International Comparison of Time to Treatment Intensification and Rates of Complications in Metformin Monotherapy Treated Type 2 Diabetes Patients

by

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Abstract

Type 2 diabetes mellitus is a progressive disease which affects many people in Canada and the United States, and the prevalence of type 2 diabetes is only expected to increase in the future. Pharmacological interventions are a cornerstone of the management of type 2 diabetes as they help to attain substantial and sustainable lowering of a patient's blood glucose levels. Moreover, they contribute to enhancing a patient's overall quality of life by reducing complications throughout the duration of this disease. In practice, type 2 diabetes patients in both Canada and the United States are managed according to clinical practice guideline (CPG) recommendations, which involve the utilization of metformin as a first line antihyperglycemic agent to bring blood glucose levels to a target level. Subsequent treatment intensification with other antihyperglycemic agents, including insulin, is often required when a patient's blood glucose is no longer under control. A lack of glucose control or untimely intensification of drug therapy for type 2 diabetes patients can lead to major complications.

The first objective of this research program was to determine if differences exist between the way that newly treated type 2 diabetes patients are managed in Canada and the United States. This was accomplished using a retrospective cohort of type 2 diabetes patients from Canada and the United States who were just starting antihyperglycemic therapy. The study period was 2004-2010. To ensure comparability, the cohorts were restricted to patients initiating guideline-recommended metformin monotherapy treatment as directed by the CPGs in the two countries. We then determined the time from the initiation of guideline-concordant antihyperglycemic therapy to the addition of a second antihyperglycemic agent. The results showed that patients in the United States are more likely to intensify drug therapy sooner than patients in Canada and at a lower hemoglobin A1c value. This suggests that although CPGs are similar between Canada and the United States, adherence to the guidelines may be different between the two countries

and patients in Canada may have more clinical inertia compared to their United States counterparts with respect to antihyperglycemic drug changes.

The second objective was to determine if there are differences between Canada and the United States in terms of the time from the initiation of type 2 diabetes treatment to any major diabetes-related complications. In this study, we retrospectively determined the time from the initiation of guideline-concordant metformin monotherapy to the first occurrence of macrovascular and microvascular complications of interest. Our results show that, for the most part, there are minimal differences in rates of complications between the countries; however, patients in the United States have higher rates of coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) compared to patients in Canada.

Collectively, our studies suggest that even though patients in the United States are experiencing intensification of type 2 diabetes treatment sooner and at a lower hemoglobin A1c level, there is minimal difference in the time from initiation of treatment to the incidence of macro- or microvascular complications in our population. Historically, the clinical benefits of timely treatment intensification have been shown; however, newer clinical trials suggest that the benefits of intensification may not be substantial. Thus, although the United States intensified treatments more quickly, the minimal difference in rates of complications is in line with current evidence on the role of blood glucose on major macrovascular and microvascular complications.

Preface

This thesis is an original work by Tyler Benjamin Dubois. A version of chapter 2 of this thesis has been submitted for approval for publication at the time of submission of this thesis.

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1 CHAPTER 1: INTRODUCTION

1.1 Statement of the Problem

Type 2 diabetes mellitus is a progressive disease which affects the body's ability to utilize or produce insulin effectively, leading to chronic hyperglycemia [1]. Diabetes has unfortunately become more common in Canada and the United States, with an estimated prevalence of diabetes in Canada of 3.0 million (8.1%) in 2014, and 30 million (9.4%) in the United States as of 2017 [2, 3]. The management of type 2 diabetes mellitus is an ongoing and often lifelong undertaking as diabetes treatment must be responsive and ongoing through drug therapy intensification and blood glucose management [1]. In Canada and the United States, metformin is recommended as a first antihyperglycemic medication unless contraindicated within clinical practice guidelines (CPGs) [4].

Timely escalation of antihyperglycemic drug therapy and initiating other preventative agents such as lipid-lowering medications is important for reducing occurrences of macrovascular and microvascular complications over time in a type 2 diabetes patient [5]. Complications such as heart disease, stroke, and end-stage renal disease are unfortunately commonly related to type 2 diabetes. In 2010 in the United States, heart disease, stroke, and end-stage renal disease in diabetes patients occurred at rates of 45.5, 52.9, and 20 per 10,000 persons respectively [6]. To assist clinicians in preventing and managing these complications, Canada and the United States have created clinical practice guidelines (CPGs) which have evolved over time to recommend the best course of treatment for type 2 diabetes [7, 8]. CPGs are in place to help practitioners and their patients maintain control of this disease, increase quality of life, and avoid complications which arise due to this disease. While the CPGs for the treatment of type 2 diabetes in Canada and the United States are similar, no study has directly compared the time

between treatment intensification and the addition of a second antihyperglycemic agent in Canada and the United States. Moreover, no study has compared rates of major diabetes-related complications between the two countries.

