for a broad range of health literacy levels and was iteratively refined with input from patients in the target population, features content that attempts to address adherence-related beliefs, and provides explicit, actionable instructions to discuss the matter with the family physician as well as a summary to be given to the outpatient pharmacist to facilitate coordination of renewals.

Comparator/usual care

Usual care in this context may include some contact between the admitting physician (generally not the interventional cardiologist) for the STEMI patient and the primary care provider (generally the family physician). This is usually in the form of a standard discharge summary mailed to the family physician's

office at the end of the hospitalization. The quality of such discharge summaries varies widely even within the same institution (and summaries frequently lack necessary information regarding medications) [75]. In keeping with the pragmatic nature of the trial, no attempt will be made to standardize the usual care arm [105].

Allocation

The randomization schedule was computer-generated by a statistician independent of the study, using a permuted block design with randomly varying block lengths of four, six, or eight. Eligible patients are randomly allocated to one of the two treatment arms. Although enrolment of more than one patient treated by a particular family physician is expected to occur infrequently, randomization will be carried out to ensure that, once a patient from any family physician is randomized, all future patients seen by that family physician will automatically be assigned to the same arm. This is necessary to avoid contamination (with one family physician having patients in different intervention arms). Roughly one-half of patients will be allocated to each study arm (the actual allocation ratio will depend on the size of the clusters). Based on pilot data, we anticipate that approximately 10% to 15% of patients will not have a family physician. In keeping with the pragmatic design of the trial, a patient without a family physician will be included (receiving only the patient-level intervention).

Randomization is delayed by one week (after the angiogram) to permit time to identify and exclude patients with in-hospital death. Randomization will continue until the target sample size is achieved. The anticipated duration of enrolment is 15 months. The allocation sequence will be concealed from the investigators and outcome assessors; only the study coordinator who will be sending out the letters will have access to the un-blinded allocation list.

Outcomes

The primary outcome is the proportion of living patients who describe taking all cardiac medication classes of interest measured at twelve months. This type of ‘all-or-none’ measure has been recommended for evaluating quality improvement interventions, especially related to medication utilization [106]. Specifically, we will assess whether patients are taking a statin, beta-blocker, angiotensin modifier (ACE or ARB), and aspirin at twelve months. All STEMI patients have reasonable evidence supporting these medications [4]; we anticipate that randomization will balance those patients for whom evidence is less clear or who might have contraindications to any of these medications.

We will also assess whether patients are taking these four medication classes plus a secondary antiplatelet (clopidogrel, prasugrel, or ticagrelor) at three months. Therefore, patients at three months will be dichotomized as to whether or not they are taking all five cardiac medication classes, and at twelve months they will be dichotomized according to whether they are taking all four relevant medication classes. The difference in the number of medication classes considered at three and twelve months relates to uncertainty in the evidence regarding the appropriateness of a secondary antiplatelet at this timeframe. Additional secondary outcomes include a comparison of: the proportion of patients who report actively taking each cardiac medication class of interest (item-by-item) at three and twelve months; the proportion of patients who report stopping medications due to side effects at three and twelve months; the proportion taking one or two or three medication classes concurrently at three and twelve months; and the proportion of patients with a perfect Morisky Medication Adherence Score (MMAS) for cardiac medication compliance at three and twelve months. The MMAS is a brief, standardized adherence questionnaire which excellent reliability [107], and has been shown to be predictive of cardiovascular medication adherence [108] and to be associated with control of blood pressure and cholesterol [107, 109]. In addition, all patients will be asked at three months and twelve months whether they had a discussion with their family physician during past three months in which the provider had encouraged long-term cardiac medication compliance.

Data collection

Baseline patient characteristics will be obtained from standard patient-registry information at the HIU. This includes demographic information, comorbidities, and the findings at the time of angiography.

Outcomes will be assessed 3 and 12 months post-index angiogram through patient phone calls by a research coordinator associated with the HIU who will be trained expressly for this function. The research coordinator conducting the phone calls will not have access to the allocation list. The calls are made on behalf of the treating cardiologist at the HIU, and all patients will be encouraged to review cardio-protective meds with their family physician. The phone call follow-ups will ask patients to list their current, daily medications (and doses) without specific prompting in order to reduce bias. Attempts will be made to contact patients for a maximum of 30 days prior to being considered lost-to-follow-up. Reasons for loss-to-follow-up will be tracked.

For a sample of patients aged 65 and older, the Ontario Drug Benefit database will be used to examine the accuracy of the self-reported primary outcome and to further evaluate adherence using the medication possession ratio over the preceding year, which has been shown to be associated with both pill counts and clinical effects [110].

Ethical considerations

Research Ethics Board (REB) approval was received at Hamilton Health Sciences Centre and McMaster University (project number 11-191). Given the low risk nature of the intervention, which falls within the realm of continuity-of-care and circle-of-care, the REB agreed that verbal consent at the time of outcome assessment is the most appropriate design to test this pragmatic intervention. Thus, there is no formal recruitment process; as mentioned above, all eligible patients within the registry at the HIU are allocated to intervention or control one-week post-STEMI. To gain REB approval, we agreed to provide

a note to the family physician of all included patients describing the patient-reported outcomes (*e.g.*, current medications and adherence) at the end of the trial.

Data management

All patient data will be collected directly into a password-protected database and will not be removed from the server at the HIU research office. Necessary information for contacting the participants (*e.g.*, name, phone number) will be kept in a separate, password-protected file from the study data, which will have no patient identifiers. The outcome data (without any identifiers) will be transferred from the database into a statistical package for analysis.

Analysis

Descriptive statistics will be calculated for all variables of interest: continuous variables with a normal distribution will be summarized using means and standard deviations (medians and inter-quartile ranges in the case of skewed distributions), whereas categorical variables will be summarized using frequencies and proportions.

We hypothesize that the intervention will result in a greater proportion of patients who report taking each cardiovascular medication class of interest at 12 months post-angiography. The absolute difference in proportions will be calculated for all primary and secondary dichotomous outcomes, together with 95% confidence intervals adjusting for clustering by family physician [111]. The statistical significance of differences between arms will be evaluated using chi-squared tests, adjusted for clustering by family physician.

Exploratory multivariable analyses will be carried out using generalized estimating equations (GEE) to identify potential baseline predictors of adherence. Potential effect modification by treatment—medical management versus coronary artery bypass graft (CABG) versus angioplasty—and attendance at cardiac rehabilitation will be explored by including interactions between these two variables and treatment. It is

plausible that this analysis will suggest a need for tailored interventions for these subgroups. A further exploratory analysis will be conducted focusing on patients who reported taking all five cardiac medication classes and had perfect MMAS scores at three months using a multivariable model to examine covariates predicting late-onset discontinuation. In addition, a planned sensitivity analysis will exclude those patients who did not have a family physician, as we would expect such patients to be more likely to discontinue their cardiac medications.

Analyses will be performed on an intention-to-treat basis. No interim analyses are planned. All analyses will be carried out using the SAS Version 9.2 statistical program (SAS Institute, Cary, NC, USA).

Sample size

The sample size for this design is based on the following assumptions: an assumed absolute increase in the proportion of patients taking all four cardiovascular medication classes of 11% at twelve months post-STEMI; an estimated control group proportion of 50%, and a variance inflation factor of 1.02 (derived from an intra-cluster correlation coefficient of 0.019 calculated from data in the SMART-AMI registry and assuming an average cluster size of 1.2 based on pilot data). To achieve 80% power to detect a significant main effect of the intervention using a Chi-squared test at the 5% level of significance, 652 patients would be required. We will randomize 815 patients to account for an estimated participation rate of 80% at the 12-month follow-up. This dropout rate is conservative based on similar studies at the HIU where the participation rate has been greater than 90% over even longer time periods [104].

The expected effect size is slightly higher than the effect seen in the previous Canadian trial to account for the fact that the intervention is multifaceted (directed at both physician and patient) and occurring later post-STEMI (reducing the expected control group rate and therefore the possibility of a ceiling

effect). Based on this sample size calculation, and the rate of STEMI patients presenting to the HIU, we anticipate that it will take approximately 15 months to complete the recruitment for this study.

We will use a kappa statistic to assess agreement between the self-report of the primary outcome and the corresponding objective data from the Ontario Drug Benefit database. Based on an anticipated overall proportion of 56% at 12 months (average of intervention and control arm) and an anticipated kappa of 0.88, we would consider acceptable agreement if the lower limit of the 95% confidence interval around kappa does not drop below 0.80. Therefore we will evaluate validity of the primary outcome in a random selection of 138 patients aged 65 or greater.

Process evaluation—optimizing the intervention

A random sample of participating patients will be asked a series of additional, structured questions at the time of outcome assessment 90 days post-STEMI. Specifically, a 20% random selection of patients who received the intervention will be sampled, equating to approximately 80 patients. In addition, all family physicians in the intervention group will be mailed a one-page questionnaire along with the second iteration of the provider letter (month five post-STEMI). A response rate of only 15% will allow us to get feedback from about 50 family physicians. The questionnaires to both patient and provider assess acceptability of the intervention and the reasons for any (lack of) action taken (See Appendix D for patient process evaluation questionnaire and Appendix E for provider process evaluation questionnaire). The answers to these questionnaires will be summarized descriptively and used to inform future iterations of the intervention.

We also plan to conduct focus groups with both patients and providers to better understand both why the intervention did (or did not) work and how it might be optimized. Participants for these focus groups will be purposively recruited based on the responses to the questionnaires. We plan to conduct one or two focus groups of six to eight patients and one focus group of four to six physicians, each group

lasting about one hour occurring at the HIU. These focus groups will follow a semi-structured guide that will be informed by the issues identified in the questionnaires. The overarching goal of the focus groups will be to compare and contrast various designs and approaches of sending reminders to decrease the risk of inappropriate medication discontinuation. To this end, a variety of reminder designs will be handed out among the focus group participants to encourage discussion (similar to how marketing firms traditionally have used focus groups). Physician participants will be provided with \$75 (and refreshments). Patient participants will be offered a \$25 gift certificate (and refreshments) as remuneration for attending the focus group. The sessions will be recorded and transcribed verbatim.

Discussion

Discontinuation of cardiac medications post-STEMI occurs due to patient, provider, and system-level factors and has important consequences for the patient. This two-arm, pragmatic, cluster-randomized controlled trial will test whether mailed reminder letters sent from the interventional cardiologist to the patient and their family physician can successfully increase adherence. Even if the trial does not show a significant effect on medication discontinuation, the embedded process evaluation will provide helpful information for planning future interventions aiming to address this important issue.

Limitations

Although our overall goal is to improve adherence to medications, it is important to note that our primary outcome evaluates discontinuation (or ‘persistence’). This represents the most extreme form of non-adherence. The allocation is clustered at the level of the family physician to limit contamination, but it was deemed not feasible to do the same with pharmacists. Although the tear-away page in the patient letter for pharmacists could theoretically bias toward a null finding if pharmacists transfer their learning from one patient to another, we considered this risk to be small in comparison to the potential benefit of facilitating interactions with these key primary care providers.

It is important to note that this trial will not be able to discern the relative importance of intervention at patient versus family physician level. A larger sample size would be preferable to provide an opportunity to test multiple ways of designing and delivering this type of intervention within a single trial. In the case of a positive effect, the pragmatic approach utilized will not allow for inferences regarding the ‘most important’ active ingredients in the intervention. We intend to explore these issues through the process evaluation. The questionnaires developed for the process evaluation are not independently validated for assessing acceptability and usability of the reminder intervention. However, they will be evaluated qualitatively to inform iterative improvements to the program after the trial is completed, and will allow us to identify interested participants for focus groups.

Although the research coordinator conducting the outcome assessment will be blinded to allocation, it is possible that some patients will discuss receiving the intervention with the coordinator. Another important caveat is that we will be using patient self-report for main outcome measurements—an approach which has previously been used in a similar trial [86]. We are planning to evaluate the validity of self-report data in our study by comparing patient reported medication use (including the MMAS) with data recorded in administrative databases for a subsample of participants above age 65 (for whom data are accessible using the Ontario Drug Database). Through these administrative databases, we can also pursue proxy measures for adherence (rather than strictly discontinuation) by assessing the medication possession ratio.

Implications

Given the proven effectiveness of secondary prevention medications for reducing morbidity and mortality and the high risk for poor outcomes in the post-STEMI population, we believe it is appropriate to power this trial to show relatively small increases in adherence. Although we would hesitate to extrapolate the findings of this study without further research, we believe it is important for quality improvement trials measuring process outcomes such as adherence to consider the potential for patient-

relevant outcomes. To illustrate, consider the systematic review of RCTs of statin-therapy, which found a number needed to treat (NNT) of 86 to reduce mortality in patients with CAD [112]. We estimate that the NNT for avoiding statin discontinuation with the reminder interventions tested in this trial is approximately 10. If this were the case, then the NNT for the reminder interventions to prevent a single mortality would be 860. In fact, the number might be lower than this since the intervention may also increase utilization of the other cardiac medications known to reduce mortality. Given the low-cost, low-risk nature of the intervention in this trial, we believe that NNTs of this size merit further study for potential population-wide implementation.

Summary

The major strengths of this trial are the pragmatic nature of the intervention the study design. The trial is well powered and designed specifically to improve health services for a common problem in patients at high risk of cardiovascular events. Many quality improvement trials embark upon highly sophisticated and expensive interventions; even if successful, sustainability of such interventions beyond the trial period proves challenging. Conversely, the DERLA-STEMI intervention would be easily testable in other healthcare settings and for other conditions where long-term adherence is suboptimal. We believe this study will demonstrate the feasibility, acceptability, and (hopefully) the effectiveness of a sustainable and generalizable quality improvement intervention for STEMI patients.

Competing interests

The authors declare no conflicts of interest.

Author contributions

All authors contributed to the study concept and design and all approved the final version of this manuscript.

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Table 1. Summary of Guideline Recommendations for Secondary Prevention Medications post-STEMI.

Table 1 Summary of guideline recommendations for medications post-STEMI

Medication	Recommendation	Strength of evidence*
Anti-platelets	Aspirin therapy (75-162 mg/day) indefinitely post-STEMI.	I A
	P2Y ₁₂ -receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) in combination with aspirin in patients post ACS	I A
	P2Y ₁₂ -receptor inhibitor continued for at least 12 months if ACS managed with PCI and stent placement	I A
Statins	Statin therapy indefinitely for all patients with a prior cardiovascular event.	I A
Angiotensin-system agent	ACE inhibitor (or ARB if intolerant) post-STEMI indefinitely for all patients with left ventricular ejection fraction <40% and in those with hypertension, diabetes, or chronic kidney disease	I A
	ACE inhibitor (or ARB) for all patients post-STEMI	Ia B
Beta-blockers	Beta-blockers for all patients post-STEMI	I A
	Beta-blockers continued for at least three years post-STEMI	I B

*Strength of Evidence.

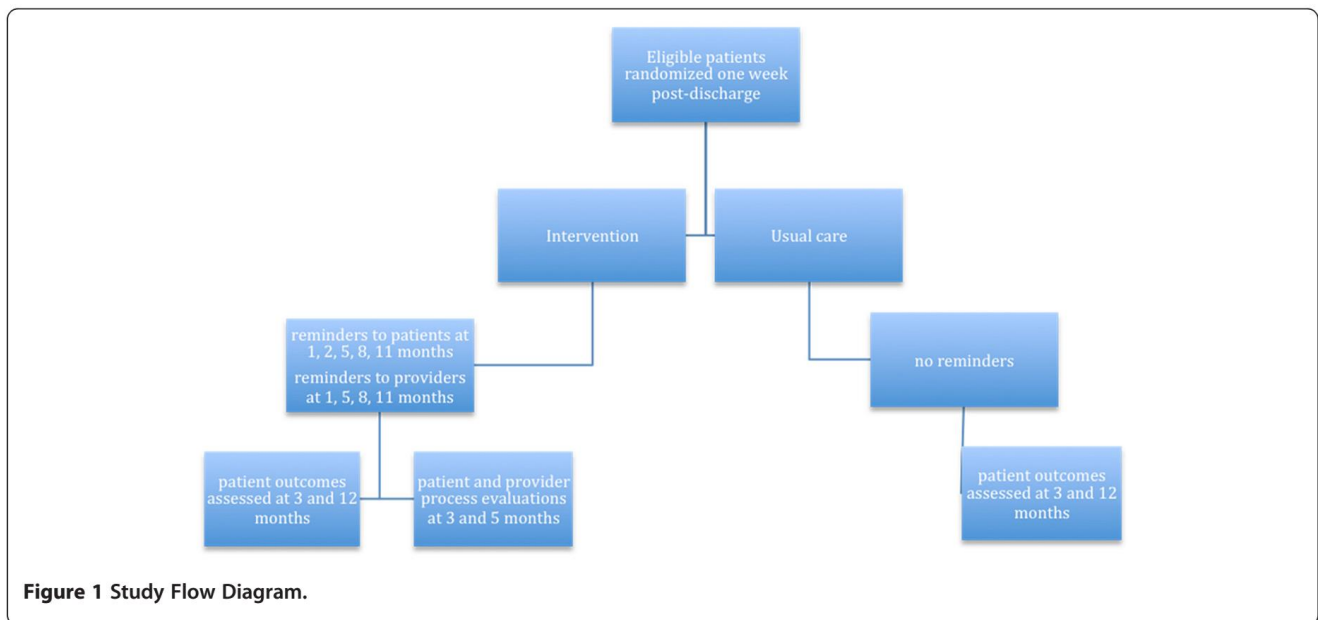
I: Conditions for which there is evidence and/or general agreement that a given treatment is beneficial, useful, and effective.

Ia: Weight of evidence/opinion is in favor of usefulness/efficacy.

A: Data derived from multiple randomized clinical trials or meta-analyses.

B: Data derived from a single randomized trial, or nonrandomized studies.

Figure 2. Study Flow Diagram



* Manuscript 2 Reprints (Supplement B)

Chapter 5: “Evaluate Outcomes”

Running Title: DERLA-STEMI

Jon-David Schwalm^{1,2,3}, Noah M Ivers^{4,5}, Madhu K Natarajan^{1,2}, Monica Taljaard^{3,6}, Purnima Rao-Melacini², Holly Witteman⁷, Merrick Zwarenstein⁸, and Jeremy M Grimshaw^{3,9}

¹Heart Investigation Unit, Hamilton General Hospital, Hamilton, Ontario, Canada

²Population Health Research Unit, McMaster University, Hamilton, Ontario, Canada

³Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa Ontario, Canada

⁴Family Practice Health Centre and Institute for Health Systems Solutions, Women’s College Hospital, Toronto, Ontario, Canada

⁵Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

⁶Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital

⁷Department of Family and Emergency Medicine, University of Laval, Quebec City, Quebec

⁸Director, Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario

⁹Department of Medicine, University of Ottawa, Ottawa Ontario, Canada

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

Introduction:

In the last chapter, we outlined the development of an intervention designed to promote the use of evidence-based secondary prevention cardiac medications post-STEMI. The next stage in the KTA framework requires the evaluation of the KT intervention [11]. The protocol for this study was described in Chapter 4 and the full study with results will be highlighted in this chapter. This chapter includes the manuscript for the completed DERLA STEMI cRCT that will be submitted for publication in a peer reviewed journal. However, the manuscript in its current form is too long and will need to be truncated prior to submission. We have left the manuscript at this length to be more inclusive with respect to the methods, analyses, and discussion, for the purposes of this thesis submission.

The DERLA STEMI trial:

The DERLA STEMI trial is a pragmatic cRCT, which included all STEMI patients from one health region in Ontario who underwent an angiogram between September 2011 and December 2012 and survived to discharge. Over 850 participants were recruited during the study period and there was > 85% follow-up at 12 months.

Design and Analysis of the DERLA STEMI cRCT:

The DERLA STEMI trial was designed as a cluster RCT. A cluster design was felt to be most appropriate in order to reduce contamination. During the development of the study design, concerns were raised regarding the involvement of FPs with more than one patient in the study. For instance, if one patient was enrolled in the intervention arm of the study, then both the patient and their FP would receive the reminders promoting long-term use of cardiac secondary prevention medications. These reminders could then influence the behavior of the FP as she manages other patients in her practice, particularly if she is managing a participant in the control arm [113]. Given the pragmatic nature of this study, patients without a FP were still enrolled and counted as each their own cluster. In these cases,

reminders were only sent to the patient, with tear-outs for their pharmacist. There were 572 clusters with a mean size of 1.8, with 106 of these clusters had patients (18.5%) who did not have a FP. The identified cluster size and patients without a FP were higher than the estimates as described in the study protocol (chapter 4) [13].

The DERLA STEMI manuscript outlines an analytic plan for the primary outcome that is different from what is described in the published protocol [13]. In the published protocol, the primary outcome was described as the absolute difference in the proportion of patients between the two groups that were taking 4 of 4 medications at 12 months. Chi squared analysis, adjusting for clustering by FP was to be used to test statistical significance. However, in the final manuscript (chapter 5), outcomes at discharge, 3 months, and 12 months were analyzed using hierarchical logistic regression analyses accounting for clustering by family physician and correlations due to repeated measures on the same patient over time. Time (measured as a categorical variable), the interaction between group and time, and pre-specified baseline covariates, were all included as fixed effects, while the family physician and the patient were specified as random effects. For hierarchical models that yielded negative variance estimates for the family physician random effects, the intra-cluster correlation coefficient (ICC) was assumed to be 0, and models were re-estimated using Generalized Estimating Equations (GEE) accounting for correlation in repeated measures on the same patient using an unstructured correlation matrix [114]. This analysis was felt to be more appropriate than that described in the design protocol, as we needed to account for the repeated measures (medications were collected at discharge, 3 months and at 12 months). The pre-specified baselines covariates were also included in the model, regardless of significance, as they were felt, a priori, to clinically impact medication use at 12 months (see explanation in manuscript-Methods).

Summary of Results:

The results of the DERLA STEMI trial suggest suboptimal adherence to all 4 of 4 cardiac medication classes at 12-months. There was no significant difference compared to usual care in the use of guideline-recommended medications post-STEMI when participants (and their family physicians) receive repeated postal reminders. However, there was a statistically significant increase in medication adherence using the Morisky Medication Adherence Score (MMAS), as a predefined secondary outcome [107].

Manuscript Three:

Cluster Randomized Controlled Trial of Delayed Educational Reminders for Long-term Medication Adherence in ST-Elevation Myocardial Infarction (DERLA-STEMI)

Running Title: DERLA-STEMI

Jon-David Schwalm^{1,2,3}, Noah M Ivers^{4,5}, Madhu K Natarajan^{1,2}, Monica Taljaard^{3,6}, Purnima Rao-Melacini², Holly Witteman⁷, Merrick Zwarenstein⁸, and Jeremy M Grimshaw^{3,9}

¹Heart Investigation Unit, Hamilton General Hospital, Hamilton, Ontario, Canada

²Population Health Research Unit, McMaster University, Hamilton, Ontario, Canada

³Department of Epidemiology and Community Medicine, University of Ottawa, Ottawa Ontario, Canada

⁴Family Practice Health Centre and Institute for Health Systems Solutions, Women's College Hospital, Toronto, Ontario, Canada

⁵Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

⁶Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital

⁷Department of Family and Emergency Medicine, University of Laval, Quebec City, Quebec

⁸Director, Centre for Studies in Family Medicine, Department of Family Medicine, Schulich School of Medicine & Dentistry, Western University, London, Ontario

⁹Department of Medicine, University of Ottawa, Ottawa Ontario, Canada

Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa

11-Jan-2015

Abstract:

Background: Discontinuation of guideline-recommended cardiac medications post-ST-elevation myocardial infarction (STEMI) is common and associated with increased mortality.