1.2 Use of Antihyperglycemics to Control Blood Glucose in the Management of Type 2 Diabetes Mellitus

Clinical practice guidelines in both Canada and the United States recommend lifestyle changes and metformin therapy as the first line of antihyperglycemic therapy for the majority of newly diagnosed type 2 diabetes patients [7, 8]. Additional oral agents or insulin may also be recommended depending on level of A1c and desired A1c reductions [7, 8]. Metformin has been proven in clinical trials to safely and effectively reduceßß blood glucose (as measured by hemoglobin A1c) by approximately 1% without major side effects in most individuals [9]. Metformin also has other potentially beneficial effects for type 2 diabetes patients, with protective effects reported for cardiovascular disease when compared to sulfonylureas, and a lower reported incidence of cancer in new metformin users [10, 11]. Moreover, metformin is not associated with hypoglycemia *per se* and is relatively weight-neutral which is important to most patients.

When a patient's A1c is no longer able to be controlled or the patient is not able to achieve his or her target goals, additional antihyperglycemic agents are required. This could include using additional oral agents (preferred), switching to other oral agents (e.g., DPP-4s) or adding or switching to insulin [7, 8]. The drug regimen for type 2 diabetes, especially in the long term, requires complex treatment in response to the progressive nature of this disease. Therapies will often begin with a single antihyperglycemic therapy, and a majority of patients

will be on two or more antihyperglycemic drugs or insulin within six to nine years, as hyperglycemia intensifies with duration of diabetes [12].

1.3 Cardiovascular Risk Management and Complications in Type 2 Diabetes Mellitus

Type 2 diabetes is a major risk factor for cardiovascular disease, and cardiovascular disease is the leading cause of death in adults with diabetes [7, 8, 13]. Nephropathy and end-stage renal disease are also two common complications for patients with type 2 diabetes [8]. There is a close association between diabetes and macrovascular and microvascular disease which a patient's treatment plan must take into account. Intensive glycemic control with the appropriate timing of adjustments to pharmacological therapy is associated with a reduction in risk of some microvascular complications; however, evidence of the reduction of cardiovascular complications from intensive glycemic control is lacking [5, 14-17]. As such, blood pressure and lipid control play an important role in reducing macrovascular complications in patients with type 2 diabetes. Randomized control trials have shown that in patients with type 2 diabetes, intensive blood pressure control significantly reduced diabetes-related mortality, stroke, heart failure, vision loss, and other microvascular complications [14, 18-20]. Additionally, lipid control and statin therapy have been shown to reduce the risk of cardiovascular complications [21-24]. Thus, the importance of blood pressure control, lipid control, and statin therapy are stressed in the treatment of type 2 diabetes, and medications controlling these factors are often incorporated in a type 2 diabetes patient's drug regimen [25].

Several antidiabetic agents have also been shown to have cardiovascular benefits in addition to beneficial antihyperglycemic properties [11, 26-28]. Metformin used in the treatment

of type 2 diabetes mellitus has been shown to reduce the risk of cardiovascular disease in observational studies; however, clinical trial evidence to support this is lacking [11]. More recently, clinical trials have shown that newer antidiabetic agents provide protective effects against cardiovascular disease. In a study that used the glucagon-like peptide drug ligralutide and a placebo, ligralutide reduced mortality and non-fatal myocardial infarction and stroke [26]. Further, the Subtype 2 sodium-glucose transport (SGLT-2) medications canagliflozin and empagliflozinn have been shown in the CANVAS trial and the EMPA-REG OUTCOME trial, respectively, to reduce the risk of cardiovascular events when added to a type 2 diabetes patient's drug regimen [27, 28]. Other agents, including the sulfonylureas, are currently being investigated in large-scale clinical trials for cardiovascular benefit or harms.

1.4 Comparisons Between Canada and the United States

There is increasing interest in international comparisons of health systems, management strategies, and outcomes across a wide range of diseases. These comparisons often focus on potential differences in disease-related outcomes of hospitalizations, mortality, or other disease-related measures as a means of "bench-marking" quality of care between countries. For example, in a worldwide study of patients who underwent an allogenic bone marrow transplant, Silberman et al. reported that patients in Canada and the United States have similar proportions of overall transplants and reasons for transplants, with the proportion of transplants for acute lymphoblastic leukemia in Canada being slightly lower than in the United States [29]. Coyte et al. found that in a population of patients from Canada and Medicare recipients from the United States who underwent a knee replacement surgery, waiting times for initial consultation and for knee replacement surgery were longer in Canada than in the United States [30]. Using comparable populations of low income patients with cancer from Canada and the United States, Gorey et al.

found that there was a significant survival advantage for patients in Canada compared to the United States [31]. While these three studies are not directly related to the topic of diabetes, they highlight the fact that outcomes are not consistently better or worse between Canada and the United States and are dependent on the disease and outcomes being considered.

With respect to diabetes, as Canada and the United States use similar CPGs for type 2 diabetes, patient care in these two countries, and therefore patient outcomes, should be comparable. However,there is a lack of research comparing diabetes patients in Canada and the United States. Indeed, only one study that we are aware of has directly compared diabetes patients in Canada to those in the United States. Using data from a randomized controlled trial of type 1 diabetes patients in Canada and the United States, Booth et al. found no country-specific differences in glycemic control [32]. However, this study was conducted in a highly controlled and highly selected population and is unlikely to reflect real-world practice. For example, in studies conducted exclusively in the United States, time to treatment intensification varies considerably following the initiation of metformin monotherapy patients. The time ranges from an average of 220 days to 16.9 months [33-37]. Moreover, no study has directly compared diabetes-related outcomes between patients in Canada and the United States. These comparisons are important to identify if one country is outperforming the other. If differences are identified, it may provide the opportunity to develop interventions or policies to improve the quality of care to close treatments gaps. Indeed, “clinical inertia” with respect to diabetes care has previously been noted among Canadian patients [38-40]. Whether this is associated with significant harms relative to other patients in other health systems is currently unknown.

1.5 Summary

The focus of this research program is to evaluate treatment and prescribing practices and clinical outcomes between patients in Canada and those in the United States. CPGs for type 2 diabetes management are quite similar between Canada and the United States. However, there may be differences in the implementation of these recommendations due to fundamental differences in the private healthcare system in the United States and the public healthcare system in Canada. Indeed, research into other diseases shows that system-level characteristics have produced differences in pharmacotherapy, procedures, wait times, and mortality. Therefore, the potential exists for differences in the treatment of type 2 diabetes. This research program aims to determine if practice patterns with respect to the use of antihyperglycemic agents are similar in Canada and the United States and to determine if there are any differences in the incidence of diabetes-related complications between Canada and the United States. This unique comparison-based research will assist in determining which country is experiencing faster intensification of diabetes treatment, and further examine if one country experiences a higher proportion of or shortened time to major diabetes-related complications. Ultimately this research may provide the opportunity to develop interventions or policies to improve patient care.

1.6 Objectives

The two objectives of this program of research were:

1) To determine and compare the use and timing of second-line antihyperglycemic drugs in type 2 diabetes patients who initiated therapy with metformin in Canada and the United States.

2) To analyze and compare the time to, and incidence of, diabetes-related complications in newly treated type 2 diabetes patients in Canada and the United States.

The first objective was realized using two large population-based cohorts of 6414 new oral antihyperglycemic users between 2004 and 2007 and 42,340 users between 2008 and 2009 from Alberta, Canada and the United States. We examined oral antihyperglycemic medication by restricting the cohort to new users of metformin monotherapy and then determined the time to treatment intensification (i.e., the addition of a second antihyperglycemic agent). We hypothesized that although type 2 diabetes CPGs between Canada and the United States are similar, potential differences exist in the time to treatment intensification due to demonstrated differences between Canada and the United States in other medical conditions and drug therapy treatments. Specifically, we hypothesized that patients in Canada would be better managed due to our public healthcare system.

The second objective was accomplished using a large population-based cohort of 3843 new oral antihyperglycemic users over the age of 65 from Alberta, Canada and the United States. The time period studied was 2004-2007 and the cohort was based on administrative data combined with hospitalization and emergency visit data. Among new users of metformin monotherapy, we determined the time from diabetes treatment initiation to any hospitalization or emergency visit for three major complications (any cardiovascular hospitalization, end-stage renal disease or nephropathy, and coronary artery bypass graft or percutaneous coronary intervention procedures). We hypothesized that differences in time to complications in newly treated type 2 diabetes patients may be different between Canada and the United States. Specifically, we hypothesized that patients in Canada would have better outcomes relative to their counterparts in the United States.