Objectives: To test an automated, scalable intervention to improve long-term adherence to cardiac medications post-STEMI.

Design: Pragmatic, cluster-randomized controlled trial.

Participants: All STEMI patients from one health region in Ontario who underwent an angiogram between September 2011 and December 2012 and survived to discharge.

Intervention group: The intervention was an automated system that sends recurrent, personalized, educational reminders to the patient, their family physician, and their pharmacist urging long-term use of secondary prevention medications. Interventions were sent via regular mail at 1, 2 (patient only), 5, 8, and 11-months post-discharge. Reminders were tailored for each type of recipient (patient, family physician, or pharmacist); patient reminders used plain language and were refined via iterative usability testing to ensure comprehension.

Control group: No reminders above and beyond usual care were sent to the control group.

Randomization: Eligible participants were randomly allocated to intervention or usual care one week after the angiogram to permit time to identify and exclude patients with early in-hospital death. Once a patient from any family physician was randomized, all future participants seen by that family physician were automatically assigned to the same study arm.

Main Outcome Measure: Proportion taking all 4 guideline-recommended classes of cardiac medications (acetylsalicylic acid, angiotensin blockers, statin, and beta-blocker) at one year. Outcome

assessors were blind to group assignment. Logistic regression analysis, accounting for clustering by family physician and for repeated measures of the outcome at discharge, 3-months, and 1-year was used.

Results: 852 eligible participants were randomized to intervention (n=424, 287 clusters) and control (n=428, 295 clusters) (mean cluster size 1.8, variance 0.91); 85% in the intervention arm and 89% in the control arm completed 12-month follow-up. The proportions taking 4/4 medication classes at discharge were 73.6% and 75.5% in intervention and control arms, respectively. At 12 months, proportions were 58.4% and 58.9% in the intervention and control group, respectively, (adjusted OR 1.03, 95% CI 0.77-1.36). The process evaluation revealed that 51% of participants remembered receiving the intervention, and of these 52% discussed it with their health care provider. Participants reported that discontinuation of medication was most commonly at the direction of the internist/cardiologist (8.5%), and due to medication-related side-effects (8.1%).

Conclusion: The results suggest suboptimal persistence to all 4 of 4 cardiac medication classes at 12-months. There was no significant difference compared to usual care in the use of guideline-recommended medications post-STEMI when participants (and their family physicians) receive repeated postal reminders.

Trial Registration: clinicaltrials.gov (NCT01325116)

Introduction:

ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute coronary syndromes, constituting approximately 30% of all cases [2]. Post-STEMI, patients are at high risk for subsequent cardiac events (18% of men and 35% of women will have a repeat MI within six years) [90]. International guidelines emphasize the initiation and long-term maintenance of evidence-based secondary preventative therapies [21, 23,91]. Despite strong evidence supporting these guidelines, studies show that adherence to evidence-based cardiac therapies begins decreasing at 30 days and falls to as low as 50% adherence at six months post-discharge [5, 7, 12, 29, 31, 81]. Unfortunately, discontinuation of evidence-based therapies is associated with increased mortality in patients with coronary artery disease (CAD) [6, 8, 9, 25].

A study conducted by the authors identified the current Ontario trends in adherence to cardiac medications and factors associated with adherence to cardiac secondary prevention medications in patients in whom CAD was evident during angiography [12]. This study demonstrated four significant findings. First, there is poor persistence of cardiac medications in patients with identified CAD on angiography in the province of Ontario. Despite all patients having a class IA indication for the selected classes of medications (beta blockers, statins, and ACEI/ARB), and all patients having full medication coverage for financial costs (all patients \geq 65 years old), medication use steadily declined to approximately 60% by 18 months post-coronary angiogram [12]. Second, poor adherence was consistent across all subgroups of patients, highlighting the need for broad, population-based interventions to promote persistence of cardiac secondary prevention medications. Third, there are vulnerable periods at the time of prescription refills in which premature medication discontinuation may occur. Finally, it was found that the length of the initial prescription for a cardiac medication was the biggest predictor for medication persistence at follow-up [12].

Numerous studies have been published regarding interventions to improve adherence to medications. One previous trial has shown that brief evidence summaries regarding medications, attached to discharge letters sent to primary care providers resulted in improved adherence [102]. Two trials evaluated the role of reminder letters to the primary care provider (with or without patient reminders) to improve adherence to evidenced-based cardiovascular therapies [83, 86] demonstrating an absolute increase in medication use of 9-10%, but were underpowered for effects of that size. One trial demonstrated improved adherence, but not persistence to beta-blocker therapy post-MI with 2 reminders sent to the patient [84]. Recognizing that non-adherence tends to worsen over time, a recent Cochrane review recommended testing a delayed intervention as opposed to the immediate reminders used in similar previous trials, as one would expect a larger effect size in a delayed intervention [10]. Therefore, DERLA-STEMI was designed to evaluate the effects of delayed and repeated educational reminders on the proportion of participants who discontinue evidence-based secondary-prevention medications.

Methods:*Study Design:*

DERLA-STEMI is a pragmatic, cluster-randomized controlled trial (cRCT), conducted at a single tertiary care centre that services 22 hospital sites in one health region (population: 1.5 million) in Ontario, Canada. Details of the study protocol have been previously published [13].

Participants and Setting:

Eligible participants included adult participants with a diagnosis of STEMI, who underwent a coronary angiography procedure, with or without percutaneous coronary intervention (PCI) and who were discharged alive.

Intervention:

The intervention was developed in concert with clinical experts from both primary care and cardiology as well as experts in knowledge translation and medical decision-making. It consisted of personalized letters sent via the post to the patient and their family physician at one, five, eight, and

eleven months after their angiogram, signed by an interventional cardiologist on behalf of all invasive and interventional cardiologists from the PCI centre. The patient letter provided a review of the importance and role of each evidence-based cardiac medication and urged long-term adherence (Appendix 4-2). The intervention explicitly encouraged discussion of medication adherence with the family physician by asking participants to take the letter to their family physician. It also asked participants to take the final page of their letter to their pharmacist; this page urged pharmacists to participate in promoting long-term adherence. A brief reminder postcard was also mailed to the patient at 2 months (Appendix 4-1). The language was simplified to a grade 6 level and the intervention was developed iteratively to ensure understanding and acceptability amongst a series of cardiac care inpatients. The letter for the family physician identified the patient and provided brief evidence in support of long-term medication use (Appendix 4-3). This was refined based on discussions with family physicians from a different area of the province.

The timing of the intervention was specifically chosen based on data indicating that adherence starts decreasing by thirty days and continues to decrease in an almost linear fashion [12]. Finally, the common practice in Ontario is for pharmacists to dispense medications for no more than 3 months at a time (regardless of duration of the prescription ordered by the physician). Therefore, we decided to deliver the intervention at regular intervals (1, 2, 5, 8, and 11 months post-STEMI) corresponding to the likely time periods prior to participants requiring a prescription renewal/refill.

Control / Usual care:

The control group did not receive any intervention. In keeping with the pragmatic nature of the trial, no attempt was made to standardize the usual care arm.

Outcomes:

The primary outcome was the proportion of living participants who describe taking a statin, beta-blocker (BB), angiotensin blocker (ACEI or ARB), **and** ASA (acetylsalicylic acid) at 12 months (4 of 4 medication classes). We also assessed whether participants were taking these four medication classes

plus a secondary antiplatelet (clopidogrel, prasugrel, or ticagrelor) at three months (5 of 5 medication classes). Additional secondary outcomes included a comparison of (1) the proportion of participants who report actively taking each cardiac medication class of interest (item-by-item) at three and twelve months; (2) proportion of participants taking high dose statins at three and twelve months; (3) the proportion taking three medication classes concurrently at three and twelve months (3 of 4 medication classes); (4) the proportion of participants who report stopping medications due to side effects at three months; (5) the proportion of participants with a perfect Morisky Medication Adherence Score (MMAS) for cardiac medication adherence at three months [107], and (6) whether participants had discussed their medications with their family physician or specialist in the first three months following hospital discharge.

Baseline patient characteristics were obtained from standard patient-registry information. Outcomes were assessed through structured phone calls to the participant by a blinded research coordinator, following a previously published approach [115].

Sample Size:

The sample size required for this trial was 815 participants to achieve 80% power to detect a difference at the 5% significance level between intervention and control arms at 12 months, assuming: 80% follow-up, an absolute increase in the proportion of participants taking all four cardiovascular medication classes of 11%; an estimated control group proportion of 50%, and a variance inflation factor of 1.02. The variance inflation factor assumed an intra-cluster correlation coefficient of 0.019, calculated from data in the hospital registry and an average cluster size of 1.2, based on pilot data [13].

Descriptive data, was reviewed at 3 months as part of an ongoing STEMI registry that was previously underway [116].

Allocation and Blinding:

The randomization schedule was computer-generated, using a permuted block design with randomly varying block lengths of 4, 6 or 8. Eligible participants were randomly allocated 1:1 to

intervention or control. Randomization was carried out to ensure that, once a patient from any family physician was randomized, all future participants seen by that family physician were automatically assigned to the same arm to avoid contamination (with individual family physicians having participants in different arms of the study). Participants without a family physician at the time of randomization were enrolled and evaluated as each their own cluster. Randomization was delayed by one week (after the index angiogram) to permit time to identify and exclude patients with early in-hospital death. Randomization continued until the target sample size was achieved. The allocation sequence (individual participants and clusters) was concealed from the investigators and outcome assessors; only the study coordinator who sent out the letters had access to the un-blinded allocation list.

Ethics:

Local Research Ethics Board (REB) approval was received (#11-191). Given the low risk nature of the intervention, which falls within the realm of continuity-of-care and circle-of-care, the REB agreed that verbal consent at the time of outcome assessment was the most appropriate design to test this pragmatic intervention.

Statistical Analysis:

Baseline characteristics for participants in the intervention and control arms were described using means and standard deviations, or frequencies and percentages as appropriate. Outcomes at discharge, 3 months, and 12 months were analyzed using hierarchical logistic regression analyses accounting for clustering by family physician and correlations due to repeated measures on the same patient over time. Time (measured as a categorical variable), and the interaction between group and time were included as fixed effects, while the family physician and the patient were specified as random effects. The intervention effect was estimated as adjusted odds ratios with 95% confidence intervals. The following pre-specified baseline covariates were included as fixed effects: age<65 years; history of CAD; history of diabetes; medications prior to admission that includes ASA, any secondary antiplatelets (clopidogrel or other antiplatelets), ACEI/ARB, BB, and statins; in hospital blood transfusion; renal insufficiency,

defined as Creatinine Clearance ≤ 60 ml/min [117]; and participant enrolment in the TOTAL trial [118].

These covariates were included in the model, regardless of statistical significance, as they were considered to be important predictors of medication use at follow-up. We dichotomized age, as participants ≥ 65 years in Ontario have full medication insurance, and cost of medications can therefore be a factor in those < 65 years old. Younger age has also been associated with medication non-adherence, regardless of costs [71, 119]. Co-morbidities, including a history of CAD and diabetes, as well as prior medication use can influence future medication adherence [119-121]. Peri-ACS blood transfusions and renal dysfunction can limit future use of secondary preventative medications [122, 123]. Finally, some DERLA-STEMI participants were also enrolled in the TOTAL trial [118]. The TOTAL trial evaluated the impact of thrombectomy at the time of primary PCI and the authors were concerned that the close follow-up of participants in TOTAL could have influenced medication use [118]. For hierarchical models that yielded negative variance estimates for the family physician random effects, the intra-cluster correlation coefficient was assumed to be 0, and models were re-estimated using Generalized Estimating Equations (GEE) accounting for correlation in repeated measures on the same patient using an unstructured correlation matrix [114].

Secondary outcomes measured cross-sectionally were analyzed using GEE, accounting for clustering by family physician using an exchangeable correlation structure.

We performed all analyses using SAS, version 9.2 for UNIX and statistical significance was assessed at the 5% level.

Validity of Outcome Assessment:

One hundred and five consecutive participants, aged 65 years and older, underwent assessment of the accuracy of the self-reported primary outcome. Their medication lists were compared against their prescriptions filled as reported in the Ontario Drug Benefit database.

Process Evaluation:

A 20% random sample of participants in the intervention group was asked a series of additional, structured questions at the time of outcome assessment. This process evaluation was elicited after the outcome data was obtained and was designed to describe the acceptability of the intervention and the reasons for any (lack of) action taken. The answers to these questionnaires were summarized descriptively.

Results

Between September 2011 and December 2012, 852 participants from 466 family practices were randomized to intervention (n=424, 287 clusters) and control (n=428, 295 clusters) (mean cluster size 1.49, variance 0.91) (Figure 1). Of the 572 clusters, there were 106 clusters (18.5%) in which the participants did not have a FP but were still randomized. Ten FP had one patient in both the intervention and control arms, as the FP was unknown at the time of randomization. Recruitment ceased when the sample size was achieved. A total of 361 (85%) participants in the intervention arm and 380 (89%) in the control arm completed 12-month follow-up.

Baseline characteristics of participants who underwent randomization are presented in Table 1. The two groups were well balanced with a mean age of approximately 63 years old, 29% female, 19% with a Killip class 4, and 77% undergoing primary PCI. The intervention group had a higher proportion of diabetics (26.4% versus 18.9%), participants with a history of atrial fibrillation (5.9% versus 3.5%) and blood transfusions in hospital (5.2% versus 3.7%).

Primary Outcome:

The proportions taking 4/4 medication classes at discharge were 73.6% and 75.5% in intervention and control arms, respectively. At 12 months, observed proportions were 58.4% and 58.9% in the intervention and control group, respectively, (adjusted OR 1.03, 95% CI 0.77-1.36) (Table 2). In-hospital blood transfusion and renal dysfunction were the only variables found to be statistically significantly associated with adherence: both decreasing the odds of adherence. Figure 2 highlights the low baseline-use of cardiac medications before their STEMI, despite 84% of the study population

having a history of cardiovascular disease or a significant cardiac risk factor. At discharge, there is a marked increase in the prescription of evidence-based cardiac medications in both groups, with declining adherence over time: at 12 months, the odds of adherence to 4 of 4 medications (ASA, BB, ACEI/ARB, and statin) combined across groups was only 0.47 relative to baseline (95% CI 0.39-0.56).

Secondary Outcomes:

There were no significant differences between the intervention and control groups with respect to the use of 5 of 5 medications at 3 and 12 months (Table 3a). While there were no statistically differences in the use of ASA, BB, ACEI/ARB, or statins (high or low dose) at 12 months, there was a potentially important difference in proportion of participants in the intervention group on a second antiplatelet at one year compared to control (68.1% versus 62.1%, OR 1.36, 95% CI 0.99-1.85).

Table 3b highlights that medication adherence, as assessed by the MMAS, was statistically significantly better in the intervention group as compared to control (65.3% versus 58%, adjusted OR 1.35, 95% CI 1.01-1.81). There appears to be increased discussions of their medications with their health care providers in the intervention group, but this was not statistically significant (OR 1.67, 95% CI 0.95-2.93). There was a decreased attendance to cardiac rehab in the intervention (36.2%) versus control group (43.5%) (OR 0.74, 95% CI 0.55-1).

Participants in both groups reported that discontinuation of medication was most commonly at the direction of the internist/cardiologist (9.5% intervention and 7.4% control, P=0.29). Medication-related side-effects was the most common cause for medication discontinuation (9.5% intervention and 6.6 % control, P=0.83).

Validation of self-reported outcome:

Validation of the self-reported primary outcome revealed that 98%, 93%, and 97% of participants that reported they were taking a statin, BB and/or ACEI/ARB at 12 months, respectively, had medication prescriptions filled from their pharmacy.

Process Evaluation:

Of the 91 participants surveyed in the intervention group, only 46 (51%) recalled receiving the reminders. In this sample, 89% understood the contents of the letter, 50% took them to their health care provider, and 43% to their pharmacy. Only 30% agreed that the reminders helped them to take their medications and only 20% that it prompted them to renew their medications.

Discussion:

Our findings show that delayed and repeated educational reminders sent to the patient and family physician did not change the proportion of participants taking guideline-recommended cardiac medications at 12 months post-STEMI. This study was sufficiently powered to rule out clinically important differences in medication use at 12 months. However, there was a statistically significant benefit in the intervention group with respect to the secondary outcome, MMAS for medication adherence. This study is novel for two key reasons. First, to our knowledge, this is the largest study to assess the impact of delayed and repeated post-event reminders directed at the patient and family physician, with tear-outs for the pharmacist. Second, this trial utilized a pragmatic design in which every STEMI patient that survived to discharge was included. Verbal consent was obtained at the time of outcome assessment and loss-to-follow-up rates were minimal for such a pragmatic design (13% at 12 months). By capturing all possible participants with minimal selection criteria, this pragmatic evaluation of a quality improvement program supports generalizability of the results.

Our team has also conducted a systematic review of post-event automated reminder systems for improving adherence to medical recommendations among chronic disease [82]. This review indicates that automated reminder systems can increase adherence rates to medical recommendations, particularly if the following features are employed: (1) the intervention is delivered after hospital contact, (2) the reminders are repeated, (3) primary care physicians are included in the reminders, and (4) the reminders must be specific in reinforcing not only the intended behavior, but also the reasons for taking such action [82]. The DERLA STEMI intervention captured all four of these highlighted features and yet, the study

failed to detect an increase in adherence. Three key factors in the design and implementation of this study may account for the discrepancy in the DERLA study results as compared to the literature. First, the content and/or the design of the reminders used in this study may not have been adequate. While the reminders were developed in concert with clinical experts (in both primary care and cardiology), as well as researchers in knowledge translation and medical decision-making, we only tested the comprehensibility and acceptability of the intervention with patients while in hospital and thus the content may not have addressed the salient beliefs that affect medication adherence following discharge. Tailoring the message of the intervention to target specific sub-groups of patients could also be considered [82]. The letters were not sent directly to the patient's pharmacist or the outpatient cardiologist because data identifying these care providers was not collected in the registry. Finally, despite the mailing addresses of the participants being confirmed while they were in hospital, only 53% of participants recalled receiving the intervention. We think it is unlikely that they were mailed to the wrong address, but rather, it is more likely that the design and/or content was not salient enough for the patient to remember the intervention, let alone impact medication adherence.

A second factor that may have contributed to the lack of effect of the intervention is the chosen outcome measure. While self-reported medication non-adherence is associated with adverse cardiac events [124], the "all or none" definition of outcome for medication use at follow-up may not have been sufficiently sensitive to detect an effect of the intervention. The majority of post-event reminder studies use the proportion of days covered (PDC) or medication possession ratio (MPR) as a proxy for medication adherence [71, 82]. Unfortunately, this method of outcome assessment was not feasible for this pragmatic trial. A score of zero on the four-question MMAS is associated with a PDC of >80% [107], which has been shown to be associated with reduced mortality post-MI [8]. There was a statistically significantly greater proportion of participants in the intervention group with a score of zero

on the MMAS as compared to the control group (OR 1.35, 95% CI 1.01-1.81). This suggests that a more sensitive outcome measure may have detected a difference between the two groups.

Finally, the higher than expected rates of medication use at one-year follow-up may be another factor contributing to the findings of this trial. It was estimated that 50% of the control group would be taking 4 of 4 cardiac medications at one year but the measured rate was 59%. Furthermore, the use of individual cardiac medications at 12 months post-STEMI was 90% for statins and ASA, >80% for ACEI/ARB, and >75% for BB, all approaching expected benchmarks that take side-effects and contraindications into consideration [81]. These reasonable rates of evidence-based medication use one-year post-STEMI may be due to several factors: (1) a combination of full medication coverage for participants over 65 years-old in the province of Ontario and lower medication costs for those without insurance (all evidence-based cardiac medications classes are now available in a generic formulation) [26]; (2) the evidence for secondary prevention is well established with guidelines recommending the same classes of medications for over 8 years [125]; (3) STEMI is the most acute and symptomatic presentation of acute coronary syndromes, and thus may promote better medication adherence as compared to unstable angina and non-ST-elevation MI [120]; (4) the phone call follow-up at 3 months in both intervention and control groups, as part of the existing STEMI registry, may have positively influenced medication use at one year.

Our findings demonstrated that medications were most frequently discontinued by the physician, rather than the patient. The most frequent reason for discontinuation was medication-related side-effects. Similar findings have been previously reported in “real-world” studies [126]. It is likely that patients that experience medication-related side-effects express this concern to their physician, who then discontinue the medication, rather than the patient stopping the medication at their own discretion. We did find that medications were more often discontinued by the specialist (cardiologist or internist), rather than the family physician. Given, that the majority of the participants were being followed by a

specialist post-STEMI, it is hypothesized that the family physician would defer any cardiac medication-related concerns to the specialist involved in their care.

Limitations:

This study does have limitations. First, the results presented are only applicable to the exact interventions used in this study. Given significant effects seen in other studies, we cannot assume that a set of reminders, varied in design, content, timing or mode of delivery (text messaging, emails) would not improve medication use in the post-STEMI setting [82]. Second, this study used participant-reported phone call follow-up as the outcome assessment. As outlined above, PDC or MPR is a more sensitive measure of adherence [71]. Finally, this study did not capture outcomes related to cardiac medication use, including recurrent cardiac events.

Conclusion:

DERLA-STEMI demonstrates the feasibility of recruiting and randomizing all eligible STEMI patients in a provincial health region into a quality improvement program. The results suggest suboptimal but better than previously reported persistence to all 4 cardiac medication classes at 12-months. There was no significant difference in the use of guideline-recommended medications post-STEMI between those receiving delayed and repeated reminders versus usual care.

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Table 1: Baseline Characteristics of study participants. Table entries are frequency (%) unless otherwise indicated.

Characteristics*	Intervention (N=424)	Control (N=428)
Age (years) (Mean and SD)	63.3 (12.6)	62.4 (13.2)
Female	133 (31.4)	115 (26.9)
History of CAD	79 (18.6)	83 (19.4)
Previous PCI	41 (9.7)	45 (10.5)
Previous Stroke/TIA	22 (5.2)	19 (4.4)
Diabetes	112 (26.4)	81 (18.9)
Hypertension	211 (49.8)	204 (47.7)
Current Smoker	181 (42.7)	177 (41.4)
Dyslipidemia	154 (36.3)	157 (36.7)
History of Atrial Fibrillation	25 (5.9)	15 (3.5)
Any PCI	381 (89.9)	397 (92.8)
Primary PCI	322 (75.9)	335 (78.3)
Rescue PCI	32 (7.5)	33 (7.7)
Worst Killip Class 4	82 (19.3)	81 (18.9)
TIMI Score for STEMI (Mean and SD)	3.8 (2.5)	3.4 (2.3)
In Hospital Events:		
Re-MI	4 (0.9)	4 (0.9)
PCI	42 (9.9)	35 (8.2)
CABG	21 (5.0)	16 (3.7)
Stroke	2 (0.5)	3 (0.7)
Blood Transfusion	22 (5.2)	16 (3.7)
Medications at Discharge:		
ASA	418 (98.6)	422 (98.6)
Secondary Antiplatelet	393 (92.7)	397 (92.8)
ACEI/ARB	362 (85.4)	377 (88.1)
Beta-blocker	372 (87.7)	372 (86.9)
Statin	403 (95)	408 (95.3)

*CAD=Coronary Artery Disease, PCI=Percutaneous Coronary intervention, TIA=Transient Ischemic Attack, TIMI=Thrombolysis in Myocardial Infarction, STEMI=ST-elevation Myocardial infarction, CABG=Coronary Artery Bypass Grafting

Table 2: Longitudinal logistic regression analysis of the primary outcome measure: 4 of 4 cardiac medications

Variable	Adjusted Odds Ratio (OR)	95% Confidence Interval (CI) for OR
Treatment vs. Control		
3 months	1.10	0.83-1.45
12 months	1.03	0.77-1.36
Blood Transfusion	0.38	0.22-0.66
Age <65 years	1.12	0.88-1.43
History of CAD	0.80	0.57-1.13
History of DM	0.90	0.67-1.19
Prior ASA	0.89	0.64-1.23
Prior Secondary Antiplatelet	0.70	0.41-1.19
Prior ACEI/ARB	1.32	0.96-1.81
Prior Beta-blocker	1.18	0.81-1.72
Prior Statin	1.06	0.77-1.45
Renal Dysfunction	0.70	0.52-0.94
Enrollment in the TOTAL trial	1.14	0.90-1.45

*CAD=Coronary Artery Disease, DM=diabetes mellitus, ASA=acetylsalicylic acid, ACEI=Angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker

Table 3a: Secondary Outcomes for treatment versus control

Variable ¹	Intervention		Control		Adjusted OR	95% CI for OR
	Frequency	%	Frequency	%		
5/5 Medications at 12 months	152	42.1	156	41.1	1.12	0.84-1.5
3/4 medications at 12 months	286	79.5	306	80.5	0.92	0.67-1.26
ASA at 12 months	334	92.5	349	91.8	1.09	0.63-1.88
2 nd Anti-platelet at 12 months	246	68.1	236	62.1	1.36	0.99-1.85
ACEI/ARB at 12 months	294	81.4	327	86.1	0.71	0.48-1.04
BB at 12 months	281	77.8	285	75.0	1.14	0.80-1.61
Statin at 12 months	322	89.2	345	90.8	0.89	0.55-1.45

¹OR=Odds ratio (refers to intervention versus control), CI=Confidence intervals, ASA=acetylsalicylic acid, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker, BB =beta blocker

Table 3b: Secondary Outcomes Continued

Variable ¹	Intervention		Control		Adjusted Analysis	
	Frequency	%	Frequency	%	OR	95% CI
Discussed Medications with Family physician/ Specialist***	305	80.7	294	77.6	1.67	0.95-2.93
Perfect MMAS Score at 3 months**	247	65.3	220	58.0	1.35	1.01-1.81
Attendance to Cardiac Rehab at 3 months*	137	36.2	165	43.5	0.74	0.55-1.00

¹OR=Odds ratio (refers to intervention versus control), CI=Confidence intervals, MMAS= Morisky Medication Adherence Score, CAD= Coronary Heart Disease, ASA=acetylsalicylic acid, ACEI=Angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker

*** Adjusted by HX CAD, In TOTAL study, Hx ASA, Hx 2ndary Antiplatelets, Hx ACE/ARB, Hx BB, Hx Statins

**adjusted by HX CAD, In TOTAL study, Hx ASA, Hx 2ndary Antiplatelets, Hx ACE/ARB, Hx BB, Hx Statins, Age<65yrs, Hx DM, Hosp Blood transfusion, Renal dysfunction

* Adjusted by HX CAD, In TOTAL study

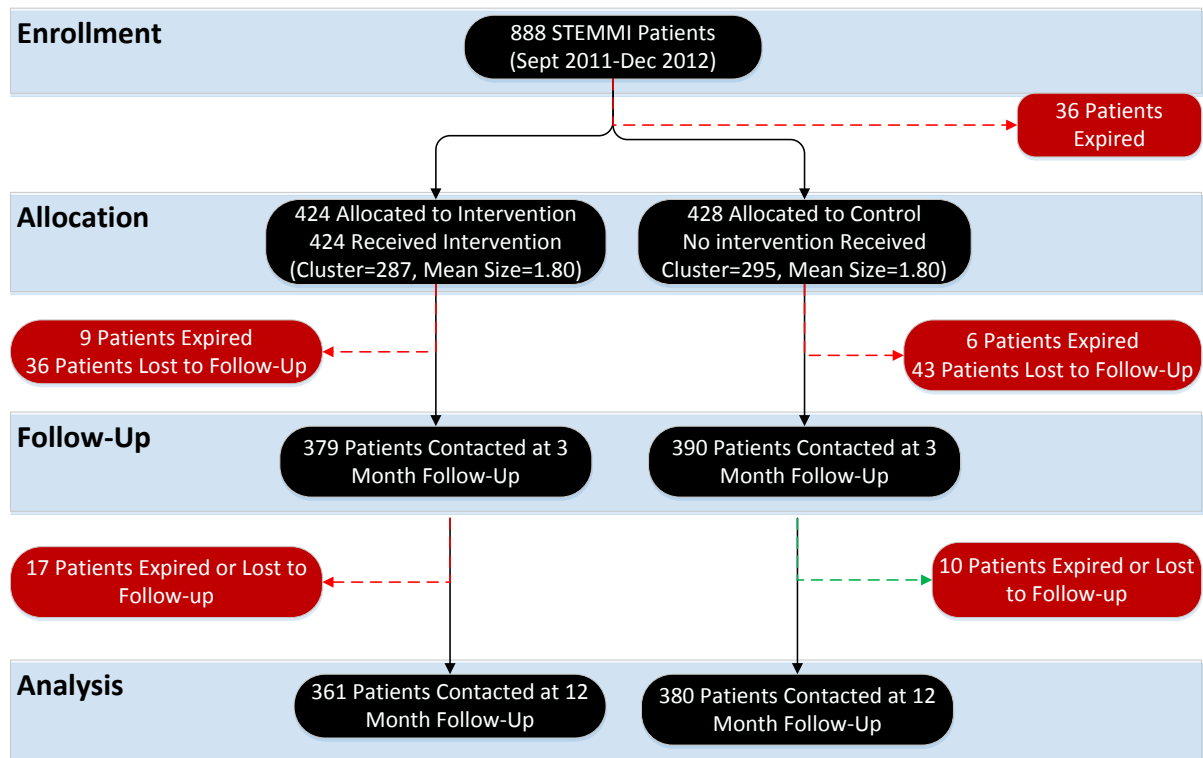


Figure 1: Flow Diagram of progress of clusters and individuals through phases of RCT

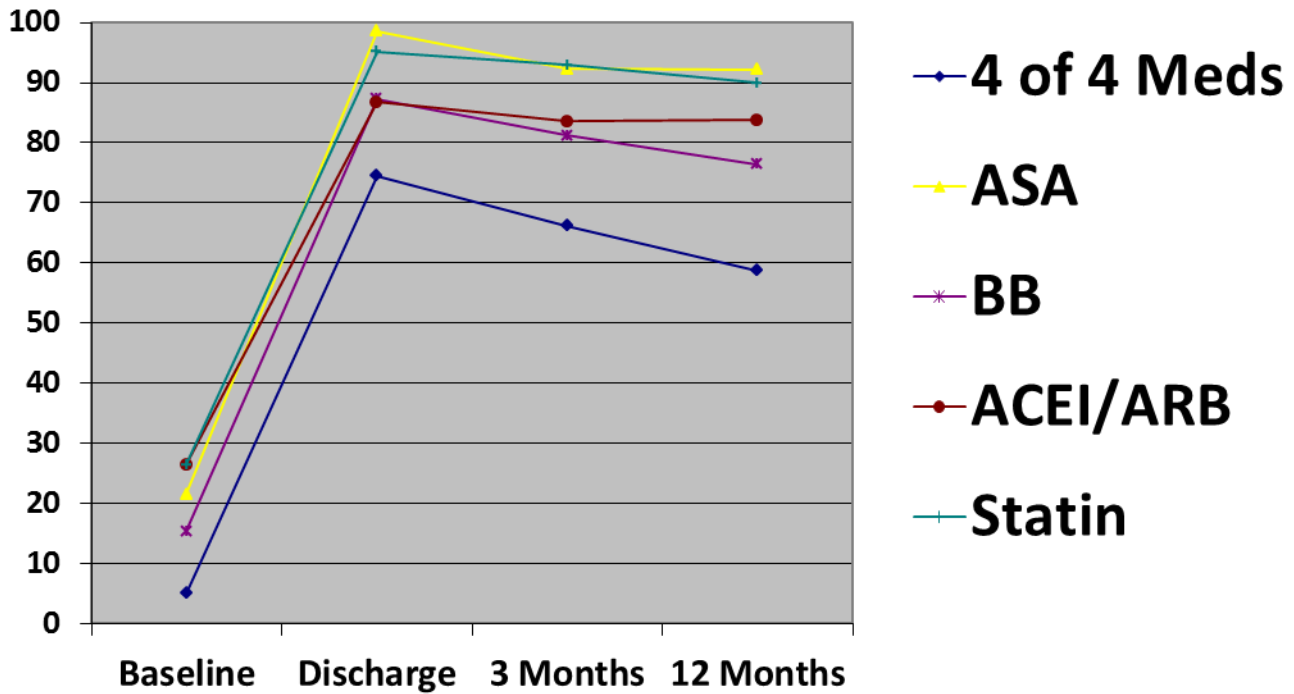


Figure 2: Trends in percent of medication use at baseline, discharge, 3 months and 12 months. The OR for 4 of 4 medication (ASA, BB, ACEI/ARB, and statin) use between discharge and 12 months for both groups combined is 0.47, 95%CI 0.39-0.56.

* OR=Odds ratio (refers to discharge versus 12 months), CI=Confidence intervals, BB = Beta Blocker, ASA=acetylsalicylic acid, ACEI=Angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blocker

Chapter 6: “Discussion and Sustain Knowledge Use”

Jon-David Schwalm¹

¹University of Ottawa and McMaster University/Hamilton Health Sciences/Population Health Research
Institute

**Department of Epidemiology and Community Medicine
Faculty of Medicine
University of Ottawa**

Summary of the KTA Framework:

This thesis presents a program of KT research to promote the use of secondary prevention cardiac medications. Following the KTA framework [11], a solid foundation of evidence supporting the use of cardiac medications in patients with established CAD was first identified (Chapter 2). Next, the evidence-practice gap was confirmed using provincial administrative databases (Chapter 3). In Chapter 4, the intervention was developed and adapted to the local context (Hamilton Health Sciences). Finally, the intervention designed to promote cardiac medication use, was evaluated in a cRCT of over 850 patients post-STEMI (Chapter 5). This discussion will highlight the novel findings presented in this thesis and the key limitations of the two studies. Furthermore, to complete the KTA framework, we will discuss plans for future research, and implications to health policy and clinical practice as it relates to the sustainability of the potential KT interventions.

Novel Findings:

This thesis had two primary objectives. The first objective was to identify the current Ontario trends in adherence to cardiac medications and factors associated with adherence to cardiac secondary prevention medications in patients in whom CAD was evident during angiography. This section of the thesis was novel for four reasons. First, using administrative data from the province of Ontario, it was demonstrated that there is poor persistence of cardiac medications in patients with identified CAD. Despite all patients having a class IA indication for the selected classes of medications (beta blockers, statins, and ACEI/ARB), and all patients having full medication coverage for financial costs (all patients ≥ 65 years old), medication use steadily declined to approximately 60% by 18 months post-coronary angiogram [12]. Second, this study also showed that poor adherence was consistent across all subgroups, highlighting the need for broad, population-based interventions to promote persistence of cardiac secondary prevention medications. Third, this population study highlighted vulnerable periods at the time of prescription refills in which premature medication discontinuation may occur. Finally, it

was found that the length of the initial prescription for a cardiac medication was the biggest predictor for medication adherence at follow-up. This finding has been described in two other smaller studies, both looking at individual medication use in cardiac patients (digoxin and statins) [65, 66]. The research presented in Chapter 3 is the *only* (1) population-based study to report the significant impact of initial prescription length on the adherence to (2) multiple classes of cardiac medications. Such findings warrant further investigation (See Limitations and Next Steps).

The second objective of this thesis was to assess if repeated mailing of an educational reminder to the FP and the patient would decrease the proportion of patients who discontinue evidence-based secondary prevention medications at 12 months post-STEMI. This section of the thesis was novel for two reasons. First, the results of DERLA STEMI trial suggest suboptimal persistence to all 4 cardiac medication classes (Aspirin, beta blocker, statin, ACEI/ARB) at 12-months post-STEMI but better than previously reported persistence to the individual medications. Second, there was no significant difference in the primary outcome of guideline-recommended medication use post-STEMI in those receiving delayed and repeated reminders as compared to usual care. However, there was a statistically significant increase in medication adherence, as measured by the MMAS (secondary outcome), in the intervention group (65.3% versus 58%, adjusted OR 1.35, 95% CI 1.01-1.81).

Limitations:

The research presented in this thesis has several limitations that warrant discussion. Such limitations have been outlined in the chapter 3 (introduction and manuscript) and 5 (manuscript), but the key limitations will be reviewed in this section. While the DERLA baseline study (chapter 3) has limitations including the pitfalls of administrative databases, the outcome measures used, and limited generalizability of the findings to those under 65 years old, the primary limitation of the study is the design [12]. Given this was a non-randomized observational study; caution must be taken in the interpretation of the study findings. The non-randomized design cannot fully address all known and

unknown biases. However, given the size of the study population (18000 patients), the robustness of the findings, the replication of the results in other similar studies [65, 66], and the fact that the results make clinical sense, it is hypothesized that prescription length does positively affect long-term medication adherence.

The key limitation identified in the DERLA STEMI trial (chapter 5), relates to the method of the outcome assessment. The DERLA STEMI trial used an “all or none” primary outcome for medication use at 12 months. This outcome measure was chosen due to the limitations with phone call follow-up as part of the pragmatic design. The proportion of days covered (PDC) or medication possession ratio (MPR) is a continuous variable that more accurately reflects medication adherence and is more commonly used as a proxy for medication adherence in other post-event reminder trials [71, 82]. The DERLA STEMI trial did demonstrate a statistically significant improvement in medication adherence in the intervention group as measured by the MMAS. The MMAS is better associated with PDC as compared to the “all or none” primary outcome used in the DERLA STEMI trial [107]. This suggests that a more sensitive outcome measure may have detected a difference between the two groups and the findings would be more consistent with those of other post-event reminder studies [82].

Plans for Future Research:

Prescription Duration:

The DERLA baseline study identified that the duration of the initial prescription post-coronary angiogram, was the biggest predictor of long-term adherence to guideline recommended therapies [12]. This finding was robust, with an odds ratio of 4.0 (95% CI 3.6-4.7) for ACEI/ARBs for a three-month prescription versus a one-month prescription [12]. The findings were consistent across all cardiac medications evaluated. Furthermore, the effect size was proportional to the duration of the prescription with better long-term adherence with a 3- versus 2- versus 1-month prescription [12]. This finding

makes clinical sense as shorter prescriptions may cause an increased inconvenience for the patient and added pharmacy dispensation fees that in-turn promote reduced medication adherence.

The findings in the DERLA baseline study have led to a sub-study of the DERLA STEMI cRCT (REB approval-Amendment 11-191). Confirmation of the length of the initial prescription of cardiac medications post-STEMI, as a predictor of long-term medication adherence, is being evaluated in a sub-group of patients in the DERLA STEMI cRCT that were discharged from a Hamilton Health Sciences Hospital. This sub-group has been selected as the investigators have access to scanned copies of patient's discharge prescriptions on the hospitals' computerized medical record system. 538 patients will be included in this sub study (63% of the DERLA STEMI study population). The length of the initial prescription will be evaluated as a predictive variable for medication use at 12-months follow-up and MMAS at 3 months.

The ISLAND ACS Study:

As outlined in the discussion of Chapter 5, we do not think that reminders promoting the use of long-term secondary preventative medications post-STEMI should be abandoned as a KT intervention based on the results of the DERLA STEMI trial. The results presented in Chapter 5, are only applicable to the exact interventions used in the DERLA STEMI study. A contemporary systematic review and meta-analysis of automated post-event reminders for improving adherence to medical recommendations is being submitted for publication [82]. This review highlights the benefits of post-health event reminders, with a RR of 1.30, 95% CI 1.09-1.58. [82]. Given the significant effects seen in this review, we cannot assume that a set of reminders, varied in design, content, timing or mode of delivery (text messaging, emails, telephone calls) would not improve medication use in the post-STEMI setting [82]. Therefore, the investigators of DERLA STEMI, have successfully secured funding from the Ministry of Health (\$1,039,155.92) to further evaluate post-ACS reminders to promote both attendance to cardiac rehabilitation programs and medications use (Appendix 6-1, Summary).

The ISLAND ACS study will implement and evaluate province-wide systems for providing reminders to cardiac patients and their primary care providers in the year following an ACS. Working with provincial decision makers and cardiac centers around the province, the investigators will conduct an RCT to compare both the effectiveness and the cost of strategies to improve adherence to proven therapies. The first stage of the ISLAND ACS trial will involve refinement of the DERLA STEMI mail-out reminder intervention through an iterative process of patient surveys, interviews, and user-testing with the help of experts in Knowledge translation, clinical cardiology, behavioral psychology, and human factors research. Furthermore, this process will also evaluate the changes in patient perceptions over time following discharge from hospital. This stage will also involve the development of an automated phone call algorithm and lay-health worker training. The second stage of the study will entail a three-arm RCT with all eligible patients post-ACS being randomized to (1) recurrent, tailored postal reminder letters to patients and their family physician, OR (2) letters to patients and their physician plus automated phone calls with interactive voice response and lay-health worker (with nurse back-up) telephone follow-up to patients reporting discontinuation of treatments, OR (3) usual care.

Implications for Clinical Practice and Health Policy:

The research presented in this thesis has potential implications for both clinical practice and health policy. First, if the findings in chapter 3, relating to prescription length and long-term medication use, are confirmed in the DERLA-STEMI sub-study that is currently underway, then this low-cost and low-risk intervention could be easily sustained and implemented at a population level. Hospital ACS standardized discharge prescriptions orders could be easily revised to support three-month dispensation of cardiac medications. However, it could be argued that the observational study presented in this thesis (chapter 3) and the sub-study of DERLA STEMI that is currently underway, is not enough to support wide-spread recommendations for the increased length of prescriptions. Furthermore, evaluation of the patient and provincial costs potentially associated with longer prescriptions should be undertaken.

Second, The DERLA STEMI trial results demonstrate that there is insufficient evidence to support widespread adoption of patient reminders in the province of Ontario. However, given the findings of our systematic review [82], further rigorous evaluation of ‘optimized’ reminders is warranted. Furthermore, the relative low cost and scalable nature of an intervention with even a small increase in medication adherence might be efficient.

Finally, both the DERLA STEMI intervention and the ISLAND ACS interventions were designed to be evaluated and implemented using established infrastructures, including existing registries at Hamilton Health Sciences (SMART AMI) and the province of Ontario (CCN/ICES). The pragmatic designs for the implementation and evaluation of these KT interventions will help facilitate its wide-scale implementation. Using an integrated KT approach for both studies, by including key stakeholders in their design and implementation (patients, physicians, hospital administrators, and provincial partners including CCN, ICES, and the Ministry of Health and Long-Term Care) will ensure that the research results meet decision makers’ needs and increases the likelihood of translating the findings to policy.

Conclusion:

Significant evidence-practice gaps exist in the province of Ontario with respect to the persistence of secondary preventative medications in all sub-groups of patients with CAD. These gaps worsen with time from the index-event. The DERLA-STEMI trial demonstrates the feasibility of recruiting and randomizing all eligible STEMI patients in a provincial health region into a quality improvement program to address the identified evidence-practice gaps. There was no significant difference in the use of guideline-recommended medications post-STEMI in those receiving delayed and repeated reminders as compared to usual care in the DERLA STEMI trial. However, an increase in medication adherence as measured by the MMAS was identified in the intervention group. Further refinement of the DERLA STEMI mail-outs and assessment of novel mechanisms to deliver post-event reminders is required and underway.

Appendix

Appendix 1-1: CCS Montreal Abstract 2013 (Oral Presentation-Published)

Schwalm JD, Ivers N, Witteman HO, Taljaard M, RaoMelacini P, Zwarenstein M, Grimshaw J, Natarajan MK. Pragmatic, cluster-randomized controlled trial of Delayed Educational Reminders for Long-term medication Adherence in ST-Elevation Myocardial Infarction (DERLA-STEMI). *Canadian Journal of Cardiology* 2013; 29: S265.

Background: Discontinuation of guideline-recommended cardiac medications post- ST-elevation myocardial infarction (STEMI) is common and associated with increased mortality. DERLA-STEMI tests an intervention aiming to improve long-term persistence to cardiac medications post-STEMI.

Methods: Between September 2011 and December 2012 STEMI patients from one health region in Ontario, who underwent an angiogram during their admission and survived to discharge, were cluster-randomized to a quality improvement initiative. Patients with the same family physician, received the same intervention, to avoid contamination. The intervention is an automated system that sends recurrent, personalized, educational-reminders to the patient, their family physician, and their pharmacist urging long-term use of secondary-prevention medications. Interventions are sent via regular mail at 1, 2, 5, 8, and 11 months post-discharge. Reminders are tailored for each type of recipient; patient reminders use plain language and were refined via iterative usability testing to ensure comprehension. The primary outcome is the proportion of patients taking all 5 guideline-recommended classes of cardiac medications (ASA, second antiplatelet, ACEI/ARB, statin, and beta-blocker). Interim 3-month feasibility results are reported, along with data from an embedded process evaluation.

Results: 861 eligible patients were randomized (intervention=415, control=446); 89% in the intervention arm and 88% in the control arm have completed 3-month follow-up. The baseline characteristics in the two groups were well balanced: mean age 63, 29% female, 23% diabetics, 21% Killip 4, and 76% undergoing primary PCI. The proportions taking all 5 medication classes at discharge were 60.7% and 64.8% in intervention and control arms, respectively. At 3 months, proportions were 54.4% intervention and 54.8% control. Of patients on 5/5 medication classes at discharge (n=221 in intervention and 252 in control), 73.8% intervention and 70.2% control were still taking 5/5 at 3 months (absolute difference in persistence, 3.6%). Patients reported that discontinuation of medication was most commonly at the direction of the internist/cardiologist (64%), and due to medication-related side-effects (62%). The process evaluation indicates that 59% of patients remembered receiving the intervention, and of these 53% took it for discussion with their health care provider.

Discussion: DERLA-STEMI demonstrates the feasibility of recruiting and randomizing all eligible STEMI patients in a provincial health region. Preliminary results suggest low persistence to all 5 cardiac medication classes at 3-months. A small absolute difference in early medication persistence between the groups after only 3-months, indicates the promise of this readily scalable and sustainable intervention. Long-term follow up is ongoing.