1.7 References

1. American Diabetes, A., *Diagnosis and Classification of Diabetes Mellitus.* Diabetes Care, 2013. **36**(Suppl 1): p. S67-S74.

2. Canada, P.H.A.o., *Highlights from the Canadian Chronic Disease Surveillance System*. 2017.

3. Prevention, C.f.D.C.a., *National Diabetes Statistics Report 2017*. 2017.

4. Nathan, D.M., et al., *Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2009. **32**(1): p. 193-203.

5. *Effects of Intensive Glucose Lowering in Type 2 Diabetes.* New England Journal of Medicine, 2008. **358**(24): p. 2545-2559.

6. Gregg, E.W., et al., *Changes in Diabetes-Related Complications in the United States, 1990–2010.* New England Journal of Medicine, 2014. **370**(16): p. 1514-1523.

7. Association, A.D., *American Diabetes Association Standards of Medical Care in Diabetes 2017.* Diabetes Care, 2017. **40 (suppl 1)**.

8. Cheng, A.Y.Y., *Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction.* Canadian Journal Of Diabetes, 2013. **37 Suppl 1**: p. S1-S3.

9. Sherifali, D., et al., *The Effect of Oral Antidiabetic Agents on A1C Levels: A systematic review and meta-analysis.* Diabetes Care, 2010. **33**(8): p. 1859-1864.

10. Libby, G., et al., *New users of metformin are at low risk of incident cancer: A cohort study among people with type 2 diabetes.* Diabetes Care, 2009.

11. Evans, J.M.M., et al., *Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin.* Diabetologia, 2006. **49**(5): p. 930.

12. Harris, S.B., et al., *Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study).* Diabetes Research and Clinical Practice, 2005. **70**(1): p. 90-97.

13. Sarwar, N., et al., *Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.* Lancet, 2010. **375**(9733): p. 2215-22.

14. Association, A.D., *Implications of the United Kingdom Prospective Diabetes Study.* Diabetes Care, 2002. **25**(suppl 1): p. s28.

15. Duckworth, W., et al., *Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes.* New England Journal of Medicine, 2009. **360**(2): p. 129-139.

16. M, S., et al., - *Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients.* Diabetes Care, 2000. **23**(2): p. B21-9.

17. Heller, S.R., *A Summary of the ADVANCE Trial.* Diabetes Care, 2009. **32**(suppl 2): p. S357.

18. BMJ, *Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.* BMJ, 1998. **317**(7160): p. 703.

19. Adler, A.I., et al., *Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study.* BMJ : British Medical Journal, 2000. **321**(7258): p. 412-419.

20. Hansson, L., et al., *Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.* The Lancet, 1998. **351**(9118): p. 1755-1762.

21. Jaiswal, M., A. Schinske, and R. Pop-Busui, *Lipids and lipid management in diabetes.* Best Practice & Research Clinical Endocrinology & Metabolism, 2014. **28**(3): p. 325-338.

22. Chahil, T.J. and H.N. Ginsberg, *Diabetic Dyslipidemia.* Endocrinology and Metabolism Clinics of North America, 2006. **35**(3): p. 491-510.

23. *MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.* The Lancet, 2003. **361**(9374): p. 2005-2016.

24. Colhoun, H.M., et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial.* The Lancet, 2004. **364**(9435): p. 685-696.

25. Stark Casagrande, S., et al., *The Prevalence of Meeting A1C, Blood Pressure, and LDL Goals Among People With Diabetes, 1988–2010.* Diabetes Care, 2013. **36**(8): p. 2271-2279.

26. Marso, S.P., et al., *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.* New England Journal of Medicine, 2016. **375**(4): p. 311-322.

27. Neal, B., et al., *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.* New England Journal of Medicine, 2017. **377**(7): p. 644-657.

28. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* New England Journal of Medicine, 2015. **373**(22): p. 2117-2128.

29. Silberman, G., et al., *Availability and Appropriateness of Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia in 10 Countries.* New England Journal of Medicine, 1994. **331**(16): p. 1063-1067.

30. Peter C, C., et al., *Waiting Times For Knee-Replacement Surgery In The United States And Ontario.* The New England Journal of Medicine, 1994(16): p. 1068.