Appendix 1-2: CCS Vancouver Abstract 2014 (Oral Presentation-Accepted)

13/5/2014

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Author Block: JR Schwalm, NM Ivers, MK Natarajan, M Taljaard, P Rao-Melacini, H Witteman, M Zwarenstein, JM Grimshaw
Hamilton, Ontario

Abstract:

Background: Discontinuation of guideline-recommended cardiac medications post-ST-elevation myocardial infarction (STEMI) is common and associated with increased mortality. DERLA-STEMI tests an intervention aiming to improve long-term adherence to cardiac medications post-STEMI.

Methods: Between September 2011 and December 2012, STEMI patients from one health region in Ontario, who underwent an angiogram during their admission and survived to discharge, were cluster-randomized (by primary care provider) to a quality improvement initiative. The intervention is an automated system that sends recurrent, personalized, educational-reminders to the patient, their family physician, and their pharmacist urging long-term use of secondary-prevention medications. Interventions are sent via regular mail at 1, 2, 5, 8, and 11-months post-discharge. Reminders are tailored for each type of recipient; patient reminders use plain language and were refined via iterative usability testing to ensure comprehension. No reminders were sent to the control group. The primary outcome is the proportion of patients taking all 4 guideline-recommended classes of cardiac medications (ASA, ACEI/ARB, statin, and beta-blocker) at one year. Outcome assessors were blinded to the group assignment. Logistic regression with Generalized Estimating Equations was used to account for repeated measures of the outcome at baseline, 3-months, and 1-year.

Results: 852 eligible patients were randomized (intervention=424, control=428); 85% in the intervention arm and 89% in the control arm have completed 12-month follow-up. The baseline characteristics in the two groups were well balanced: mean age 63, 29% female, 23% diabetics, 19% Killip 4, and 77% undergoing primary PCI. The proportions taking 4/4 medication classes at discharge were 73.6% and 75.5% in intervention and control arms, respectively. At 12 months, proportions were 58.4% and 58.9% in the intervention and control group, respectively, (model-based OR 1.1, 95% CI 0.83-1.45). The process evaluation indicates that 51% of patients remembered receiving the intervention, and of these 52% took it for discussion with their health care provider. Patients reported that discontinuation of medication was most commonly at the direction of the internist/cardiologist (64%), and due to medication-related side-effects (62%).

Discussion: DERLA-STEMI demonstrates the feasibility of recruiting and randomizing all eligible STEMI patients in a provincial health region. Preliminary results suggest low persistence to all 4 cardiac medication classes at 12-months. There was no significant difference in the use of guideline-recommended medications post-STEMI in patients (and their family physicians) receiving delayed and repeated reminders as compared to usual care. This trial is registered with clinicaltrials.gov (NCT01325116) and funded by the NIF at Hamilton Health Sciences.

:

Author Disclosure Information: J.R. Schwalm: None. N.M. Ivers: None. M.K. Natarajan: None. M. Taljaard:

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None. **P. Rao-Melacini:** None. **H. Witteman:** None. **M. Zwarenstein:** None. **J.M. Grimshaw:** None.

Awards (Complete):

*Do you wish to be considered for an award?: No

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Learning Track (Complete): CAD-ACS & AMI

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: Clinical Science

***Organization:** Canadian Cardiovascular Society (CCS)

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Appendix 3-1: Supplementary Analysis for DERLA Baseline (A)

Table S1: Patient characteristics and proportion of patients with high adherence in the patient cohort for each of the medications of interest. *

	ACE-I/ARB N=13,305	BB N=5,792	Statin N=16,134
	High adherence n=9,504 (71%)	High adherence n=3,827 (66%)	High adherence n=12,868 (80%)
Demographics:			
Age (Mean ± SD)	74.54 ± 6.02	75.20 ± 6.43	74.54 ± 6.04
Male	6226/8778 (70.9%)	2410/3744 (64.4%)	8750/10837 (80.7%)
Female	3278/4527 (72.4%)	1417/2048 (69.2%)	4118/5297 (77.7%)
Rural	1432/1965 (72.9%)	587/865 (67.9%)	1923/2410 (79.8%)
Urban	8072/11340 (71.2%)	3240/4927 (65.8%)	10945/13724 (79.8%)
Income quintile 1 (lowest)	1763/2558 (68.9%)	779/1164 (66.9%)	2347/3000 (78.2%)
Income quintile 5 (highest)	1894/2574 (73.6%)	689/1076 (64.0%)	2641/3255 (81.1%)
Indication:			
NSTEACS	4200/5876 (71.5%)	2404/3653 (65.8%)	5512/6928 (79.6%)
STEACS	1025/1348 (76.0%)	1111/1701 (65.3%)	1400/1701 (82.3%)
Non-ACS	4279/6081 (70.1%)	312/438 (71.2%)	5956/7505 (79.4%)
Disease severity:			
1 vessel	3392/4678 (72.5%)	1340/2080 (64.4%)	4636/5893 (78.7%)
2 vessels	2593/3586 (72.3%)	1062/1593 (66.7%)	3452/4328 (79.8%)
3 vessels	2223/3136 (70.9%)	930/1365 (68.1%)	2891/3618 (79.9%)
Left main	1296/1905 (68.0%)	495/754 (65.6%)	1889/2295 (82.3%)
Treatment:			
CABG	1823/2904 (62.8%)	702/1131 (62.1%)	2862/3533 (81.0%)
Medical management	3298/4622 (71.4%)	1050/1505 (69.8%)	4199/5460 (76.9%)
PCI	4383/5779 (75.8%)	2075/3156 (65.7%)	5807/7141 (81.3%)
Ejection Fraction:			
<35%	932/1220 (76.4%)	686/965 (71.1%)	1098/1374 (79.9%)
35-50%	1539/2112 (72.9%)	895/1308 (68.4%)	1908/2343 (81.4%)
>50%	3363/4780 (70.1%)	955/1518 (62.9%)	4756/6006 (79.2%)
Other Comorbidities:			
Mental health disorder	1493/2199 (67.9%)	586/930 (63.0%)	2087/2660 (78.5%)
Past MI	3208/4433 (72.4%)	1925/3395 (56.7%)	4111/5169 (79.5%)
Past CABG	1988/2616 (76.0%)	541/775 (69.8%)	2452/3017 (81.3%)
Past CVA/TIA	860/1265 (68.0%)	336/519 (64.7%)	1074/1396 (76.9%)
PVD	1021/1443 (70.8%)	350/570 (61.4%)	1225/1573 (77.9%)
CCS 1 or 2	3332/4746 (70.2%)	392/583 (67.2%)	4682/5906 (79.3%)
CCS 3 or 4	6172/8559 (72.1%)	3435/5209 (65.9%)	8186/10228 (80.0%)
NYHA 1 or 2	8555/11906 (71.9%)	3299/5011 (65.8%)	11675/14554 (80.2%)
NYHA 3 or 4	949/1399 (67.8%)	528/781 (67.6%)	1193/1580 (75.5%)
Hypertension	8651/12054 (71.8%)	2785/4070 (68.4%)	9598/12054 (79.6%)
Hyperlipidemia	7560/10530 (71.8%)	2511/3690 (68.0%)	9604/11871 (80.9%)
Smoking	4696/6561 (71.6%)	1814/2828 (64.1%)	6249/7778 (80.3%)
COPD	665/970 (68.6%)	291/471 (61.8%)	883/1132 (78.0%)
Diabetes	3716/5053 (73.5%)	1247/1804 (69.1%)	3977/5053 (78.7%)
Previous adherence[^]	7746/9570 (80.9%)	2311/3292 (70.2%)	9282/10657 (87.1%)

* Number with high adherence at 540 days, the total number with characteristic, and the proportion is reported for each cell, unless otherwise noted. [^] High adherence to prescription of interest during 12 months prior to angiography. ACE-I/ARB = ACE-inhibitors or angiotensin receptor blockers; BB = beta blockers; NSTEACS = non-ST elevation acute coronary syndrome; STEACS = ST elevation acute coronary syndrome; non-ACS = non acute coronary syndrome; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; MI = myocardial infarction; CVA/TIA = cerebrovascular attack / transient ischemic attack; PVD = peripheral vascular disease; COPD = chronic obstructive pulmonary disease

Appendix 4-1: Post card to patients



Personal and Confidential for: John Doe

If you are not **John Doe**, please call immediately:
XXX-XXX-XXXX.

We sent you a letter a month ago about how
taking the right pills can protect your heart.

Most people who have a heart attack should take 5 kinds of pills each day for a long time: *Blood thinners* (usually aspirin combined with either clopidogrel, prasugrel, or ticagrelor), cholesterol pill (*statin*), and blood pressure pills (*beta-blocker*, and *ACE-inhibitor* or *ARB*).

Bring your pills to your doctor and **make sure you are taking the right pills** for your heart.

In case you did not get our letter last month, we have included a copy in this envelope.

Sincerely,

Dr. J-D Schwalm on behalf of the cardiologists at
the Heart Investigation Unit,
Hamilton Health Sciences

Appendix 4-2: Reminder letter to patient

PERSONAL AND CONFIDENTIAL FOR [PATIENT NAME]

If you are not John Doe, please tell us immediately by calling XXX-XXX-XXXX

Date: DD-MMM-YYYY

Dear Mr. [PATIENT LAST NAME],

In [MONTH, YEAR], we cared for you in our hospital after you had a heart attack. A heart attack can be a very difficult event. We hope you are feeling better these days.

As you may already know, once you have had a heart attack, you have a higher risk of having another heart attack or a stroke. Fortunately, there are ways you can lower your risk of future heart attacks and strokes.

Even if your lifestyle is very healthy, scientific research has clearly shown that **taking the right pills will lower your risk** of future heart attacks and strokes.

Make sure you are taking the right pills

Please bring this letter and all your pills with you to your next appointment with your family doctor and heart doctor (also called a cardiologist).

Talk to your family doctor and heart doctor about the 5 kinds of pills listed in this box. The same kind of pill can be called by different names. Make sure you are taking the right pills for you.

National medical guidelines strongly recommend that patients who have had a heart attack take these 5 pills for a long time. For most of the pills, a long time means for the rest of your life.

- Cholesterol Pills
 1. Cholesterol pills are called 'statins'. A statin keeps cholesterol from building up on the inside of the walls of your blood vessels. Taking a statin is important because it will significantly lower your risk of future heart attacks or strokes, even if your cholesterol number is already low.

(continued on the next page ...)

- Blood Thinners (both of the following):
 2. Aspirin prevents heart attacks and strokes by making your blood less 'sticky'.
 - and*
 3. Clopidogrel (Plavix) also makes your blood less sticky, especially in patients who have had an 'angioplasty' (balloon and stent to open the artery and help keep it open.) Unlike the other pills, this pill may be taken for as little as one month or up to two years, depending on your heart doctor's recommendations.
- Blood Pressure Medications (both of the following)
 4. An 'ACE Inhibitor' or 'ARB' has a special, protective effect for your heart. It lowers your blood pressure and also does other things that help keep your heart healthy.
 - and*
 5. A 'beta-blocker' protects your heart by making sure that it does not beat too fast or work too hard.

It is important to take your heart pills every day. Taking your pills as directed will make you less likely to have heart attacks and strokes in the future.

Most people who have had a heart attack should take most of these pills for the rest of their lives. However, some people have important reasons to stop or never take these medications, including other medical conditions, side effects, or allergies. For these people, other pills may be available.

Talk to your doctor about your pills

It is important to talk about all of your medications with your doctor **on a regular basis**.

Lifestyle changes help, too

In addition to taking your heart pills, you can also lower your risk of future heart attacks and strokes by living a healthy lifestyle. If you are a smoker, you need to try to quit. If you have trouble quitting, cutting back is better than nothing. Exercising at least 4 times each week and eating a heart-healthy diet will also help your heart.

See the next page for groups that can help you live a healthy lifestyle. You can also ask your doctor to refer you to a program called 'cardiac rehab' to help you make these changes.

Even if you live a healthy lifestyle, it is still very important that you keep taking your pills. Your best chance of staying healthy happens when you live a healthy lifestyle and take the right pills.

- Blood Thinners (both of the following):
 2. Aspirin prevents heart attacks and strokes by making your blood less 'sticky'.
 - and*
 3. Clopidogrel (Plavix) also makes your blood less sticky, especially in patients who have had an 'angioplasty' (balloon and stent to open the artery and help keep it open.) Unlike the other pills, this pill may be taken for as little as one month or up to two years, depending on your heart doctor's recommendations.
- Blood Pressure Medications (both of the following)
 4. An 'ACE Inhibitor' or 'ARB' has a special, protective effect for your heart. It lowers your blood pressure and also does other things that help keep your heart healthy.
 - and*
 5. A 'beta-blocker' protects your heart by making sure that it does not beat too fast or work too hard.

It is important to take your heart pills every day. Taking your pills as directed will make you less likely to have heart attacks and strokes in the future.

Most people who have had a heart attack should take most of these pills for the rest of their lives. However, some people have important reasons to stop or never take these medications, including other medical conditions, side effects, or allergies. For these people, other pills may be available.

Talk to your doctor about your pills

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See the next page for groups that can help you live a healthy lifestyle. You can also ask your doctor to refer you to a program called 'cardiac rehab' to help you make these changes.

Even if you live a healthy lifestyle, it is still very important that you keep taking your pills. Your best chance of staying healthy happens when you live a healthy lifestyle and take the right pills.

Keep your heart as healthy as possible

Since we cared for you while you were admitted with a heart attack, we feel it is very important to remind you about how to lower your risk of future heart attacks and strokes.

Taking the right pills and living a healthy lifestyle will help keep your heart as healthy as possible, for as long as possible.

Sincerely,

Dr. J-D Schwalm on behalf of the cardiologists at the Heart Investigation Unit
Hamilton Health Sciences, General Site

P.S. While waiting for your next appointment with your doctor, here are some other ways you can get information:

Quitting smoking:

Canadian Cancer Society Smokers' Helpline

Website: www.smokershelpline.ca

A heart-healthy diet:

Heart and Stroke Foundation

Website: www.HeartandStroke.com/Healthy_Recipes

Mayo Clinic

Website: <http://www.mayoclinic.com/health/mediterranean-diet/CL00011>

Coronary artery disease:

Heart and Stroke Foundation

Website: www.HeartandStroke.com/Coronary_Disease

Cardiac rehab:

Hamilton Health Sciences:

St. Catharines/Niagara: Telephone: |

Brantford: Telephone: |

Appendix 4-3: Letter to family physician

[DD-MMM-YYYY]

Dear Dr. [FAMILY PHYSICIAN NAME]

RE: Our patient with coronary artery disease: [PATIENT NAME, DOB: DD-MMM-YYYY] *(If this is not your patient, please let us know as soon as possible)*

In [MONTH, YYYY], this patient was admitted for a myocardial infarction (STEMI) and had a coronary angiogram at the Hamilton General Hospital Heart Investigation Unit.

As the family physician, we believe that you are in the best position to help this individual adhere to the medications and lifestyle changes that can improve prognosis.

Optimal cardiac medication management has been shown to reduce cardiovascular disease events in patients like [PATIENT NAME] by 75-80%.^{1,2} For most post-MI patients, optimal medical management includes long-term use of a **statin, aspirin, clopidogrel, beta-blockers, and an ace-inhibitor.**³ However, research has shown that by one year post-MI, between one third and one half of patients are non-adherent.⁴

On the next page, we include a summary of the general recommendations for medication-based management of cardiovascular risk. **We acknowledge that preventive medications must be understood as a part of this patient's overall health and wellbeing.**

We have mailed a similar letter directly to [PATIENT NAME] to remind them of the importance of their cardiac medications and may send further reminders. If you have any questions or concerns about these letters or the medication recommendations for this patient, please don't hesitate to contact us.

Please consider assessing (and encouraging) medication adherence during your next visit with this patient.

Sincerely,

The cardiologists at the Heart Investigation Unit
Hamilton Health Sciences, General Site

Medical Management post-STEMI: Combination of 5 medications

- **(1) Aspirin and (2) clopidogrel** constitute the mainstay of antiplatelet therapy post-MI.
 - Aspirin therapy (75-162 mg/day) **should be continued indefinitely** post-STEMI (IA).
 - Clopidogrel is recommended for a minimum of 14 days in patients not undergoing percutaneous coronary intervention (PCI) post-STEMI (IB), but **ideally for 1 year**. Clopidogrel is recommended for a minimum of 1 month and ideally 1 year in patients post PCI with a bare-metal stent (IB) and a minimum of 1 year post PCI with a drug-eluting stent (IB).
 - An alternative to clopidogrel is prasugrel or ticagrelor
- **(3) A Statin** should be initiated in hospital, regardless of baseline lipid status or dietary modification and **continued indefinitely**, for all patients, in the absence of contraindications, with a prior myocardial infarction (IA).
 - Early intensive statin therapy is recommended for reducing recurrent cardiovascular events (e.g. atorvastatin 80mg or simvastatin 40 mg).^{5,6}
 - Intolerance to a statin may be alleviated by switching to pravastatin or fluvastatin.⁷
- **(4) An ACE-inhibitor (ACEI)** should be initiated and **continued indefinitely** for all patients post-STEMI with reduced left ventricular ejection fraction (LVEF < 40%), hypertension, diabetes or chronic kidney disease (IA).
 - Most other STEMI patients will also benefit from and ACEI or ARB (IB).
 - An alternative to ACEI is an angiotensin receptor blocker.
- **(5) Beta-blockers** should be initiated and **continued indefinitely** in all patients post-STEMI (IA).

References:

¹ Yusuf S. Two decades of progress in preventing vascular disease. *Lancet*. 2002;360:2–3.

² Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ*. 2003;326:1419–1424.

³ The Canadian Cardiovascular Society and the American College of Cardiology support the initiation and maintenance of pharmacotherapy including aspirin, clopidogrel, statin, beta-blocker, and angiotensin blockers with Class I support and Grade A or B evidence.

⁴ Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, Muhlbauer LH, Califf RM. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation*. 2006;113(2):203–12.

⁵ Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;350:1495–504.

⁶ de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004;292:1307–16.

⁷ Graham DJ, Staffa JA, Shatin D, et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. *JAMA* 2004; 292:2585.

Appendix 4-4: Tear-out for Pharmacist

Your pharmacist can help you make sure you are taking the right pills

It is important to **use the same pharmacy every time you get your pills**. When you always use the same pharmacy, the pharmacist can help you keep track of your medications.

Please take this page to your pharmacist. Pharmacists play an important role in your health care and can help you and your doctor make sure you are taking the right pills.

Dear Pharmacist of [PATIENT NAME],

Date: [DD-MMM-YYYY]

This is a personal and confidential note regarding [PATIENT NAME].

As you may be aware, [PATIENT NAME] recently had a heart attack. It is recommended that such patients take a statin, aspirin, ace-inhibitor, and beta-blocker indefinitely. The recommended length of time for clopidogrel varies from one month to two years. These medications have been shown to significantly reduce the risk of future heart attacks and strokes.

Unfortunately, many people stop their medications too early.

The purpose of this letter is to ask for your help to support [PATIENT NAME] in continuing to use these medications. Please, if possible, notify the patient's family physician, Dr. [FAMILY PHYSICIAN NAME] when a renewal is needed. In addition, please contact [PATIENT NAME] when it is time for a refill. Finally, please encourage this patient to continue to take these medications as prescribed.

By alerting the family physician about any side effects and discussing alternative medications within the same drug class, it may be possible to improve long-term adherence. With your help, we can reduce [PATIENT NAME]'s risk of future heart attacks and strokes.

Sincerely,

Dr. J-D Schwalm on behalf of the cardiologists at the Heart Investigation Unit
Hamilton Health Sciences, General Site

|

Appendix 4-5: Copyright approval for DERLA protocol-Implementation Science

-----Original Message-----

Subject: 00521227 Request for copyright approval

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Appendix 6-1: ISLAND ACS Summary

Interventions to Support Long-term Adherence and Decrease cardiovascular events post-Acute Coronary Syndrome (ISLAND-ACS), a population-level pragmatic randomized trial.

Background: In patients who have had an acute coronary syndrome (ACS), guidelines recommend cardiac rehabilitation services and the long-term use of cardiac medications to reduce the risk of recurrent cardiovascular events. Adherence to these recommendations substantially reduces morbidity and mortality post-ACS. For a variety of patient, provider, and system-level reasons, only 30-40% of patients participate in cardiac rehabilitation and adherence to cardiac medications declines to approximately 50% by one year. Thus, **interventions to increase uptake of cardiac rehabilitation and improve adherence to secondary prevention medications are urgently needed.**

The Cardiac Care Network of Ontario (CCN) holds a registry of all patients in the province who have a cardiac catheterization. The registry has been used to identify gaps in care and to plan health system strategies for high-risk patients. More recently, a pilot trial has been conducted in Hamilton by our team using data in the registry to send recurrent postal reminders regarding the importance of treatment adherence to patients, their pharmacists, and family physicians. A similar program is underway in Ottawa using automated phone calls with interactive voice response (IVR) and nurse follow up. These interventions both have the potential to address known determinants of adherence. **The CCN, health system decision makers and the clinical leads of cardiac centres across Ontario are interested in evaluating the comparative effectiveness and costs of these interventions.**

Research Questions: The research objectives were informed by the decision makers' need to evaluate whether and in what format to sustain the interventions. The primary questions are: (1) Can reminders delivered via post and/or using IVR with nurse follow up improve secondary prevention medication utilization or participation in cardiac rehabilitation after acute coronary syndrome? (2) How do different approaches to improve adherence to these recommendations compare in terms of clinical effectiveness and costs? The integrated knowledge translation approach aims to ensure that the project results meet decision makers' needs and to increase the likelihood of translating the findings in policy.

Research Approach: Pragmatic randomized controlled trial with blinded outcome assessment. Patients in centers throughout Ontario who undergo a coronary catheterization finding coronary artery disease post-ACS and who survive their initial hospitalization will be included. Patients will be randomized to i) usual care; ii) tailored postal letters sent on behalf of the interventional cardiologist to the patient 1, 2, 5, 8, and 11 months post-ACS to coincide with likely need for medication renewals, and to the family physician at 1, 5, and 11 months post-ACS to prompt discussions about secondary prevention; iii) IVR phone calls with tailored educational prompts 1, 2, 5, 8, and 11 months post-ACS, and nurse follow up for patients having difficulty with adherence; or iv) both postal letters and phone calls. The interventions will be refined with input from decision makers, patients and researchers with a range of disciplines. Outcomes will be assessed 12 months post-ACS. Analyses will be by intention to treat. With 1000 patients per arm, the trial has 90% power to find a 10% absolute increase in medication persistence or cardiac rehabilitation participation in any intervention arm at a family-wise error rate of 5%. Secondary outcomes include: mortality and CV outcomes, health utilization, additional measures of adherence, and discussion of secondary prevention with providers. The economic evaluation will be conducted from the perspective of the public health care payer.

Feasibility and Outcomes: The interventions are feasible and await robust evidence of cost effectiveness. The team has the necessary combination of expertise in research methods and partners committed to applying the findings. **If effective, this project will lead to improvements in care for patients at high cardiovascular risk as well as provide generalizable insights regarding how to optimize interventions to improve adherence.** Further, it has the potential to inform how other health databases could be used to improve health system performance; end-of-grant KT efforts will aim to support sustained implementation of the cost-effective interventions and to engage various stakeholders to develop and test similar interventions for other diseases or conditions.