31. Gorey, K.M., et al., *An International Comparison of Cancer Survival: Toronto, Ontario, and Detroit, Michigan, Metropolitan Areas.* American Journal of Public Health, 1997. **87**(7): p. 1156-1163.

32. Booth, G.L., B. Zinman, and D.A. Redelmeier, *Diabetes care in the U.S. and Canada.* Diabetes Care, 2002. **25**(7): p. 1149-1153.

33. Boccuzzi, S.J., et al., *Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population.* Diabetes Care, 2001. **24**(8): p. 1411.

34. Ulcickas Yood, M., *Time to pharmacotherapy change in response to elevated HbA(1c) test results.* CURRENT MEDICAL RESEARCH AND OPINION, 2006. **22**(8): p. 1567-1574.

35. Pantalone, K.M., et al., *Intensification of Diabetes Therapy and Time Until A1C Goal Attainment Among Patients With Newly Diagnosed Type 2 Diabetes Who Fail Metformin Monotherapy Within a Large Integrated Health System.* Diabetes Care, 2016. **39**(9): p. 1527-1534.

36. Fu, A.Z., et al., *Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.* DIABETES OBESITY & METABOLISM, 2011. **13**(8): p. 765-769.

37. Brown, J.B., C. Conner, and G.A. Nichols, *Secondary failure of metformin monotherapy in clinical practice.* DIABETES CARE -ALEXANDRIA VA-, 2010. **33**(3): p. 501-506.

38. Bajaj, H.S., et al., *The Need Associated with Diabetes Primary Care and the Impact of Referral to a Specialist-Centered Multidisciplinary Diabetes Program (the NADIR Study).* Can J Diabetes, 2016. **40**(2): p. 120-5.

39. Shah, B.R., et al., *Clinical Inertia in Response to Inadequate Glycemic Control.* Diabetes Care, 2005. **28**(3): p. 600.

40. McAlister, F.A., et al., *The effect of specialist care within the first year on subsequent outcomes in 24 232 adults with new-onset diabetes mellitus: population-based cohort study.* Quality & Safety in Health Care, 2007. **16**(1): p. 6-11.

2 CHAPTER 2: TIME TO TREATMENT INTENSIFICATION IN NEWLY TREATED TYPE 2 DIABETES PATIENTS: COMPARISON OF CANADA AND THE UNITED STATES

2.1 Introduction

Current clinical practice guidelines (CPGs) in Canada and the United States recommend a similar approach to the management of glycemic control in type 2 diabetes patients. In addition to lifestyle changes, antihyperglycemic drugs are recommended to bring blood glucose levels into an individual target range. Unless contraindicated, metformin is recommended in both CPGs as a preferred first-line agent [4]. Treatment intensification, through dose escalation or additional antihyperglycemic agents, is recommended if glucose targets are not achieved or maintained [7, 8, 41].

Although both CPGs are similar, fundamental differences in the structure of the health systems (i.e., universal healthcare system in Canada vs. a more private healthcare system in the United States) may influence the implementation of guideline-concordant care. Moreover, the approaches that individual physicians or allied health professionals take to diabetes management may be substantially different between the countries, as could patients' receptiveness to changes in therapy. These potential factors could all be driving decisions about when and how second-line antihyperglycemic drugs are added in the management of type 2 diabetes.

Previous studies on the use of quality of care, procedures, and outcomes in diabetes and cardiovascular disease management have produced mixed results. In 2002, an analysis of randomized control trial data of type 1 diabetes patients in Canada and the United States was conducted which suggested no difference in glycemic control between the two populations [32].

Analyses in cardiovascular disease management in other disease populations have suggested differences. For example, the usage of fibrates and ezetimibe was previously compared between the countries and higher utilization of both drugs was observed in the United States relative to Canada [42, 43]. Conversely, studies in kidney disease, cancer, cardiac care, orthopedics, and transplants have also shown major differences in the use of procedures, wait times, and mortality, but these differences have not been consistently in favor of one country over the other [29-31, 44, 45].

To date, to our knowledge, no one has directly compared the intensification of antihyperglycemic drug therapy in newly treated type 2 diabetes patients in the United States and Canada. Although the CPGs are similar, there are clear differences in the healthcare systems and in the approach that physicians or patients may take to diabetes management. These differences may affect the way that type 2 diabetes is managed in each of the countries. There is evidence of inconsistent management patterns between Canada and the United States in other diseases; thus, our objective was to determine and compare the use and timing of second-line antihyperglycemic drugs in type 2 diabetes patients who initiated therapy with metformin monotherapy in Canada and the United States.

2.2 Methods

We conducted a retrospective cohort study of newly treated type 2 diabetes patients using data formed by combining administrative health claims, laboratory data, and prescription data from both Canada and the United States between 2004 and 2010.

Data

United States data were obtained from a large de-identified claims-and-integrated-laboratory database that included employed, commercially insured individuals from all 50 states (Clinformatics® Data Mart, OptumInsight, Eden Prairie, MN). Patient-level data included administrative and demographic information, pharmacy claims data, and billable medical services claims including inpatient and outpatient visits and medical procedures, laboratory tests and results. Clinformatics® Data Mart is one of the few data sources approved by the FDA's Mini-Sentinel Program to perform active surveillance of the safety of marketed medical products, including drugs and biologics [46]. Furthermore, this database has been used to evaluate health outcomes related to the use of drugs in patients with diabetes [47-49].

Data from Canada were obtained from the administrative databases of Alberta Health (AH) and Alberta Health Services (AHS). Similar to the Clinformatics® Data Mart, these databases maintain current demographic information and billable medical services claims including inpatient and outpatient visits and medical procedures for all patients within Alberta's universal, publicly funded healthcare system. Prescription drug dispensations were routinely recorded by a provincial agency for all registrants ≥65 years of age prior to 2008. After 2008 all prescription drug dispensations were captured for all Albertans regardless of age. Similarly, laboratory data was only universally captured after 2008 and reported in AHS databases.

Subjects

Since prescription drug data and laboratory data were not routinely collected from all patients in Alberta until 2008, we constructed two study groups to maximize the use of available data to compare treatment intensification between the United States and Canada. The first study group was restricted to type 2 diabetes patients over 65 years of age who initiated antihyperglycemic therapy between 2004 and 2007. The second study group consisted of all type

2 diabetes patients initiating therapy in 2008 and 2009, irrespective of age. All patients were actively followed until December 31, 2010.

Each of our study groups was established based on a new user design [50]. Newly treated type 2 diabetes patients were identified within each time period (i.e., 2004-2008; 2008-2009) as individuals who received their first prescription for an oral antihyperglycemic drug and did not have any history of oral antihyperglycemic drug use or insulin use in the year prior to starting their first oral antihyperglycemic drug (i.e., one-year wash-out).

From this group of new users of antihyperglycemic agents, we selected all patients whose first agent was metformin monotherapy. This restriction was done to ensure all patients were initially managed in accordance with CPG recommendations within each country. To ensure these patients were truly metformin monotherapy users, we excluded all patients who initiated another antihyperglycemic medication or insulin at the time of the metformin initiation or within two weeks of metformin initiation. As treatment failure is unlikely to occur within two weeks of initiating metformin monotherapy, additional antihyperglycemic agents within the two-week window are more likely to represent the preplanned use of combination therapies, switches due to initial side effects, or other treatment factors that arose in therapy (e.g., delays in drug fills due to drug coverage reimbursement). Furthermore, we also excluded all female patients with an International Classification of Diseases (ICD) code for polycystic ovary disease (ICD-9: 256.4 ICD-10: E28.2) to ensure that metformin was being used for type 2 diabetes in female patients as others have done [51].

Outcome

Our primary outcome was the time from the initial metformin prescription to the addition of a second antihyperglycemic agent. This treatment intensification follows guideline recommendations to adjust antihyperglycemic therapy if metformin monotherapy is unable to achieve or maintain the desired glycemic target [7, 8, 41]. This definition is also consistent with previous studies examining treatment intensification [52, 53]. Prescription records were used to identify patients starting a second oral antihyperglycemic agent in combination with metformin, switching from initial metformin monotherapy to alternative oral antihyperglycemic therapy, or starting insulin. Patients were followed from the index metformin dispensation date until the end of coverage within the databases, death, or until 2010.

Statistical Analysis

For all analyses, multivariate Cox proportional hazard models were used to evaluate the time to treatment intensification. The index date (i.e., time zero) was the date of the initial metformin dispensation and patients were followed until the dispensation date for a second antihyperglycemic agent or censoring. Canada served as our reference in all analyses. In addition to our dummy variable representing the country, we included numerous confounding variables in the Cox regression models as time-fixed variables. Specifically, age, sex, use of other drugs commonly prescribed in diabetes in the year prior to metformin initiation (e.g., statins, beta blockers, and ACE inhibitors) and the well-validated Elixhauser comorbidity score were included. The Elixhauser comorbidity score was calculated based on hospital ICD codes in the year prior to the initiation of metformin [54, 55].