References

- [1] Simes RJ, Topol EJ, Holmes DR, Jr., White HD, Rutsch WR, Vahanian A, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion. Importance of early and complete infarct artery reperfusion. GUSTO-I Investigators. *Circulation* 1995;91:1923-8.
- [2] Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, et al. Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:e85-151.
- [3] Genest J, McPherson R, Frohlich J, Anderson T, Campbell N, Carpentier A, et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *Can J Cardiol* 2009;25:567-79.
- [4] Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;124:2458-73.
- [5] Hudson M, Richard H, Pilote L. Parabolas of medication use and discontinuation after myocardial infarction--are we closing the treatment gap? *Pharmacoepidemiol Drug Saf* 2007;16:773-85.
- [6] Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Archives of internal medicine* 2009;169:260-8.
- [7] Shah ND, Dunlay SM, Ting HH, Montori VM, Thomas RJ, Wagie AE, et al. Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med* 2009;122:961 e7-13.
- [8] Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA : the journal of the American Medical Association* 2007;297:177-86.
- [9] Rublee DA, Chen SY, Mardekian J, Wu N, Rao P, Boulanger L. Evaluation of cardiovascular morbidity associated with adherence to atorvastatin therapy. *Am J Ther* 2012;19:24-32.
- [10] Schedlbauer A, Davies P, Fahey T. Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev* 2010:CD004371.
- [11] Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? *The Journal of continuing education in the health professions* 2006;26:13-24.
- [12] Ivers NM, Schwalm JD, Jackevicius CA, Guo H, Tu JV, Natarajan M. Length of initial prescription at hospital discharge and long-term medication adherence for elderly patients with coronary artery disease: a population-level study. *Can J Cardiol* 2013;29:1408-14.
- [13] Ivers NM, Schwalm JD, Grimshaw JM, Witteman H, Taljaard M, Zwarenstein M, et al. Delayed educational reminders for long-term medication adherence in ST-elevation myocardial infarction (DERLA-STEMI): protocol for a pragmatic, cluster-randomized controlled trial. *Implement Sci* 2012;7:54.
- [14] Nieuwlaat R, Schwalm JD, Khatib R, Yusuf S. Why are we failing to implement effective therapies in cardiovascular disease? *European heart journal* 2013;34:1262-9.
- [15] McGovern PG, Pankow JS, Shahar E, Doliszny KM, Folsom AR, Blackburn H, et al. Recent trends in acute coronary heart disease--mortality, morbidity, medical care, and risk factors. The Minnesota Heart Survey Investigators. *The New England journal of medicine* 1996;334:884-90.
- [16] Wijeyesundera HC, Machado M, Farahati F, Wang X, Witteman W, van der Velde G, et al. Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994-2005. *JAMA : the journal of the American Medical Association* 2010;303:1841-7.

- [17] Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation* 2010;121:948-54.
- [18] Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. *Lancet* 1999;353:89-92.
- [19] Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
- [20] Hippisley-Cox J, Coupland C. Effect of statins on the mortality of patients with ischaemic heart disease: population based cohort study with nested case-control analysis. *Heart* 2006;92:752-8.
- [21] Fitchett DH, Theroux P, Brophy JM, Cantor WJ, Cox JL, Gupta M, et al. Assessment and management of acute coronary syndromes (ACS): a Canadian perspective on current guideline-recommended treatment--part 2: ST-segment elevation myocardial infarction. *Can J Cardiol* 2011;27 Suppl A:S402-12.
- [22] Fitchett DH, Theroux P, Brophy JM, Cantor WJ, Cox JL, Gupta M, et al. Assessment and management of acute coronary syndromes (ACS): a Canadian perspective on current guideline-recommended treatment--part 1: non-ST-segment elevation ACS. *Can J Cardiol* 2011;27 Suppl A:S387-401.
- [23] Smith SC, Jr., Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, et al. AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011;124:2458-73.
- [24] Kirchmayer U, Di Martino M, Agabiti N, Bauleo L, Fusco D, Belleudi V, et al. Effect of evidence-based drug therapy on long-term outcomes in patients discharged after myocardial infarction: a nested case-control study in Italy. *Pharmacoepidemiol Drug Saf* 2013;22:649-57.
- [25] Rodríguez LAG, Cea-Soriano L, Martín-Merino E, Johansson S. Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011;343.
- [26] Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. *The New England journal of medicine* 2011;365:2088-97.
- [27] Aubert RE, Yao J, Xia F, Garavaglia SB. Is there a relationship between early statin compliance and a reduction in healthcare utilization? *Am J Manag Care* 2010;16:459-66.
- [28] Tanguay JF, Bell AD, Ackman ML, Bauer RD, Cartier R, Chan WS, et al. Focused 2012 update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. *Can J Cardiol* 2013;29:1334-45.
- [29] Ahmad M, Schwalm JD, Velianou JL, Natarajan MK. Impact of routine in-hospital assessment of low-density lipoprotein levels and standardized orders on statin therapy in patients undergoing percutaneous coronary interventions. *J Invasive Cardiol* 2005;17:518-20.
- [30] Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, et al. Impracticability of informed consent in the Registry of the Canadian Stroke Network. *The New England journal of medicine* 2004;350:1414-21.
- [31] Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006;113:203-12.
- [32] Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet* 2011;378:1231-43.

- [33] Kreps GL, Villagran MM, Zhao X, McHorney CA, Ledford C, Weathers M, et al. Development and validation of motivational messages to improve prescription medication adherence for patients with chronic health problems. *Patient Educ Couns* 2011;83:375-81.
- [34] Walid F, Gellad JG, Elizabeth A, McGlynn. A Review of Barriers to Medication Adherence. A Framework for Driving Policy Options. Santa Monica, CA: RAND Corporation; 2009. p. 66.
- [35] Ab E, Denig P, van Vliet T, Dekker JH. Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: a qualitative study. *BMC Fam Pract* 2009;10:24.
- [36] Hickling J, Rogers S, Nazareth I. Barriers to detecting and treating hypercholesterolaemia in patients with ischaemic heart disease: primary care perceptions. *Br J Gen Pract* 2005;55:534-8.
- [37] Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, Scales DC, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA : the journal of the American Medical Association* 2011;306:840-7.
- [38] Austin PC, Tu JV, Ko DT, Alter DA. Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2008;179:901-8.
- [39] Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C, et al. Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circ Cardiovasc Qual Outcomes* 2010;3:530-7.
- [40] Zolnieriek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. *Medical care* 2009;47:826-34.
- [41] Meddings J, Kerr EA, Heisler M, Hofer TP. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. *BMC health services research* 2012;12:270.
- [42] Rasmussen JN, Gislason GH, Rasmussen S, Abildstrom SZ, Schramm TK, Kober L, et al. Use of statins and beta-blockers after acute myocardial infarction according to income and education. *J Epidemiol Community Health* 2007;61:1091-7.
- [43] Sud A, Kline-Rogers EM, Eagle KA, Fang J, Armstrong DF, Rangarajan K, et al. Adherence to medications by patients after acute coronary syndromes. *The Annals of pharmacotherapy* 2005;39:1792-7.
- [44] Garavalia L, Garavalia B, Spertus JA, Decker C. Exploring patients' reasons for discontinuance of heart medications. *J Cardiovasc Nurs* 2009;24:371-9.
- [45] Clifford S, Barber N, Horne R. Understanding different beliefs held by adherers, unintentional nonadherers, and intentional nonadherers: application of the Necessity-Concerns Framework. *J Psychosom Res* 2008;64:41-6.
- [46] Furniss D, Barber N, Lyons I, Eliasson L, Blandford A. Unintentional non-adherence: can a spoon full of resilience help the medicine go down? *BMJ Qual Saf* 2014;23:95-8.
- [47] Armitage J. The safety of statins in clinical practice. *Lancet* 2007;370:1781-90.
- [48] Kashani A, Phillips CO, Foody JM, Wang Y, Mangalmurti S, Ko DT, et al. Risks associated with statin therapy: a systematic overview of randomized clinical trials. *Circulation* 2006;114:2788-97.
- [49] Joy TR, Hegele RA. Narrative review: statin-related myopathy. *Annals of internal medicine* 2009;150:858-68.
- [50] INC L-C. 1978-2011.
- [51] Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the ontario drug benefit database. *Can J Clin Pharmacol.* 2003; 10:67-71.
- [52] Jackevicius CA, Paterson JM, Naglie G. Concordance between discharge prescriptions and insurance claims in post-myocardial infarction patients. *Pharmacoepidemiol Drug Saf.* 2007; 16:207-15.

- [53] Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu JV. Canadian institute for health information discharge abstract database: A validation study. Toronto, ON: Institute for Clinical Evaluative Sciences; 2006.
- [54] Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005; 43:1130-9.
- [55] Williams JI, Young W. *A summary of studies on the quality of health care administrative databases in Canada*. In: Goel V, Williams JI, Anderson GM, Blackstien-Hirsch P, Fooks C, Naylor D, editors. *Patterns of health care in Ontario: the ICES practice atlas*. 2nd ed. Canada: Canadian Medical Association; 1996. p. 339-45.
- [56] Lee DS, Stitt A, Wang X, Yu JS, Gurevich Y, Kingsbury KJ, et al. Administrative hospitalization database validation of cardiac procedure codes. *Med Care*. 2011; DOI: 10.1097/MLR.0b013e3182329778.
- [57] Wilkens R. Automated geographic coding based on the statistics Canada postal code conversion files. Ottawa, ON: Statistics Canada; 2001. Report No.: 82F0086-XDB.
- [58] Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. *JAMA*. 2002; 288:455-61.
- [59] Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA*. 2002; 288:462-7.
- [60] Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. *Am Heart J*. 2006; 151:185-91.
- [61] Schneeweiss S, Seeger JD, Maclure M, Wang PS, Avorn J, Glynn RJ. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol*. 2001; 154:854-6.
- [62] Lopez-Carmona D, Bernal-Lopez M, Mancera-Romero J, Jansen-Chaparro S, Portales-Fernandez I, Baca-Osorio A, et al. Compliance with cardiovascular drug prevention measures in a general population: The multidisciplinary intervention in primary care (IMAP) study. *Eur J Prev Cardiol*. 2012; 19:1074-81.
- [63] Steele LS, Glazier RH, Lin E, Evans M. Using administrative data to measure ambulatory mental health service provision in primary care. *Med Care*. 2004; 42:960-5.
- [64] Katz MH. *Multivariable analysis: A practical guide for clinicians and public health researchers*. 3rd ed. UK: Cambridge University Press; 2011.
- [65] Batal HA, Krantz MJ, Dale RA, Mehler PS, Steiner JF. Impact of prescription size on statin adherence and cholesterol levels. *BMC Health Serv Res*. 2007; 7:175.
- [66] Steiner JF, Robbins LJ, Roth SC, Hammond WS. The effect of prescription size on acquisition of maintenance medications. *J Gen Intern Med*. 1993; 8:306-10.
- [67] Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005; 353:487-9.
- [68] Austin PC, Tu JV, Ko DT, Alter DA. Use of evidence-based therapies after discharge among elderly patients with acute myocardial infarction. *CMAJ*. 2008; 179:895-900.
- [69] Sabate E, editor. *Adherence to long-term therapies: Evidence for action*. 1st ed. Switzerland: World Health Organization; 2003.
- [70] Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C, et al. Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: Exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circ Cardiovasc Qual Outcomes*. 2010; 3:530-7.
- [71] Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: Its importance in cardiovascular outcomes. *Circulation*. 2009; 119:3028-35.
- [72]. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: Prevalence and contributing factors. *Arch Intern Med*. 2005; 165:1842-7.

- [73] Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2007; 50:e1-e157.
- [74] Daugherty SL, Ho PM, Spertus JA, Jones PG, Bach RG, Krumholz HM, et al. Association of early follow-up after acute myocardial infarction with higher rates of medication use. *Arch Intern Med*. 2008; 168:485-91.
- [75] Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW. Deficits in communication and information transfer between hospital-based and primary care physicians: Implications for patient safety and continuity of care. *JAMA*. 2007; 297:831-4.
- [76] Lemstra M, Blackburn D, Crawley A, Fung R. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. *Can J Cardiol*. 2012; 28(5):574-80.
- [77] Baker R, Camosso-Stefinovic J, Gillies C, Shaw EJ, Cheater F, Flottorp S, et al. Tailored interventions to overcome identified barriers to change: effects on professional practice and health care outcomes. *Cochrane Database Syst Rev* 2010:CD005470.
- [78] Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. *Cochrane Database Syst Rev* 2008:CD000011.
- [79] Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, et al. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. *Annals of internal medicine* 2012;157:785-95.
- [80] Van Camp YP, Van Rompaey B, Elseviers MM. Nurse-led interventions to enhance adherence to chronic medication: systematic review and meta-analysis of randomised controlled trials. *Eur J Clin Pharmacol* 2013;69:761-70.
- [81] Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA, Ko DT: Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. *JAMA* 2009, **302**(21):2330-2337.
- [82] Ciara Pendrith BSc1 NMIMP, 2,3, Samir Nazarali4, Laure Perrier MLIS, Med5, Andrea Tricco PhD5, Jemila Hamid PhD4, J-D Schwalm MD4,6, Jeremy Grimshaw MBChB PhD7,8, Sharon Straus MD MSc5,9. Automated patient reminders post health event for improving adherence to medical recommendations: a systematic review and meta-analysis. Submitted for publication 2014.
- [83] Feder G, Griffiths C, Eldridge S, Spence M. Effect of postal prompts to patients and general practitioners on the quality of primary care after a coronary event (POST): randomised controlled trial. *BMJ* 1999;318:1522-6.
- [84] Smith DH, Kramer JM, Perrin N, Platt R, Roblin DW, Lane K, et al. A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. *Archives of internal medicine* 2008;168:477-83; discussion 83; quiz 47.
- [85] Guthrie RM. The effects of postal and telephone reminders on compliance with pravastatin therapy in a national registry: results of the first myocardial infarction risk reduction program. *Clin Ther* 2001;23:970-80.
- [86] McAlister FA, Fradette M, Majumdar SR, Williams R, Graham M, McMeekin J, et al. The Enhancing Secondary Prevention in Coronary Artery Disease trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 2009;181:897-904.
- [87] Munoz MA, Vila J, Cabanero M, Rebato C, Subirana I, Sala J, et al. Efficacy of an intensive prevention program in coronary patients in primary care, a randomised clinical trial. *International journal of cardiology* 2007;118:312-20.
- [88] Riesen WF, Noll G, Dariolo R, trialists O. Impact of enhanced compliance initiatives on the efficacy of rosuvastatin in reducing low density lipoprotein cholesterol levels in patients with primary hypercholesterolaemia. *Swiss medical weekly* 2008;138:420-6.
- [89] Murray CJ, Lopez AD: Evidence-based health policy--lessons from the Global Burden of Disease Study. *Science* 1996, **274**(5288):740-743.

- [90] Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Annals of internal medicine* 1993;119:1187-97.
- [91] Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, et al. 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation* 2008;117:296-329.
- [92] Rublee DA, Chen SY, Mardekian J, Wu N, Rao P, Boulanger L: Evaluation of Cardiovascular Morbidity Associated with Adherence to Atorvastatin Therapy. *Am J Ther* 2010, .
- [93] Rodriguez LA, Cea-Soriano L, Martin-Merino E, Johansson S: Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011, **343**:d4094.
- [94] Brown MT, Bussell JK: Medication adherence: WHO cares? *Mayo Clin Proc* 2011, **86**(4):304-314.
- [95] Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, Daniel JG, Ekman I, Ho M, Johnson M, Kimmel SE, Liu LZ, Musaus J, Shrank WH, Whalley Buono E, Weiss K, Granger CB: Medication adherence: a call for action. *Am Heart J* 2011, **162**(3):412-424.
- [96]. Gill PS, Quirke TP, Mant JW, Allan TF: The use of lipid-lowering drugs across ethnic groups in the secondary prevention of ischaemic heart disease: analysis of cross-sectional surveys in England. *Br J Gen Pract* 2004, **54**(503):442-443.
- [97] Chiu M, Austin PC, Manuel DG, Tu JV: Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. *CMAJ* 2010, **182**(8):E301-10.
- [98] Rabi DM, Edwards AL, Svenson LW, Graham MM, Knudtson ML, Ghali WA, Alberta Provincial Project for Assessing Outcomes in Coronary Heart Disease Investigators: Association of median household income with burden of coronary artery disease among individuals with diabetes. *Circ Cardiovasc Qual Outcomes* 2010, **3**(1):48-53.
- [99] Ryan R, Santesso N, Hill S, Lowe D, Kaufman C, Grimshaw J: Consumer-oriented interventions for evidence-based prescribing and medicines use: an overview of systematic reviews. *Cochrane Database Syst Rev* 2011, **(5)**(5):CD007768.
- [100] Chong WW, Aslani P, Chen TF: Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. *Int J Clin Pract* 2011, **65**(9):954-975.
- [101] Al-Aqeel S, Al-Sabhan J: Strategies for improving adherence to antiepileptic drug treatment in patients with epilepsy. *Cochrane Database Syst Rev* 2011, **(1)**(1):CD008312.
- [102] Kunz R, Vist G, Oxman AD: Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev* 2007, **(2)**(2):MR000012.
- [103] Ahmad M, Schwalm JD, Velianou JL, Pericak D, Natarajan MK: Comparison of one-year clinical outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice. *Can J Cardiol* 2008, **24**(10):771-775.
- [104] Schwalm JD, Ahmad M, Velianou JL, Pericak D, Natarajan MK: Long-term outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice: a Canadian experience. *Can J Cardiol* 2010, **26**(2):e40-4.
- [105] Treweek S, Zwarenstein M: Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials* 2009, **10**:37.
- [106] Nolan T, Berwick DM: All-or-none measurement raises the bar on performance. *JAMA* 2006, **295**(10):1168-1170.
- [107] Morisky DE, Green LW, Levine DM: Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care* 1986, **24**(1):67-74.

- [108] Shalansky SJ, Levy AR, Ignaszewski AP: Self-reported Morisky score for identifying nonadherence with cardiovascular medications. *Ann Pharmacother* 2004, **38**(9):1363-1368.
- [109] Bermingham M, Hayden J, Dawkins I, Miwa S, Gibson D, McDonald K, Ledwidge M: Prospective analysis of LDL-C goal achievement and self-reported medication adherence among statin users in primary care. *Clin Ther* 2011, **33**(9):1180-1189.
- [110] Steiner JF, Prochazka AV: The assessment of refill compliance using pharmacy records: methods, validity, and applications. *J Clin Epidemiol* 1997, **50**(1):105-116.
- [111] Donner A, Klar N: *Design and Analysis of Cluster Randomization Trials in Health Research*: New York: Oxford University Press; 2000.
- [112] Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005, **366**(9493):1267-1278.
- [113] Eccles M, Grimshaw J, Campbell M, Ramsay C. Research designs for studies evaluating the effectiveness of change and improvement strategies. *Quality & safety in health care* 2003;12:47-52.
- [114] Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121-30.
- [115] Schwalm J-DR, Ahmad M, Velianou JL, Pericak D, Natarajan MK. Long-term outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice: A Canadian experience. *Canadian Journal of Cardiology* 2010;26:e40-e4.
- [116] Schwalm JD IN, Witteman HO, Taljaard M, RaoMelacini P, Zwarenstein M, Grimshaw J, Natarajan MK. . Pragmatic, cluster-randomized controlled trial of Delayed Educational Reminders for Long-term medication Adherence in ST-Elevation Myocardial Infarction (DERLA-STEMI). *The Canadian Journal of Cardiology* 2013;29:265.
- [117] Sadeghi HM, Stone GW, Grines CL, Mehran R, Dixon SR, Lansky AJ, et al. Impact of renal insufficiency in patients undergoing primary angioplasty for acute myocardial infarction. *Circulation* 2003;108:2769-75.
- [118] Jolly SS, Cairns J, Yusuf S, Meeks B, Shestakovska O, Thabane L, et al. Design and rationale of the TOTAL trial: a randomized trial of routine aspiration Thrombectomy with percutaneous coronary intervention (PCI) versus PCI Alone in patients with ST-elevation myocardial infarction undergoing primary PCI. *American heart journal* 2014;167:315-21 e1.
- [119] Cohen MJ, Shaykevich S, Cawthon C, Kripalani S, Paasche-Orlow MK, Schnipper JL. Predictors of medication adherence postdischarge: the impact of patient age, insurance status, and prior adherence. *Journal of hospital medicine : an official publication of the Society of Hospital Medicine* 2012;7:470-5.
- [120] Rodriguez F, Cannon CP, Steg PG, Kumbhani DJ, Goto S, Smith SC, et al. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic disease: findings from the REACH Registry. *Clinical cardiology* 2013;36:721-7.
- [121] Molfenter TD, Bhattacharya A, Gustafson DH. The roles of past behavior and health beliefs in predicting medication adherence to a statin regimen. *Patient preference and adherence* 2012;6:643-51.
- [122] Chang TI, Desai M, Solomon DH, Winkelmayer WC. Kidney function and long-term medication adherence after myocardial infarction in the elderly. *Clinical journal of the American Society of Nephrology : CJASN* 2011;6:864-9.
- [123] Suh JW, Mehran R, Claessen BE, Xu K, Baber U, Dangas G, et al. Impact of in-hospital major bleeding on late clinical outcomes after primary percutaneous coronary intervention in acute myocardial infarction the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) trial. *Journal of the American College of Cardiology* 2011;58:1750-6.
- [124] Gehi AK, Ali S, Na B, Whooley MA. Self-reported medication adherence and cardiovascular events in patients with stable coronary heart disease: the heart and soul study. *Archives of internal medicine* 2007;167:1798-803.

- [125] Smith SC, Jr., Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113:2363-72.
- [126] Bally K, Buechel RR, Buser P, Tschudia P, Martinaa B, Zeller A. Discontinuation of secondary prevention medication after myocardial infarction - the role of general practitioners and patients. *Swiss medical weekly* 2013;143:w13896.

Supplemental Material (Reprints of Manuscripts One and Two):

Clinical Research

Length of Initial Prescription at Hospital Discharge and Long-term Medication Adherence for Elderly Patients With Coronary Artery Disease: A Population-Level Study

Noah M. Ivers, MD,^{a,b} J.-D. Schwalm, MD,^{c,d} Cynthia A. Jackevicius, PharmD, MSc,^{e,f,g,h,i}
Helen Guo, MSc,ⁱ Jack V. Tu, MD, PhD,^{i,j} and Madhu Natarajan, MD, MSc^{c,d,k}

^aFamily Practice Health Centre, Women's College Hospital, Toronto, Ontario, Canada

^bDepartment of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

^cHeart Investigation Unit, Hamilton General Hospital, Hamilton, Ontario, Canada

^dPopulation Health Research Unit, McMaster University, Hamilton, Ontario, Canada

^eCollege of Pharmacy, Western University of Health Sciences, Pomona, California, USA

^fDepartment of Pharmacy, Veterans Affairs Greater Los Angeles Health Care System, Los Angeles, California, USA

^gDepartment of Pharmacy, University Health Network, Toronto, Ontario, Canada

^hInstitute of Health Policy Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

ⁱInstitute for Clinical Evaluative Sciences, Toronto, Ontario, Canada

^jSunnybrook Schulich Heart Centre, University of Toronto, Toronto, Ontario, Canada

^kCardiac Care Network of Ontario, Toronto, Ontario, Canada

ABSTRACT

Background: Patient adherence to cardiac secondary prevention medications declines over time. We examined whether the length of the initial prescription at hospital discharge after coronary angiography would be associated with long-term adherence.

Methods: We conducted a population-level cohort study to examine adherence to cardiac medications for 18 months after coronary angiography in elderly patients with coronary artery disease (CAD). We

RÉSUMÉ

Introduction : L'observance médicamenteuse en matière de prévention secondaire de la maladie du cœur diminue avec le temps. Nous avons examiné si la durée de l'ordonnance initiale remise au congé de l'hôpital après la coronarographie pourrait être associée à l'observance à long terme.

Méthodes : Nous avons mené une étude de cohorte à l'échelle de la population pour examiner l'observance des traitements

Patients with documented coronary artery disease (CAD) have an increased risk of subsequent cardiovascular events, including myocardial infarction (MI), heart failure, and death.¹ Guidelines stress that the initiation and long-term maintenance of evidence-based secondary prevention medications such as antiplatelet agents, angiotensin-converting enzyme inhibitor or angiotensin receptor blockers (ACE-I/ARB), β -blockers (BBs), and statins are essential for improving cardiovascular outcomes.^{2,3} Unfortunately, adherence to cardiac secondary prevention medications declines

over time, and this decreased adherence is associated with increased mortality.⁴⁻⁹

The purpose of this study was to identify factors associated with adherence to cardiac secondary prevention medications in patients in whom CAD was evident during angiography. In particular, we assessed whether the length of the initial prescription given to the patient after angiography was associated with long-term adherence, based on our clinical observation that many patients were offered brief prescriptions to encourage early outpatient follow-up.

Methods

We conducted a retrospective cohort study to examine adherence to cardiac secondary prevention medication 18 months after coronary angiography. The Research Ethics Board at Sunnybrook Health Sciences Centre approved this study.

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Corresponding author: Dr Noah M. Ivers, Department of Family and Community Medicine, Women's College Hospital, 77 Grenville Street, Toronto, Ontario M5S1B3, Canada. Tel.: +1-416-323-6060 x1, then x2.

E-mail: noah.ivers@utoronto.ca

See page 1413 for disclosure information.

identified patients with clinical indications for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE-I/ARB), beta-blockers (BB), and/or statins. In each medication class cohort, we defined high adherence as proportion of days covered (PDC) > 80%. The length of the initial prescription was defined as 0-30 days, 31-60 days, and more than 60 days. We controlled for patient sociodemographic factors, previous adherence, and comorbidities.

Results: The ACE-I/ARB cohort included 13,305 patients, the BB cohort included 5,792 patients, and the statin cohort included 16,134 patients. Using < 30 days as the reference, initial prescriptions covering at least 60 days were more likely to result in high long-term adherence for ACE-I/ARB (adjusted odds ratio [aOR], 4.1; 95% confidence interval [CI], 3.6-4.7); BB (aOR, 2.4; 95% CI, 1.9-3.1), and statins (aOR, 3.0; 95% CI, 2.6-3.4). More than 80% of patients had outpatient follow-up with a primary care provider within 30 days, and this did not vary based on length of initial prescription.

Conclusions: Giving patients longer prescriptions for cardiac secondary prevention medications at hospital discharge seems to increase the likelihood of high long-term adherence in elderly patients.

Databases

We used population-based administrative records linked through a unique identifier at the Institute for Clinical Evaluative Sciences. Data were compiled from the following databases: (1) the Ontario Drug Benefits (ODB) database, covering all medications prescribed to persons in Ontario older than 65 years^{10,11}; (2) the Canadian Institute for Health Information Discharge Abstract Database covering hospital discharge diagnoses¹² using International *Classification of Disease* (ICD) codes, permitting the calculation of the Charlson comorbidity score¹³; (3) the Ontario Health Insurance Plan (OHIP) database, covering physician billings for procedures and consultations¹⁴; (4) the Registered Persons Database, covering demographic information including date of death; and (5) the Cardiac Care Network of Ontario (CCN) cardiac registry, with clinical variables collected at the time of angiography. The CCN cardiac registry has recently been used as a reference standard to validate other databases.¹⁵

Patient cohorts

We examined patients with CAD identified during coronary angiography that was performed between October 1, 2008 and September 30, 2009. The included cohort had at least 70% blockage in at least 1 vessel or at least 50% blockage in the left main coronary artery. Medication data in the ODB is captured for all patients older than 65 years. Therefore, restricting enrollment to patients aged 65 years plus 120 days allowed us to account for prescriptions started before the date of angiography.

médicamenteux contre la maladie du cœur durant les 18 mois suivant la coronarographie chez les patients âgés ayant une coronaropathie. Nous avons repéré les patients dont les indications cliniques justifient la prise d'inhibiteurs de l'enzyme de conversion de l'angiotensine ou d'antagonistes des récepteurs de l'angiotensine (IECA/ARA), de bêta-bloquants (BB), et/ou de statines. Dans chacune des cohortes par classe de médicaments, nous avons défini comme élevée l'observance dont la proportion de jours a été > 80 %. La durée de l'ordonnance initiale a été définie comme suit : de 0 à 30 jours, de 31 à 60 jours et de plus de 60 jours. Nous avons tenu compte des facteurs socio-démographiques des patients, de l'observance antérieure et des comorbidités.

Résultats : La cohorte recevant les IECA/ARA incluait 13 305 patients, la cohorte recevant les BB incluait 5 792 patients et la cohorte recevant les statines incluait 16 134 patients. En utilisant moins de 30 jours comme référence, les ordonnances initiales couvrant au moins 60 jours ont été plus susceptibles d'entraîner une observance à long terme élevée du traitement par IECA/ARA (ratio d'incidence ajusté [RIAA] = 4,1; intervalle de confiance [IC] à 95 %, 3,6-4,7); du traitement par BB (RIAA = 2,4; IC à 95 %, 1,9-3,1), et du traitement par statines (RIAA = 3,0; IC à 95 %, 2,6-3,4). Plus de 80 % des patients ont obtenu dans les 30 jours un suivi ambulatoire par un prestataire de soins primaires, et cela n'a pas varié selon la durée de l'ordonnance initiale.

Conclusion : Le fait de remettre aux patients au congé de l'hôpital des ordonnances plus longues de médicaments ayant trait à la prévention secondaire de la maladie du cœur semble augmenter la probabilité d'obtenir une observance élevée à long terme chez les patients âgés.

From the entire cohort of patients with CAD, we created 3 medication class cohorts to identify patients who had clinical indications for long-term use of ACE-I/ARB, BBs, and/or statins based on class 1A evidence from recent guidelines³: the ACEI/ARB cohort included patients with diabetes *or* hypertension *or* decreased left ventricular ejection fraction (< 50%); the BB cohort included patients with decreased left ventricular ejection fraction (< 50%) *and* New York Heart Association class II-IV *or* a history of MI before or as indication for angiography; the statin cohort was not limited because guidelines recommend long-term use of statins in all patients with evidence of CAD.² We did not assess antiplatelet medications because clopidogrel is not indicated for long-term use in many patients and because acetyl salicylic acid is usually purchased over the counter without a prescription in Ontario. We limited analyses to patients who survived 18 months after angiography.

Outcome: assessment of adherence

In each medication class cohort, we assessed adherence using the proportion of days covered (PDC) technique, in which the days supplied during each interval is divided by the number of days in the interval. The PDC was calculated 540 days (ie, 18 months) after angiography. Patients not prescribed any medication in a class would have PDC equal to zero. When patients were dispensed a prescription renewal before the end of their previous prescription period, the excess supply was carried over to the next period, but the maximum PDC for the interval was equal to 1. We dichotomized patients based on their PDC into high and not-high adherence, with high-adherence defined as PDC > 80%.⁸

Exposure: length of initial prescription after angiography

We examined the number of days supplied in the initial prescription fill for each medication class.^{10,11} Prescriptions covered by the ODB plan are dispensed for a maximum of 100 days. Therefore, we categorized the initial days supplied of the initial prescription as follows: < 1 month (0-30 days); 1-2 months (31-60 days), and > 2 months (> 60 days). For those who did not have any leftover pills from a previous prescription and who did not fill a new prescription within 30 days of their angiography procedure, the length of the initial prescription was set at zero.

Covariates

We controlled for confounding factors that might influence prescription adherence, including sex, rural location, and socioeconomic status. For the latter, we used median neighborhood income quintile using postal code linkage to census data from Statistics Canada.¹⁶ We also adjusted for comorbid disease burden,^{17,18} using the number of distinct medications dispensed in the year before cohort entry,^{19,20} as well as by Charlson Score.²¹ In addition, we accounted for the severity of the presentation leading to the angiography procedure (ST-elevation MI, non-ST-elevation MI, unstable angina, or elective), findings during angiography (number of vessels affected), subsequent treatment (medical management or percutaneous coronary intervention or coronary artery bypass within 90 days), and presence of heart failure (left ventricular function and New York Heart Association class), angina (Canadian Cardiovascular Society class), chronic obstructive pulmonary disease, diabetes, hypertension, dyslipidemia, peripheral vascular disease, and cerebrovascular disease, plus smoking status and history of coronary bypass and/or MI. These clinical variables are recorded in the CCN cardiac registry at the time of angiography. We also adjusted for history of mental health care, given the potential association with adherence.¹⁷⁻¹⁹ This was assessed using a validated algorithm for identifying patients with a relevant OHIP billing code (ICD-9 codes 295-304, 306, 309, 311, 897-902, 904-906, 909) representing an outpatient family physician assessment for mental health,²² any hospitalization for mental health (ICD-10 code F00-F99), or any billing by a psychiatrist in the previous year. Using data from ODB, we also adjusted for past medication adherence for those who were prescribed the medication of interest in the year before the angiography procedure as well as concurrent cardiovascular medications. Finally, we used OHIP to determine the number of outpatient appointments with a specialist (cardiologist or internist) or with a primary care provider (family physician or general practitioner).

Statistical analysis

We conducted multivariable logistic regression to examine the effects of initial prescription and follow-up characteristics on adherence, adjusting for potential confounding variables. The strength of the association between exposure and adherence is expressed as an adjusted odds ratio (aOR). A separate model was conducted for each medication class. All models included patient age and sex, as well as indication for angiography; other covariates were included in the model if

their *P* values were < 0.05, using a backward selection process.²³

We conducted additional post hoc analyses to further examine the findings. First, we repeated the main analysis after excluding patients with an initial prescription length of less than 7 days under the assumption that the physician in such cases was uncertain if the patient required or could tolerate the medication. Second, we explored timing of outpatient follow-up to see if this could explain the relationship between adherence and prescription length. Finally, we examined medication discontinuation after angiography for each medication class. We defined discontinuation as occurring when the prescription is inactive for at least 20% of the length of time of the previous medication.²⁴ To measure discontinuation, we included only patients who were initially taking the medication class of interest by limiting inclusion to those who had leftover pills in a medication class from a prescription before the angiography procedure or those who filled a new prescription for that class within 30 days after the angiography procedure.

All analyses were conducted using SAS, version 9.2 (SAS Institute, Cary, NC).

Results

The ACE-I/ARB cohort included 13,305 patients, the BB cohort included 5,792 patients, and the statin cohort included 16,134 patients (Fig. 1). Demographic and clinical characteristics for each medication class cohort are described in Supplemental Table S1, along with the proportion of patients achieving high adherence over 540 days. Some patient characteristics were associated with increased long-term adherence in specific medication classes but not across all medication classes. For instance, significantly more women had high adherence to BBs than did men ($P < 0.001$), and there was a trend suggesting that more women had high adherence to ACE-I/ARB class medications than did men ($P = 0.07$), whereas significantly more men had high adherence to statins than did women ($P < 0.001$).

Of all initial prescriptions, 19.5% of ACE-I/ARB medications, 11.0% of BBs, and 20.6% of statins were for more than 60 days. The association between length of initial prescription after angiography and the likelihood of high adherence at 540 days is described in Table 1. Using < 30 days as the reference, initial prescriptions > 60 days were more likely to result in high long-term adherence for ACE-I/ARB medications (aOR, 4.1; 95% confidence interval [CI] 3.6-4.7), BBs (aOR, 2.4; 95% CI, 1.9-3.1), and statins (aOR, 3.0; 95% CI, 2.6-3.4). Age and sex were significant covariates in each model. Each 10-year increase in age was associated with a reduction in long-term adherence for ACE-I/ARB medications (aOR, 0.8; 95% CI, 0.8-0.9), BBs (aOR, 0.9; 95% CI, 0.8-0.9), and statins (aOR, 0.89; 95% CI, 0.83-0.95). Male patients were less likely to have high long-term adherence to ACE-I/ARB medications (aOR, 0.88; 95% CI, 0.80-0.96) and BBs (aOR, 0.78; 95% CI, 0.69-0.88) but were more likely to have high long-term adherence to statins (aOR, 1.18; 95% CI, 1.09-1.29).

Of all prescriptions covering less than 31 days, 3292 (50.3%) prescriptions for ACE-I/ARB were prescribed for less than 7 days, 715 (23.3%) prescriptions for BB were

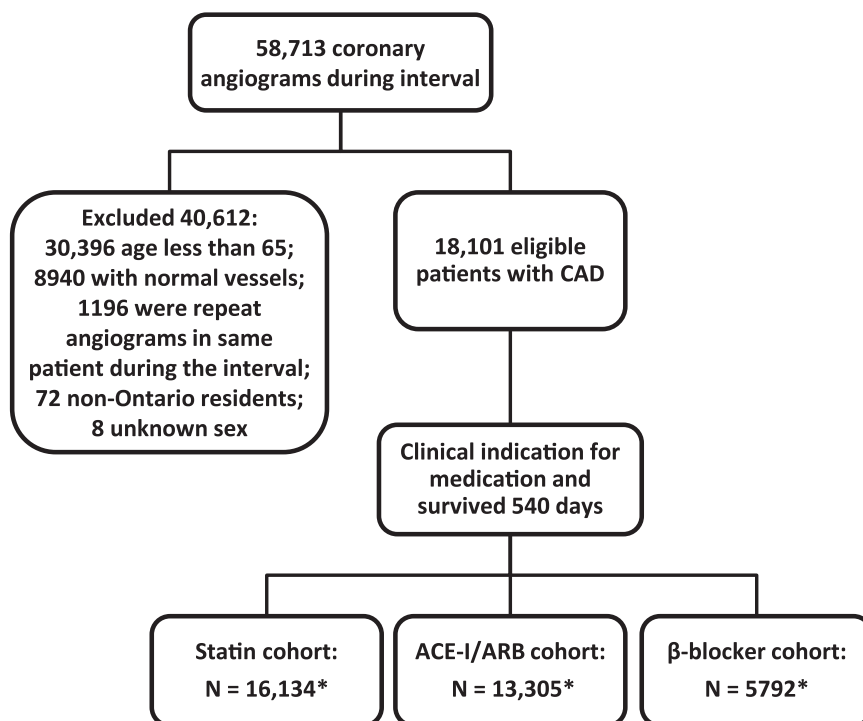


Figure 1. Patient flow diagram of study population. ACE-I/ARB, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers; CAD, coronary artery disease. * Assessment of adherence over 540 days includes all patients with a clinical indication for that class of medication. Assessment of persistence is limited to those who had leftover pills in a medication-class from a prescription prior to the angiography or those who filled a new prescription for that class within 30 days after the angiography.

prescribed for less than 7 days, and 3789 (42.3%) prescriptions for statins were prescribed for less than 7 days. After removing these cases, patients receiving initial prescriptions longer than 60 days still had greater long-term adherence for ACE-I/ARB medications (aOR, 1.3; 95% CI, 1.1-1.6) and a trend toward high long-term adherence for BBs (aOR, 1.2; 95% CI, 0.9-1.5) and statins (aOR, 1.2; 95% CI, 1.0-1.4). As seen in Figure 2, although medication adherence fell gradually over time, higher rates of discontinuation were apparent at 30 and 90 days. This coincides with the common length of initial prescriptions, marking the time when refills would be necessary.

The vast majority of patients had follow-up in primary care within 30 days after the angiography procedure (Supplemental Table S2). The proportion of patients with outpatient follow-up in primary care within 30 days was nearly equivalent for the different initial prescription lengths. However, those

receiving initial prescriptions for less than 1 month were slightly more likely to have an outpatient follow-up with a specialist within 30 days.

Discussion

This study identifies an easily modifiable factor in the control of providers and/or systems to improve adherence. The length of initial prescription was associated with long-term adherence, and the strength of the association was consistent for each cardiac secondary prevention medication, even after adjusting for relevant clinical factors and socio-demographic factors. We found that the majority of prescriptions at discharge cover less than 1 month. This may be based on a clinical assumption that short prescriptions encourage patients to attend early outpatient follow-up. Although early follow-up is essential to assess the patient

Table 1. Association between days supplied with initial prescription and long-term adherence for each drug class

Drug cohort	Initial prescription length after angiography					
	< 31 days		31-60 days		> 60 days	
	High PDC N (%)	OR*	High PDC N (%)	OR* (95% CI)	High PDC N (%)	OR* (95% CI)
ACE-I/ARB N = 13,305	6550 (65.8%)	1	640 (84.4%)	2.6 (2.1-3.2)	2314 (89.1%)	4.1 (3.6-4.7)
β-blocker N = 5792	3074 (62.9%)	1	224 (80.9%)	1.8 (1.3-2.5)	529 (84.8%)	2.4 (1.9-3.1)
Statins N = 16,134	8962 (76.1%)	1	887 (87.0%)	2.0 (1.7-2.4)	3019 (90.5%)	3.0 (2.6-3.4)

ACE-I/ARB, ACE inhibitors or angiotensin receptor blockers; BB, beta blockers; OR, odds ratio; PDC, proportion of days covered.

* ORs for high adherence at 540 days are adjusted for significant covariates and use initial prescription length < 31 days as the reference. Because the adherence value for prescriptions < 31 days in length was used as the reference for the other groups receiving longer prescriptions, by definition the value for the OR for those receiving prescriptions < 31 days is equal to 1.

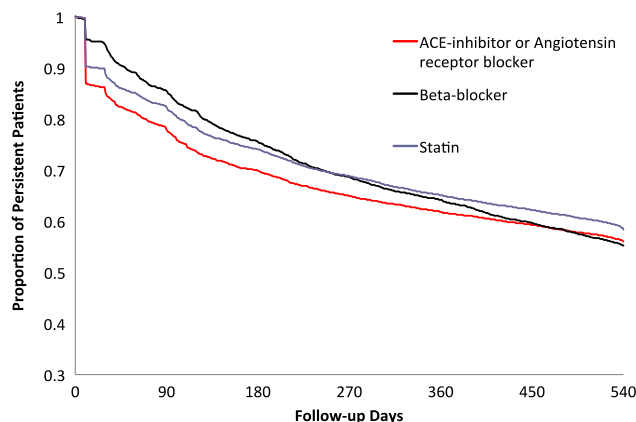


Figure 2. Persistence with secondary prevention medications after angiography. ACE, angiotensin-converting enzyme.

and to address medication side effects, the vast majority of patients did have follow-up within 1 month, regardless of prescription length. Therefore, shorter prescriptions may create an unnecessary inconvenience (ie, a refill burden) for elderly patients, and the subsequent risk of reduced adherence may outweigh other potential benefits.

Two previous small studies examined the association between length of prescriptions and long-term adherence to cardiac medications.^{25,26} The first included 290 patients and found that those with at least 90-day supplies of digoxin were less likely to run out of tablets over 9-14 months. The other study included 3386 patients and found that those receiving mostly 60-day prescriptions for statins were more likely to have high adherence than those receiving mostly 30-day prescriptions (adjusted risk ratio, 1.40; 95% CI, 1.27-1.55). We agree with the conclusion of both studies that longer prescriptions may partially address a major reason for (unintentional) nonadherence—forgetfulness.²⁷ Our findings focus specifically on the length of the first prescription after angiography rather than considering the average fill size and build on these studies by considering a population-level sample and by extending the findings to multiple cardiac medications.

The same databases as those used in our study have previously been used to reveal improvements between 1992 and 2005 in the proportion of cardiac patients dispensed secondary prevention medications at discharge.²⁸ However, we found a study with similar proportions of patients with high long-term adherence to statins and BBs using the same databases between 1999 and 2003,⁸ suggesting that quality-improvement efforts that have successfully improved rates of prescriptions at discharge should now be directed to support long-term adherence.²⁹

The World Health Organization found that patient-level, provider-level, and system-level factors each may play a role in suboptimal adherence.³⁰ Less than 4% of patients report side effects as the primary reason for discontinuation of cardiac medications after ST-elevation MI,^{31,32} suggesting that many cases of cardiac medication nonadherence are unintentional or attributable to system-level and provider-level factors.³³ Qualitative studies have found that poor adherence to cardiac medications is often due to suboptimal organization of care.^{34,35} In particular, transitions between

specialty and primary care represent an important risk factor for unintentional discontinuation of cardiac medications.^{24,36} Guidelines recommend outpatient follow-up after MI within 2-6 weeks,³⁷ although a previous study showed lower rates of evidence-based cardiac medication use at 6 months in patients with MI without an outpatient assessment within 30 days.³⁸ We found that > 80% of patients had outpatient follow-up with a primary care provider within 30 days of angiography finding significant CAD. However, in the context of poor continuity of information between providers,³⁹ the transfer of responsibility for repeated prescriptions may not be transparent. It is also possible that short prescriptions inadvertently indicate to both patients and primary care providers that long-term adherence is unnecessary.

Some methodological limitations also warrant consideration. Administrative databases evaluate prescription fills rather than swallowing of pills and cannot account for intentional discontinuation, assess medications that are not covered by the ODB plan, or evaluate patients younger than 65 years. The design of the study cannot fully exclude clinical differences between those receiving longer and those receiving shorter prescriptions. However, the consistency in findings across medication classes reduces the likelihood that the results are biased by unobserved patient-level factors.

Conclusion

In summary, long-term adherence to cardiac secondary prevention medications remains suboptimal, and forcing elderly patients to frequently visit outpatient providers to renew prescriptions may exacerbate this problem. Thus, although dosage adjustments may occasionally be necessary, the length of prescription provided for cardiac medications after angiography may represent a novel modifiable factor for long-term adherence.⁴⁰ A trial would be necessary to provide conclusive evidence, but our findings suggest that the advantages of a general approach of providing cardiac medication prescriptions for a longer interval after discharge may outweigh the potential harm resulting from oversupply.