In addition, for the 2008 to 2009 new users, we included baseline lab markers for A1c, LDL, and estimated glomerular filtration rate (eGFR). As laboratory data were not complete for

all patients included in the study, patients who did not have specific clinical laboratory data measured were accounted for using the missing indicator approach in all analyses [56].

All data were presented as hazard ratios (HR) and 95 percent confidence intervals (95% CI) with $p<0.05$ considered statistically significant.

Secondary analyses

We conducted subgroup analyses to look at the consistency of the results. First, we restricted our analyses to only those patients with an A1c test conducted within 30 days of their first antihyperglycemic prescription. Second, we examined time to treatment intensification in patients 65 years of age and older among the 2008 to 2009 new users to determine if the results were similar for the two new user groups. Third, to determine if by using the 14-day window, we were at risk of misclassifying the patients identified as initiating monotherapy, we analyzed the same outcome using the same covariates for both study groups using a 30-day window. All of these analyses were consistent with the main results.

2.3 Results

From 2004 to 2007 we identified 2116 patients in Canada and 2631 patients in the United States who were newly treated for type 2 diabetes after reaching the age of 65. From 2008 to 2009 we identified 23,022 patients in Canada and 19,318 patients in the United States of all ages newly treated for type 2 diabetes. Overall, differences in age and sex were noted between Canada and the United States. The average age was higher for patients in Canada in both study groups and Canada had more females among the 2004-2008 new users but not among the 2008-2009 new users. Elixhauser scores were relatively similar between the countries. The United

States had higher proportions of users of beta blockers, ace inhibitors, and statins in both study groups, while Canada had a higher proportion of users of calcium channel blockers among new users from 2004 to 2008, and a higher proportion of users of nitrates in both study groups.

2004 – 2007 New Users

Of the new metformin users in 2004 to 2007, we identified 698 (96.0 per 1000 person-years) with treatment intensification in Canada and 361 (38.3 per 1000 person-years) in the United States. The median time to treatment intensification was 362 days for Canadians and 170 days for Americans. Newly treated type 2 diabetes patients in the United States were more likely to have treatment intensification compared to Canadians after adjustment for covariates (aHR 1.99; 95% CI 1.69 to 2.36).

2008 – 2009 New Users

Of the new metformin users in 2008 to 2010, we identified 4676 (128.3 per 1000 person-years) in Canada and 1445 (42.1 per 1000 person-years) newly treated type 2 diabetes patients who experienced treatment intensification in the United States. Patients in Canada were shown to have a median time of 197 days to treatment intensification, and patients in the United States were shown to have a median time of 119 days to treatment intensification. Newly treated type 2 diabetes patients in the United States were more likely to have treatment intensification compared to Canadian patients after adjustment for covariates (aHR 5.62; 95% C.I. 5.246 to 6.029).

At the time of metformin initiation, A1c values were similar between countries, with patients in Canada having a mean of 8.15 (SD 2.3) and patients in the United States having a mean of 7.93 (SD 2.2) (p=0.95). However, at treatment intensification, the mean A1c was 9.0%

(SD 2.0) in Canada and 8.6% (SD 2.2) in the United States ($p<0.01$). Additional analyses whereby we limited the cohorts to only those with an A1c 30 days before the first metformin prescription showed similar results, with newly treated type 2 diabetes patients in the United States more likely to have treatment intensification compared to Canadian patients after adjustment for covariates including baseline laboratory data (aHR 5.97; 95% C.I. 6.639 to 9.803).

2.4 Discussion

Although the clinical practice guidelines are similar in the two countries, this study shows treatment intensification is delayed in Canada compared to the United States. This observation remains after adjustment for age and sex, comorbidity, usage of drugs in the previous year, and laboratory data. Although metformin is initiated at very similar A1c values in both countries, there is a clinically important difference in A1c values at the time of treatment intensification (9.0% in Canada versus 8.6% in the US) [57].