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References

1. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106:3143-421.
2. Genest J, McPherson R, Frohlich J, et al. 2009 CCS Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult—2009 recommendations. *Can J Cardiol* 2009;25:567-79.
3. Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update. *Circulation* 2011;124:2458-73.
4. Newby LK, LaPointe NM, Chen AY, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006;113:203-12.
5. Hudson M, Richard H, Pilote L. Parabolas of medication use and discontinuation after myocardial infarction—are we closing the treatment gap? *Pharmacoepidemiol Drug Saf* 2007;16:773-85.
6. Shalev V, Chodick G, Silber H, et al. Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 2009;169:260-8.
7. Shah ND, Dunlay SM, Ting HH, et al. Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med* 2009;122:961.e7-961.e13.
8. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;297:177-86.
9. Rublee DA, Chen SY, Mardekian J, et al. Evaluation of cardiovascular morbidity associated with adherence to atorvastatin therapy. *Am J Ther* 2012;19:24-32.
10. Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D. Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. *Can J Clin Pharmacol* 2003;10:67-71.
11. Jackevicius CA, Paterson JM, Naglie G. Concordance between discharge prescriptions and insurance claims in post-myocardial infarction patients. *Pharmacoepidemiol Drug Saf* 2007;16:207-15.
12. Juurlink D, Preyra C, Croxford R, et al. Canadian Institute for Health Information Discharge abstract database: a validation study. Toronto, ON: Institute for Clinical Evaluative Sciences; 2006.
13. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care* 2005;43:1130-9.
14. Williams JI, Young W. A summary of studies on the quality of health care administrative databases in Canada. In: Goel V, Williams JI, Anderson GM, et al, eds. *Patterns of Health Care in Ontario: the ICES Practice Atlas*. 2nd ed. Ottawa, Canada: Canadian Medical Association; 1996:339-45.
15. Lee DS, Stitt A, Wang X, et al. Administrative hospitalization database validation of cardiac procedure codes. *Med Care* 2013;51:e22-6.
16. Wilkens R. Automated geographic coding based on the Statistics Canada postal code conversion files. Ottawa, ON: Statistics Canada; 2001; Report No. 82F0086-XDB.
17. Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288:455-61.
18. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. *JAMA* 2002;288:462-7.
19. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. *Am Heart J* 2006;151:185-91.
20. Schneeweiss S, Seeger JD, Maclure M, et al. Performance of comorbidity scores to control for confounding in epidemiologic studies using claims data. *Am J Epidemiol* 2001;154:854-6.
21. Lopez-Carmona D, Bernal-Lopez M, Mancera-Romero J, et al. Compliance with cardiovascular drug prevention measures in a general population: the multidisciplinary intervention in primary care (IMAP) study. *Eur J Prev Cardiol* 2012;19:1074-81.
22. Steele LS, Glazier RH, Lin E, Evans M. Using administrative data to measure ambulatory mental health service provision in primary care. *Med Care* 2004;42:960-5.
23. Katz MH. *Multivariable Analysis: A Practical Guide for Clinicians and Public Health Researchers*. 3rd ed. Cambridge, UK: Cambridge University Press; 2011.
24. Bell CM, Brener SS, Gunraj N, et al. Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA* 2011;306:840-7.
25. Batal HA, Krantz MJ, Dale RA, Mehler PS, Steiner JF. Impact of prescription size on statin adherence and cholesterol levels. *BMC Health Serv Res* 2007;7:175.
26. Steiner JF, Robbins LJ, Roth SC, Hammond WS. The effect of prescription size on acquisition of maintenance medications. *J Gen Intern Med* 1993;8:306-10.
27. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005;353:487-9.
28. Austin PC, Tu JV, Ko DT, Alter DA. Use of evidence-based therapies after discharge among elderly patients with acute myocardial infarction. *CMAJ* 2008;179:895-900.
29. Ivers NM, Schwalm JD, Grimshaw JM, et al. Delayed educational reminders for long-term medication adherence in ST-elevation myocardial infarction (DERLA-STEMI): protocol for a pragmatic, cluster-randomized controlled trial. *Implement Sci* 2012;7:54.
30. Sabate E, ed. *Adherence to Long-Term Therapies: Evidence for action*. Geneva, Switzerland: World Health Organization; 2003.
31. Bagnall AJ, Yan AT, Yan RT, et al. Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circ Cardiovasc Qual Outcomes* 2010;3:530-7.

32. Sud A, Kline-Rogers EM, Eagle KA, et al. Adherence to medications by patients after acute coronary syndromes. *Ann Pharmacother* 2005;39:1792-7.
33. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. *Circulation* 2009;119:3028-35.
34. AB E, Denig P, van Vliet T, Dekker JH. Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: A qualitative study. *BMC Fam Pract* 2009;10:24.
35. Hickling J, Rogers S, Nazareth I. Barriers to detecting and treating hypercholesterolaemia in patients with ischaemic heart disease: primary care perceptions. *Br J Gen Pract* 2005;55:534-8.
36. Coleman EA, Smith JD, Raha D, Min SJ. Posthospital medication discrepancies: prevalence and contributing factors. *Arch Intern Med* 2005;165:1842-7.
37. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction. *J Am Coll Cardiol* 2007;50:e1-157.
38. Daugherty SL, Ho PM, Spertus JA, et al. Association of early follow-up after acute myocardial infarction with higher rates of medication use. *Arch Intern Med* 2008;168:485-91.
39. Kripalani S, LeFevre F, Phillips CO, et al. Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA* 2007;297:831-4.
40. Lemstra M, Blackburn D, Crawley A, Fung R. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. *Can J Cardiol* 2012;28:574-80.

Supplementary Material

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STUDY PROTOCOL

Open Access

Delayed educational reminders for long-term medication adherence in ST-elevation myocardial infarction (DERLA-STEMI): Protocol for a pragmatic, cluster-randomized controlled trial

Noah M Ivers^{1*}, Jon-David Schwalm², Jeremy M Grimshaw³, Holly Witteman⁴, Monica Taljaard⁵, Merrick Zwarenstein⁶ and Madhu K Natarajan²

Abstract

Background: Despite evidence-based recommendations supporting long-term use of cardiac medications in patients post ST-elevation myocardial infarction, adherence is known to decline over time. Discontinuation of cardiac medications in such patients is associated with increased mortality.

Methods/design: This is a pragmatic, cluster-randomized controlled trial with blinded outcome assessment and embedded qualitative process evaluation. Patients from one health region in Ontario, Canada who undergo a coronary angiogram during their admission for ST-elevation myocardial infarction and who survive their initial hospitalization will be included. Allocation of eligible patients to intervention or usual care will take place within one week after the angiogram using a computer-generated random sequence. To avoid treatment contamination, patients treated by the same family physician will be allocated to the same study arm. The intervention consists of recurrent, personalized, paper-based educational messages and reminders sent via post on behalf of the interventional cardiologist to the patient, family physician, and pharmacist urging long-term adherence to secondary prevention medications. The primary outcome is the proportion of patients who report in a phone interview taking all relevant classes of cardiac medications at twelve months. Secondary outcomes to be measured at three and twelve months include proportions of patients who report: actively taking each cardiac medication class of interest (item-by-item); stopping medications due to side effects; taking one or two or three medication classes concurrently; a perfect Morisky Medication Adherence Score for cardiac medication compliance; and having a discussion with their family physician about long-term adherence to cardiac medications. Self-reported measures of adherence will be validated using administrative data for prescriptions filled.

Discussion: This intervention is designed to be easily generalizable. If effective, it could be implemented broadly. If it does not change medication utilization, the process evaluation will offer insights regarding how such an intervention could be optimized in future.

Trial registration: Clinicaltrials.gov NCT01325116

Keywords: Randomized trial, Medication adherence, Reminders

* Correspondence: noah.ivers@utoronto.ca

¹Family Practice Health Centre/Women's College Research Institute, Women's College Hospital, 76 Grenville Ave Toronto, Toronto, Ontario, Canada
Full list of author information is available at the end of the article

Background

Cardiovascular disease burden and the role for long-term pharmacotherapy

Worldwide, cardiovascular disease (CVD) is estimated to be the leading cause of death and disability [1]. Approximately 50% of myocardial infarctions (MIs) and 70% of CVD deaths occur in patients who have already documented coronary artery disease (CAD) [2]. Therefore, the prompt identification of modifiable cardiovascular risk factors and initiation of proven secondary preventative medications post-MI are essential to the prevention of subsequent cardiac events [3]. Population-level observational studies provide evidence that the rate of cardiovascular morbidity and mortality has been decreased through the use evidence-based therapies [4,5].

ST-segment elevation myocardial infarction (STEMI) is a common presentation of acute myocardial infarction (AMI) constituting approximately 30% of all cases [6]. Post-STEMI, patients are at high risk for subsequent cardiac events—18% of men and 35% of women will have a repeat MI within six years and STEMI patients have four to six times the risk of sudden cardiac death compared to the general population [7]. While acute treatment is crucial for STEMI patients, relevant guidelines emphasize that the initiation and long-term maintenance of evidence-based secondary preventative therapies are essential for reducing the overall burden of CVD [3,8,9].

Poor long-term adherence to cardiac medications

While there is a significant body of evidence supporting these guidelines (Table 1), there remains a large gap between ideal and actual care with regard to the long-term management of cardiovascular risk for these patients.

Studies show that adherence to evidence-based therapies begins decreasing at 30 days and falls to as low as 50% adherence at six months post-discharge [10-14]. Unfortunately, discontinuation of evidence-based therapies has repeatedly been shown to be associated with increased mortality in patients with CAD [15-18].

Medication non-adherence is increasingly recognized as a very important issue due to its significant health consequences [19,20]. Many reasons for non-adherence have been proposed and these can generally be categorized as provider-level (*e.g.*, knowledge, motivation, time), patient-level (*e.g.*, knowledge, motivation, finances [21]), and system-level (*e.g.*, access to care, coordination of care). Furthermore, both ethnicity [22,23] and socio-economic status [24] seem to be related to quality of care for cardiovascular disease, even in countries with universal health-care like Canada and the United Kingdom (UK), and non-adherence related to such factors may not be readily impacted with quality improvement interventions.

Fortunately, the evidence suggests that many of the key factors contributing to cardiac medication non-adherence may be amenable to intervention. Discontinuation of evidence-based cardiac medicines post-STEMI is rarely due to an active, informed choice after discussion of risks and benefits between patient and health-care-provider; absolute contraindications are rare and side effects are infrequently reported by patients as the primary reason for discontinuation (less than 4% of patients) [25,26]. In contrast to situations where informed decisions are made to deviate from standard treatment protocols, qualitative work in primary care has found that poor adherence may be frequently due to fragmented systems of care [27] or communication problems at the interface between secondary and primary care [28]. A recent study in Canada has highlighted the

Table 1 Summary of guideline recommendations for medications post-STEMI

Medication	Recommendation	Strength of evidence*
Anti-platelets	Aspirin therapy (75-162 mg/day) indefinitely post-STEMI.	I A
	P2Y ₁₂ -receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) in combination with aspirin in patients post ACS	I A
	P2Y ₁₂ -receptor inhibitor continued for at least 12 months if ACS managed with PCI and stent placement	I A
Statins	Statin therapy indefinitely for all patients with a prior cardiovascular event.	I A
Angiotensin-system agent	ACE inhibitor (or ARB if intolerant) post-STEMI indefinitely for all patients with left ventricular ejection fraction <40% and in those with hypertension, diabetes, or chronic kidney disease	I A
	ACE inhibitor (or ARB) for all patients post-STEMI	Ila B
Beta-blockers	Beta-blockers for all patients post-STEMI	I A
	Beta-blockers continued for at least three years post-STEMI	I B

*Strength of Evidence.

I: Conditions for which there is evidence and/or general agreement that a given treatment is beneficial, useful, and effective.

Ila: Weight of evidence/opinion is in favor of usefulness/efficacy.

A: Data derived from multiple randomized clinical trials or meta-analyses.

B: Data derived from a single randomized trial, or nonrandomized studies.

risk related to transitions in care; it appears that hospitalizations increase the risk for inadvertent discontinuation of cardiac medications [29].

The provider also can have an impact; having a cardiologist involved in the patient's care may increase rates of appropriate medication adherence [30]. However, there is undesirable variation among prescription rates by specialists as well. In one study of cardiologists, the most common reason given for not prescribing secondary prevention medications was, 'not high-enough risk' [25]. However, in that study, risk scores of patients not treated for this reason were often higher than those of patients prescribed such treatment. Meanwhile, the same study found that approximately one-third of patients had stopped their medication without instruction from their doctor. This indicates a potential role for multi-pronged interventions addressing both the provider and the patient.

Previous research aiming to improve adherence

Numerous systematic reviews have been published regarding interventions to improve adherence to medications. An overview of reviews found that no patient-mediated interventions were effective across all diseases, but found that the most promising interventions included self-management, simplified dosing, and involvement of pharmacists [31]. A review focusing on anti-depressants found that patient education alone was ineffective [32], and a review focusing on anti-epileptics found that patient education was inconsistent, while interventions with multiple reminders featuring action planning were more often effective [33]. Recognizing that non-adherence tends to worsen over time, a recent Cochrane review recommended testing a delayed intervention as opposed to the immediate reminders used in similar previous trials [34], as one would expect a larger effect size in a delayed intervention.

One previous trial has shown that brief evidence summaries regarding medications attached to discharge letters sent to primary care providers resulted in improved adherence [35]. Three other trials have evaluated the role of reminder letters to the primary care provider (with or without patient reminders) to improve adherence to evidenced-based cardiovascular therapies: one in the USA, one in the UK, and one in Canada [36-38]. The American trial focused on beta-blocker use post-MI and found a small increase in compliance (proportion of days covered), with a number needed to treat of 16 for achieving high adherence, but no change in the proportion who discontinued their beta-blocker. The other two trials focused on statin use in patients with known CAD. These trials found absolute increases in adherence of 9% to 10% in statin use, but despite this being a potentially important effect size on a population basis, both were under-powered for effects this size.

Objectives

The overarching goal of this project is to improve long-term use of secondary prevention medications for patients with CAD, and thereby reduce cardiovascular events through the use of an easily generalizable and sustainable intervention. The primary objective of this study is to assess if repeated mailing of an educational message and reminder to the family physician and the patient will decrease the proportion of patients who discontinue evidence-based secondary-prevention medications at twelve months post-STEMI. A secondary objective is to encourage cardiac patients and their primary care providers to discuss the benefits of long-term adherence to cardiac medications.

Methods/design

Study design

DERLA-STEMI is a pragmatic, cluster-randomised controlled trial, with blinded outcome-assessment, and is registered with clinicaltrials.gov (NCT01325116). See Study Flow Diagram (Figure 1).

Participants and Setting

In Ontario, healthcare is financed through a single-payer (publicly administered) system. There are no co-payments for visits to generalist or specialist physicians or for care provided in hospitals for patients of any age, and almost all licensed prescription medications are covered for patients 65 and over. Patients younger than 65 years pay for medications out-of-pocket or through private insurance plans, or are covered by the provincial plan if they qualify for social support.

In this study, eligible patients are adult patients (>18 years) with a diagnosis of STEMI, who undergo a coronary angiography procedure (with or without angioplasty), at the Heart Investigation Unit (HIU) in Hamilton, Ontario, and who are alive at hospital discharge. In keeping with the pragmatic approach to study design, no other exclusion criteria will be applied. The HIU is the only catheterization lab in its region, with a catchment population of almost 1.5 million people. More than 700 STEMI patients undergo an angiogram there each year. Studies at the HIU have highlighted excellent rates of prescribing of evidence-based therapies at discharge post-STEMI, but substantial reduction in use starting three months following discharge [39,40]. While 78% of STEMI patients leave the HIU taking a statin, an ACE-inhibitor (or ARB), a beta-blocker, and aspirin, by 90 days the proportion still taking all four of these medication classes falls to 63% (unpublished data from the Strategic Management of Acute Reperfusion and Therapies in Acute Myocardial Infarction (SMART-AMI) study).

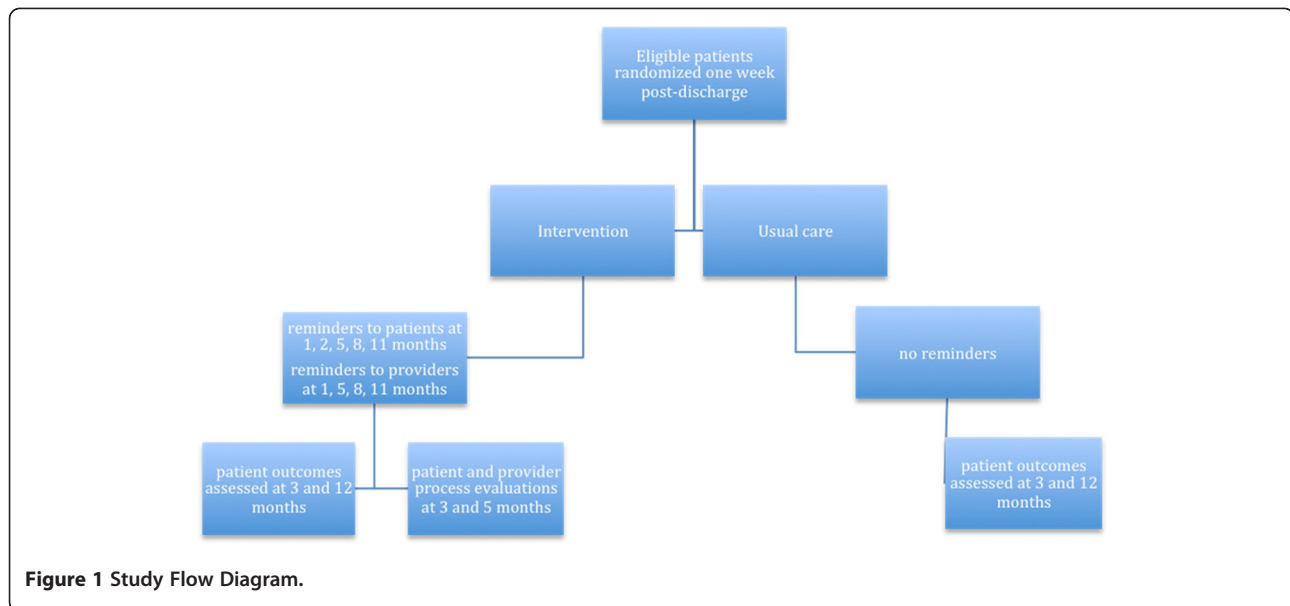


Figure 1 Study Flow Diagram.

Intervention

The intervention was developed in concert with clinical experts from both primary care and cardiology, as well as experts in knowledge translation and medical decision-making. Personalized letters sent via post to the patient and their family physician at one, five, eight, and eleven months after their angiogram, signed by the interventional cardiologist (see Additional file 1: Appendix A for prototype). The letter for the family physician names the patient and provides brief evidence in support of long-term medication use for these patients. This was reviewed and edited with a series of family physicians from a different area of the province.

The patient letter provides a review of the importance and role of each of the cardiac medications and urges short- and long-term adherence (see Additional file 1: Appendix B for prototype). The educational aspect is designed to address knowledge and beliefs about medication use as a potential cause of poor adherence. The intervention explicitly encourages discussion of medication adherence with the family physician by asking patients to bring the letter to their family physician. It also asks patients to deliver the final page of their letter to their pharmacist; this page is written to the pharmacist urging them to participate in promoting long-term adherence. The intention is to facilitate recurrent discussions with primary care providers that emphasize long-term adherence and to address coordination of care and continuity of information as barriers to medication persistence. This letter was developed with iterative evaluations of understanding and acceptability amongst a series of cardiology patients at the HIU. The language in the patient letter is simplified to a grade six-level.

The timing of the intervention was specifically chosen based on the preliminary data obtained from the SMART-AMI trial demonstrating suboptimal rates at 90 days. Furthermore, literature (referenced above) demonstrates that adherence starts decreasing by thirty days and continues to decrease in an almost linear fashion. Finally, the common practice in Ontario is for pharmacists to dispense medications for no more than three months at a time (regardless of duration of the prescription ordered by the physician). Therefore, we decided to deliver the intervention at regular intervals (1, 5, 8, and 11 months post-STEMI) corresponding to the likely time periods prior to patients requiring a prescription renewal/refill. In pilot testing the intervention with family physicians and patients, we determined that sending the full letter too frequently would be undesirable and that the physicians in particular did not want to have monthly reminders. At the same time, close examination of data from Ontario indicated large stepwise declines in adherence at 30 and 60 days post-STEMI. To address this, patients will be provided an additional postcard type reminder two months post-STEMI (see Additional file 1: Appendix C).

In summary, the unique aspects of the intervention compared to usual care include the following: the letter to the primary care provider is personalized and includes a summary of the evidence in support of long-term adherence and represents a recurrent form of contact between the cardiologist and the primary care provider; the letter to the patient use clear language suitable for a broad range of health literacy levels and was iteratively refined with input from patients in the target population, features content that attempts to address adherence-related beliefs, and provides explicit, actionable instructions

to discuss the matter with the family physician as well as a summary to be given to the outpatient pharmacist to facilitate coordination of renewals.

Comparator/usual care

Usual care in this context may include some contact between the admitting physician (generally not the interventional cardiologist) for the STEMI patient and the primary care provider (generally the family physician). This is usually in the form of a standard discharge summary mailed to the family physician's office at the end of the hospitalization. The quality of such discharge summaries varies widely even within the same institution (and summaries frequently lack necessary information regarding medications) [41]. In keeping with the pragmatic nature of the trial, no attempt will be made to standardize the usual care arm [42].

Allocation

The randomization schedule was computer-generated by a statistician independent of the study, using a permuted block design with randomly varying block lengths of four, six, or eight. Eligible patients are randomly allocated to one of the two treatment arms. Although enrolment of more than one patient treated by a particular family physician is expected to occur infrequently, randomization will be carried out to ensure that, once a patient from any family physician is randomized, all future patients seen by that family physician will automatically be assigned to the same arm. This is necessary to avoid contamination (with one family physician having patients in different intervention arms). Roughly one-half of patients will be allocated to each study arm (the actual allocation ratio will depend on the size of the clusters). Based on pilot data, we anticipate that approximately 10% to 15% of patients will not have a family physician. In keeping with the pragmatic design of the trial, a patient without a family physician will be included (receiving only the patient-level intervention).

Randomization is delayed by one week (after the angiogram) to permit time to identify and exclude patients with in-hospital death. Randomization will continue until the target sample size is achieved. The anticipated duration of enrolment is 15 months. The allocation sequence will be concealed from the investigators and outcome assessors; only the study coordinator who will be sending out the letters will have access to the un-blinded allocation list.

Outcomes

The primary outcome is the proportion of living patients who describe taking all cardiac medication classes of interest measured at twelve months. This type of 'all-or-none'

measure has been recommended for evaluating quality improvement interventions, especially related to medication utilization [43]. Specifically, we will assess whether patients are taking a statin, beta-blocker, angiotensin modifier (ACE or ARB), and aspirin at twelve months. All STEMI patients have reasonable evidence supporting these medications [3]; we anticipate that randomization will balance those patients for whom evidence is less clear or who might have contraindications to any of these medications.

We will also assess whether patients are taking these four medication classes plus a secondary antiplatelet (clopidogrel, prasugrel, or ticagrelor) at three months. Therefore, patients at three months will be dichotomized as to whether or not they are taking all five cardiac medication classes, and at twelve months they will be dichotomized according to whether they are taking all four relevant medication classes. The difference in the number of medication classes considered at three and twelve months relates to uncertainty in the evidence regarding the appropriateness of a secondary antiplatelet at this timeframe. Additional secondary outcomes include a comparison of: the proportion of patients who report actively taking each cardiac medication class of interest (item-by-item) at three and twelve months; the proportion of patients who report stopping medications due to side effects at three and twelve months; the proportion taking one or two or three medication classes concurrently at three and twelve months; and the proportion of patients with a perfect Morisky Medication Adherence Score (MMAS) for cardiac medication compliance at three and twelve months. The MMAS is a brief, standardized adherence questionnaire which excellent reliability [44], and has been shown to be predictive of cardiovascular medication adherence [45] and to be associated with control of blood pressure and cholesterol [44,46]. In addition, all patients will be asked at three months and twelve months whether they had a discussion with their family physician during past three months in which the provider had encouraged long-term cardiac medication compliance.

Data collection

Baseline patient characteristics will be obtained from standard patient-registry information at the HIU. This includes demographic information, comorbidities, and the findings at the time of angiography.

Outcomes will be assessed 3 and 12 months post-index angiogram through patient phone calls by a research coordinator associated with the HIU who will be trained expressly for this function. The research coordinator conducting the phone calls will not have access to the allocation list. The calls are made on behalf of the treating cardiologist at the HIU, and all patients will be

encouraged to review cardio-protective meds with their family physician. The phone call follow-ups will ask patients to list their current, daily medications (and doses) without specific prompting in order to reduce bias. Attempts will be made to contact patients for a maximum of 30 days prior to being considered lost-to-follow-up. Reasons for loss-to-follow-up will be tracked.

For a sample of patients aged 65 and older, the Ontario Drug Benefit database will be used to examine the accuracy of the self-reported primary outcome and to further evaluate adherence using the medication possession ratio over the preceding year, which has been shown to be associated with both pill counts and clinical effects [47].

Ethical considerations

Research Ethics Board (REB) approval was received at Hamilton Health Sciences Centre and McMaster University (project number 11–191). Given the low risk nature of the intervention, which falls within the realm of continuity-of-care and circle-of-care, the REB agreed that verbal consent at the time of outcome assessment is the most appropriate design to test this pragmatic intervention. Thus, there is no formal recruitment process; as mentioned above, all eligible patients within the registry at the HIU are allocated to intervention or control one-week post-STEMI. To gain REB approval, we agreed to provide a note to the family physician of all included patients describing the patient-reported outcomes (*e.g.*, current medications and adherence) at the end of the trial.

Data management

All patient data will be collected directly into a password-protected database and will not be removed from the server at the HIU research office. Necessary information for contacting the participants (*e.g.*, name, phone number) will be kept in a separate, password-protected file from the study data, which will have no patient identifiers. The outcome data (without any identifiers) will be transferred from the database into a statistical package for analysis.

Analysis

Descriptive statistics will be calculated for all variables of interest: continuous variables with a normal distribution will be summarized using means and standard deviations (medians and inter-quartile ranges in the case of skewed distributions), whereas categorical variables will be summarized using frequencies and proportions.

We hypothesize that the intervention will result in a greater proportion of patients who report taking each cardiovascular medication class of interest at 12 months post-angiography. The absolute difference in proportions

will be calculated for all primary and secondary dichotomous outcomes, together with 95% confidence intervals adjusting for clustering by family physician [48]. The statistical significance of differences between arms will be evaluated using chi-squared tests, adjusted for clustering by family physician.

Exploratory multivariable analyses will be carried out using generalized estimating equations (GEE) to identify potential baseline predictors of adherence. Potential effect modification by treatment—medical management versus coronary artery bypass graft (CABG) versus angioplasty—and attendance at cardiac rehabilitation will be explored by including interactions between these two variables and group. It is plausible that this analysis will suggest a need for tailored interventions for these subgroups. A further exploratory analysis will be conducted focusing on patients who reported taking all five cardiac medication classes and had perfect MMAS scores at three months using a multivariable model to examine covariates predicting late-onset discontinuation. In addition, a planned sensitivity analysis will exclude those patients who did not have a family physician, as we would expect such patients to be more likely to discontinue their cardiac medications.

Analyses will be performed on an intention-to-treat basis. No interim analyses are planned. All analyses will be carried out using the SAS Version 9.2 statistical program (SAS Institute, Cary, NC, USA).

Sample size

The sample size for this design is based on the following assumptions: an assumed absolute increase in the proportion of patients taking all four cardiovascular medication classes of 11% at twelve months post-STEMI; an estimated control group proportion of 50%, and a variance inflation factor of 1.02 (derived from an intra-cluster correlation coefficient of 0.019 calculated from data in the SMART-AMI registry and assuming an average cluster size of 1.2 based on pilot data). To achieve 80% power to detect a significant main effect of the intervention using a Chi-squared test at the 5% level of significance, 652 patients would be required. We will randomize 815 patients to account for an estimated participation rate of 80% at the 12-month follow-up. This dropout rate is conservative based on similar studies at the HIU where the participation rate has been greater than 90% over even longer time periods [40].

The expected effect size is slightly higher than the effect seen in the previous Canadian trial to account for the fact that the intervention is multifaceted (directed at both physician and patient) and occurring later post-STEMI (reducing the expected control group rate and therefore the possibility of a ceiling effect). Based on this sample size calculation, and the rate of STEMI patients

presenting to the HIU, we anticipate that it will take approximately 15 months to complete the recruitment for this study.

We will use a kappa statistic to assess agreement between the self-report of the primary outcome and the corresponding objective data from the Ontario Drug Benefit database. Based on an anticipated overall proportion of 56% at 12 months (average of intervention and control arm) and an anticipated kappa of 0.88, we would consider acceptable agreement if the lower limit of the 95% confidence interval around kappa does not drop below 0.80. Therefore we will evaluate validity of the primary outcome in a random selection of 138 patients aged 65 or greater.

Process evaluation—optimizing the intervention

A random sample of participating patients will be asked a series of additional, structured questions at the time of outcome assessment 90 days post-STEMI. Specifically, a 20% random selection of patients who received the intervention will be sampled, equating to approximately 80 patients. In addition, all family physicians in the intervention group will be mailed a one-page questionnaire along with the second iteration of the provider letter (month five post-STEMI). A response rate of only 15% will allow us to get feedback from about 50 family physicians. The questionnaires to both patient and provider assess acceptability of the intervention and the reasons for any (lack of) action taken (See Additional file 2: Appendix D for patient process evaluation questionnaire and Additional file 2: Appendix E for provider process evaluation questionnaire). The answers to these questionnaires will be summarized descriptively and used to inform future iterations of the intervention.

We also plan to conduct focus groups with both patients and providers to better understand both why the intervention did (or did not) work and how it might be optimized. Participants for these focus groups will be purposively recruited based on the responses to the questionnaires. We plan to conduct one or two focus groups of six to eight patients and one focus group of four to six physicians, each group lasting about one hour occurring at the HIU. These focus groups will follow a semi-structured guide that will be informed by the issues identified in the questionnaires. The overarching goal of the focus groups will be to compare and contrast various designs and approaches of sending reminders to decrease the risk of inappropriate medication discontinuation. To this end, a variety of reminder designs will be handed out among the focus group participants to encourage discussion (similar to how marketing firms traditionally have used focus groups). Physician participants will be provided with \$75 (and refreshments). Patient participants will be offered a \$25 gift certificate (and

refreshments) as remuneration for attending the focus group. The sessions will be recorded and transcribed verbatim.

Discussion

Discontinuation of cardiac medications post-STEMI occurs due to patient, provider, and system-level factors and has important consequences for the patient. This two-arm, pragmatic, cluster-randomized controlled trial will test whether mailed reminder letters sent from the interventional cardiologist to the patient and their family physician can successfully increase adherence. Even if the trial does not show a significant effect on medication discontinuation, the embedded process evaluation will provide helpful information for planning future interventions aiming to address this important issue.

Limitations

Although our overall goal is to improve adherence to medications, it is important to note that our primary outcome evaluates discontinuation (or 'persistence'). This represents the most extreme form of non-adherence. The allocation is clustered at the level of the family physician to limit contamination, but it was deemed not feasible to do the same with pharmacists. Although the tear-away page in the patient letter for pharmacists could theoretically bias toward a null finding if pharmacists transfer their learning from one patient to another, we considered this risk to be small in comparison to the potential benefit of facilitating interactions with these key primary care providers.

It is important to note that this trial will not be able to discern the relative importance of intervention at patient versus family physician level. A larger sample size would be preferable to provide an opportunity to test multiple ways of designing and delivering this type of intervention within a single trial. In the case of a positive effect, the pragmatic approach utilized will not allow for inferences regarding the 'most important' active ingredients in the intervention. We intend to explore these issues through the process evaluation. The questionnaires developed for the process evaluation are not independently validated for assessing acceptability and usability of the reminder intervention. However, they will be evaluated qualitatively to inform iterative improvements to the program after the trial is completed, and will allow us to identify interested participants for focus groups.

Although the research coordinator conducting the outcome assessment will be blinded to allocation, it is possible that some patients will discuss receiving the intervention with the coordinator. Another important caveat is that we will be using patient self-report for main outcome measurements—an approach which has previously been used in a similar trial [38]. We are planning to

evaluate the validity of self-report data in our study by comparing patient reported medication use (including the MMAS) with data recorded in administrative databases for a subsample of participants above age 65 (for whom data are accessible using the Ontario Drug Database). Through these administrative databases, we can also pursue proxy measures for adherence (rather than strictly discontinuation) by assessing the medication possession ratio.

Implications

Given the proven effectiveness of secondary prevention medications for reducing morbidity and mortality and the high risk for poor outcomes in the post-STEMI population, we believe it is appropriate to power this trial to show relatively small increases in adherence. Although we would hesitate to extrapolate the findings of this study without further research, we believe it is important for quality improvement trials measuring process outcomes such as adherence to consider the potential for patient-relevant outcomes. To illustrate, consider the systematic review of RCTs of statin-therapy, which found a number needed to treat (NNT) of 86 to reduce mortality in patients with CAD [49]. We estimate that the NNT for avoiding statin discontinuation with the reminder interventions tested in this trial is approximately 10. If this were the case, then the NNT for the reminder interventions to prevent a single mortality would be 860. In fact, the number might be lower than this since the intervention may also increase utilization of the other cardiac medications known to reduce mortality. Given the low-cost, low-risk nature of the intervention in this trial, we believe that NNTs of this size merit further study for potential population-wide implementation.

Summary

The major strengths of this trial are the pragmatic nature of the intervention the study design. The trial is well powered and designed specifically to improve health services for a common problem in patients at high risk of cardiovascular events. Many quality improvement trials embark upon highly sophisticated and expensive interventions; even if successful, sustainability of such interventions beyond the trial period proves challenging. Conversely, the DERLA-STEMI intervention would be easily testable in other healthcare settings and for other conditions where long-term adherence is suboptimal. We believe this study will demonstrate the feasibility, acceptability, and (hopefully) the effectiveness of a sustainable and generalizable quality improvement intervention for STEMI patients.

Additional files

Additional file 1: Appendix A. Physician Intervention Letter. **Appendix B.** Patient Intervention Letter. **Appendix C.** Patient Intervention 2-month Postcard.

Additional file 2: Appendix D. Process Evaluation, patient survey. **Appendix E.** Process Evaluation, provider survey.

Competing interests

The authors declare no conflicts of interest.

Authors' contributions

All authors contributed to the study concept and design and all approved the final version of this manuscript.

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Author details

¹Family Practice Health Centre/Women's College Research Institute, Women's College Hospital, 76 Grenville Ave Toronto, Toronto, Ontario, Canada.

²Department of Medicine, Division of Cardiology, McMaster University/Hamilton Health Sciences, 237 Barton Street, East Hamilton, Ontario, Canada.

³Ottawa Hospital - General Campus, Centre for Practice-Changing Research, 501 Smyth Road, Ottawa, Ontario, Canada. ⁴Center for Bioethics & Social Sciences in Medicine, Department of Internal Medicine, University of Michigan, 300 North Ingalls Ann Arbor, Michigan, USA. ⁵Ottawa Hospital Research Institute, Clinical Epidemiology Program, Ottawa Hospital, Civic Campus, 1053 Carling Avenue, Ottawa, Ontario, Canada. ⁶Institute for Clinical Evaluative Sciences, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario, Canada.

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References

1. Murray CJ, Lopez AD: Evidence-based health policy—lessons from the Global Burden of Disease Study. *Science* 1996, **274**(5288):740–743.
2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002, **106**(25):3143–3421.
3. Smith SC Jr, Benjamin EJ, Bonow RO, Braun LT, Creager MA, Franklin BA, Gibbons RJ, Grundy SM, Hiratzka LF, Jones DW, Lloyd-Jones DM, Minissian M, Mosca L, Peterson ED, Sacco RL, Spertus J, Stein JH, Taubert KA, World Heart Federation and the Preventive Cardiovascular Nurses Association: AHA/ACCF Secondary Prevention and Risk Reduction Therapy for Patients with Coronary and other Atherosclerotic Vascular Disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation. *Circulation* 2011, **124**(22):2458–2473.
4. Hippisley-Cox J, Coupland C: Effect of statins on the mortality of patients with ischaemic heart disease: population based cohort study with nested case-control analysis. *Heart* 2006, **92**(6):752–758.
5. Wijeyesundera HC, Machado M, Farahati F, Wang X, Wittman W, van der Velde G, Tu JV, Lee DS, Goodman SG, Petrella R, O'Flaherty M, Krahn M, Capewell S: Association of temporal trends in risk factors and treatment uptake with coronary heart disease mortality, 1994–2005. *JAMA* 2010, **303**(18):1841–1847.
6. Thom T, Haase N, Rosamond W, Howard VJ, Rumsfeld J, Manolio T, Zheng ZJ, Flegal K, O'Donnell C, Kittner S, Lloyd-Jones D, Goff DC Jr, Hong Y, Adams R, Friday G, Furie K, Gorelick P, Kissela B, Marler J, Meigs J, Roger V,

- Sidney S, Sorlie P, Steinberger J, Wasserthiel-Smoller S, Wilson M, Wolf P: American Heart Association Statistics Committee and Stroke Statistics Subcommittee: Heart disease and stroke statistics--2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006, **113**(6):e85-151.
7. Myerburg RJ, Kessler KM, Castellanos A: Sudden cardiac death: epidemiology, transient risk, and intervention assessment. *Ann Intern Med* 1993, **119**(12):1187-1197.
 8. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr: 2004 Writing Committee Members, Anbe DT, Kushner FG, Ornato JP, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Halperin JL, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B, Tarkington LG, Yancy CW: 2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaboration With the Canadian Cardiovascular Society endorsed by the American Academy of Family Physicians: 2007 Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction, Writing on Behalf of the 2004 Writing Committee. *Circulation* 2008, **117**(2):296-329.
 9. Fitchett DH, Theroux P, Brophy JM, Cantor WJ, Cox JL, Gupta M, Kertland H, Mehta SR, Welsh RC, Goodman SG: Assessment and management of acute coronary syndromes (ACS): a Canadian perspective on current guideline-recommended treatment--part 2: ST-segment elevation myocardial infarction. *Can J Cardiol* 2011, **27**(Suppl A):402-412.
 10. Tu JV, Donovan LR, Lee DS, Wang JT, Austin PC, Alter DA, Ko DT: Effectiveness of public report cards for improving the quality of cardiac care: the EFFECT study: a randomized trial. *JAMA* 2009, **302**(21):2330-2337.
 11. Ahmad M, Schwalm JD, Velianou JL, Natarajan MK: Impact of routine in-hospital assessment of low-density lipoprotein levels and standardized orders on statin therapy in patients undergoing percutaneous coronary interventions. *J Invasive Cardiol* 2005, **17**(10):518-520.
 12. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, Muhlbaier LH, Califf RM: Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. *Circulation* 2006, **113**(2):203-212.
 13. Hudson M, Richard H, Pilote L: Parabolas of medication use and discontinuation after myocardial infarction--are we closing the treatment gap? *Pharmacoepidemiol Drug Saf* 2007, **16**(7):773-785.
 14. Shah ND, Dunlay SM, Ting HH, Montori VM, Thomas RJ, Wagie AE, Roger VL: Long-term medication adherence after myocardial infarction: experience of a community. *Am J Med* 2009, **122**(10):e7-13. 961.
 15. Rasmussen JN, Chong A, Alter DA: Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007, **297**(2):177-186.
 16. Shalev V, Chodick G, Silber H, Kokia E, Jan J, Heymann AD: Continuation of statin treatment and all-cause mortality: a population-based cohort study. *Arch Intern Med* 2009, **169**(3):260-268.
 17. Rublee DA, Chen SY, Mardikian J, Wu N, Rao P, Boulanger L: Evaluation of cardiovascular morbidity associated with adherence to atorvastatin therapy. *Am J Ther* 2012, **19**(1):24-32.
 18. Rodriguez LA, Cea-Soriano L, Martin-Merino E, Johansson S: Discontinuation of low dose aspirin and risk of myocardial infarction: case-control study in UK primary care. *BMJ* 2011, **343**:4094.
 19. Brown MT, Bussell JK: Medication adherence: WHO cares? *Mayo Clin Proc* 2011, **86**(4):304-314.
 20. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, Daniel JG, Ekman I, Ho M, Johnson M, Kimmel SE, Liu LZ, Musaus J, Shrank WH: Whalley Buono E, Weiss K, Granger CB: Medication adherence: a call for action. *Am Heart J* 2011, **162**(3):412-424.
 21. Kreps GL, Villagran MM, Zhao X, McHorney CA, Ledford C, Weathers M, Keefe B: Development and validation of motivational messages to improve prescription medication adherence for patients with chronic health problems. *Patient Educ Couns* 2011, **83**(3):375-381.
 22. Gill PS, Quirke TP, Mant JW, Allan TF: The use of lipid-lowering drugs across ethnic groups in the secondary prevention of ischaemic heart disease: analysis of cross-sectional surveys in England. *Br J Gen Pract* 2004, **54**(503):442-443.
 23. Chiu M, Austin PC, Manuel DG, Tu JV: Comparison of cardiovascular risk profiles among ethnic groups using population health surveys between 1996 and 2007. *CMAJ* 2010, **182**(8):E301-E310.
 24. Rabi DM, Edwards AL, Svenson LW, Graham MM, Knudtson ML, Ghali WA: Alberta Provincial Project for Assessing Outcomes in Coronary Heart Disease Investigators: Association of median household income with burden of coronary artery disease among individuals with diabetes. *Circ Cardiovasc Qual Outcomes* 2010, **3**(1):48-53.
 25. Bagnall AJ, Yan AT, Yan RT, Lee CH, Tan M, Baer C, Polasek P, Fitchett DH, Langer A, Goodman SG: Canadian Acute Coronary Syndromes Registry II Investigators: Optimal medical therapy for non-ST-segment-elevation acute coronary syndromes: exploring why physicians do not prescribe evidence-based treatment and why patients discontinue medications after discharge. *Circ Cardiovasc Qual Outcomes* 2010, **3**(5):530-537.
 26. Sud A, Kline-Rogers EM, Eagle KA, Fang J, Armstrong DF, Rangarajan K, Otten RF, Stafkey-Mailey DR, Taylor SD, Erickson SR: Adherence to medications by patients after acute coronary syndromes. *Ann Pharmacother* 2005, **39**(11):1792-1797.
 27. Ab E, Denig P, van Vliet T, Dekker JH: Reasons of general practitioners for not prescribing lipid-lowering medication to patients with diabetes: a qualitative study. *BMC Fam Pract* 2009, **10**:24.
 28. Hickling J, Rogers S, Nazareth I: Barriers to detecting and treating hypercholesterolaemia in patients with ischaemic heart disease: primary care perceptions. *Br J Gen Pract* 2005, **55**(516):534-538.
 29. Bell CM, Brenner SS, Gunraj N, Huo C, Bierman AS, Scales DC, Bajcar J, Zwarenstein M, Urbach DR: Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. *JAMA* 2011, **306**(8):840-847.
 30. Austin PC, Tu JV, Ko DT, Alter DA: Factors associated with the use of evidence-based therapies after discharge among elderly patients with myocardial infarction. *CMAJ* 2008, **179**(9):901-908.
 31. Ryan R, Santesso N, Hill S, Lowe D, Kaufman C, Grimshaw J: Consumer-oriented interventions for evidence-based prescribing and medicines use: an overview of systematic reviews. *Cochrane Database Syst Rev* 2011, **5**(5):CD007768.
 32. Chong WW, Aslani P, Chen TF: Effectiveness of interventions to improve antidepressant medication adherence: a systematic review. *Int J Clin Pract* 2011, **65**(9):954-975.
 33. Al-Aqeel S, Al-Sabhan J: Strategies for improving adherence to antiepileptic drug treatment in patients with epilepsy. *Cochrane Database Syst Rev* 2011, **1**(1):CD008312.
 34. Schedlbauer A, Davies P, Fahey T: Interventions to improve adherence to lipid lowering medication. *Cochrane Database Syst Rev* 2010, **3**:CD004371.
 35. Kunz R, Vist G, Oxman AD: Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev* 2007, **2**(2):MR000012.
 36. Smith DH, Kramer JM, Perrin N, Platt R, Roblin DW, Lane K, Goodman M, Nelson WW, Yang X, Soumerai SB: A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction. *Arch Intern Med* 2008, **68**(5):477-483. discussion 483; quiz 447.
 37. Feder G, Griffiths C, Eldridge S, Spence M: Effect of postal prompts to patients and general practitioners on the quality of primary care after a coronary event (POST): randomised controlled trial. *BMJ* 1999, **318**(7197):1522-1526.
 38. McAlister FA, Fradette M, Majumdar SR, Williams R, Graham M, McMeekin J, Ghali WA, Tsuyuki RT, Knudtson ML, Grimshaw J: The Enhancing Secondary Prevention in Coronary Artery Disease trial. *CMAJ* 2009, **181**(12):897-904.
 39. Ahmad M, Schwalm JD, Velianou JL, Pericak D, Natarajan MK: Comparison of one-year clinical outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice. *Can J Cardiol* 2008, **24**(10):771-775.
 40. Schwalm JD, Ahmad M, Velianou JL, Pericak D, Natarajan MK: Long-term outcomes with paclitaxel-eluting stents versus bare metal stents in everyday practice: a Canadian experience. *Can J Cardiol* 2010, **26**(2):e40-e44.
 41. Kripalani S, LeFevre F, Phillips CO, Williams MV, Basaviah P, Baker DW: Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. *JAMA* 2007, **297**(8):831-841.
 42. Treweek S, Zwarenstein M: Making trials matter: pragmatic and explanatory trials and the problem of applicability. *Trials* 2009, **10**:37.
 43. Nolan T, Berwick DM: All-or-none measurement raises the bar on performance. *JAMA* 2006, **295**(10):1168-1170.

44. Morisky DE, Green LW, Levine DM: **Concurrent and predictive validity of a self-reported measure of medication adherence.** *Med Care* 1986, **24**(1):67–74.
45. Shalansky SJ, Levy AR, Ignaszewski AP: **Self-reported Morisky score for identifying nonadherence with cardiovascular medications.** *Ann Pharmacother* 2004, **38**(9):1363–1368.
46. Bermingham M, Hayden J, Dawkins I, Miwa S, Gibson D, McDonald K, Ledwidge M: **Prospective analysis of LDL-C goal achievement and self-reported medication adherence among statin users in primary care.** *Clin Ther* 2011, **33**(9):1180–1189.
47. Steiner JF, Prochazka AV: **The assessment of refill compliance using pharmacy records: methods, validity, and applications.** *J Clin Epidemiol* 1997, **50**(1):105–116.
48. Donner A, Klar N: *Design and Analysis of Cluster Randomization Trials in Health Research.* New York: Oxford University Press; 2000.
49. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R: **Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins.** *Lancet* 2005, **366**(9493):1267–1278.

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