Several studies have previously evaluated time to the addition of antihyperglycemic medication in Canada and the United States [34-36, 58]. However, this is the first study of which we are aware that specifically compares practice patterns in Canada with those in the United States. As with previous studies, we found that baseline A1c, comorbidities, and age are associated with treatment intensification [58-60]. However, the median time in the United States of approximately six months from the initial metformin therapy to treatment escalation for new users from 2004 to 2007, and four months for new users from 2008 to 2009 is similar what was reported in one study, and somewhat shorter than what was reported in other studies [33-37]. In a study of insured new metformin monotherapy patients from 1997 to 1999, Boccuzzi et al. found

that treatment intensification occurred at an average of 220 days from the date that the metformin was initially dispensed [33]. However, this represented the average time to treatment intensification within the first 12 months only, and was not reported over the complete period of time in the study. In a study of 8000 patients using metformin monotherapy in the midwestern United States, Yood et al. observed a median delay of 372 days to treatment intensification, using a population and methodological approach very similar to that in our study [34]. Similarly, a study of metformin monotherapy patients conducted by Pantalone et al. in Cleveland and a large United States-based study of metformin monotherapy patients by Fu et al. both observed median delays of 14 months to treatment intensification [35, 36]. Additionally, Brown et al. observed a mean of 16.9 months to therapy intensification with metformin monotherapy patients in Oregon and Washington [37]. It is notable that the patients analyzed by Brown et al. were restricted to those who achieved good glycemic control with metformin monotherapy, which would explain why the time to treatment intensification trended higher in their study compared to ours. In our subset of patients with A1c at the time of treatment escalation, the average A1c was sufficiently high to elicit treatment intensification for many patients with type 2 diabetes (9.0% in Canada versus 8.6% in the US). Our data would suggest that the shortened time to intensification was indeed clinically warranted.

Although differences in populations studied could influence the results, another main factor which could be contributing to this shorter time is that we included treatment intensifications which occurred after 14 days. Previous studies in both Canada and the United States have only considered treatment intensification after six months to one year following initial therapy. We believe that a window of six months to one year is unable to fully capture accurate treatment intensification given that the CPGs in Canada and the United States both recommend revisiting a patient's A1c every three months [7, 8]. Moreover, dose increases may

also be a contributing factor to differences in studies of treatment intensification. For example, Boccuzzi et al. reported that of the 22% of patients who experienced treatment intensification, only 9% of those added another antihyperglycemic agent to their drug regimen, and 30% of patients with or without treatment intensification had dose increases in metformin [33]. Additionally, Fu et al. showed that for patients who had a metformin daily dose over 1500mg, the median time to treatment intensification was 8.9 compared to a median of 20 months for patients who never exceeded 1500mg a day [36]. In our study, we only considered additional agents as treatment intensification, which would explain some discrepancies in our results compared to how others have defined treatment intensification.

Within Canada, our observed time to therapy intensification differs from previous studies which have analyzed time to treatment intensification. In a population of Toronto patients older than 65 years of age, new elderly users of metformin monotherapy in 1997, 1999, and 2004 experienced a median time to progression in therapy of 5.1, 5.7, and 6.1 years respectively [61]. However, it should be noted that this data is significantly older than ours and appears to be from a population not managed aggressively. Indeed, a gap of ~1.5 years from diabetes diagnosis to the initiation of metformin was observedwhich, potentially, partially or fully, explains the longer time to treatment intensification. Another explanation for the longer time is that these patients were not being managed according to current CPGs, which recommend immediate initiation of metformin for newly diagnosed type 2 diabetes patients. Guidelines for the treatment of diabetes during the earlier observation periods in Gomes' study recommended monotherapy only after non-pharmacological interventions. Drug options were also restricted compared to modern guidelines, and the guidelines were overall less aggressive in treatment recommendations [62].

The large population-based samples included from both Canada and the United States and the comparability of CPGs are major strengths of this paper. However, our study is not without limitations. First, we have used prescription dispensation records as our marker of treatment failure. Although reasonable for the vast majority of patients, it is possible some patients may have changed therapies due to adverse reactions to metformin. However, in most patients, adverse effects of metformin occur quickly, within the first few weeks of therapy, which we accounted for in our analyses. Moreover, there is no reason to believe that the effects would be different between patients in Canada and the United States; therefore, no bias should be expected in our estimates. Second, changes in the dosage of metformin were not assessed as therapy intensification due to a lack of sufficient data to calculate the daily dose. While dosage changes are not rare, it is unlikely that clinicians in Canada or the United States would initiate a second-line agent without first increasing metformin to the upper end of the dosing range or maximum tolerated dose. Third, we did not have complete laboratory data throughout the entire follow-up time; as a result, we were unable to fully evaluate all patients' A1c values at the time of treatment escalation. Last, our comparison to patients in the United States was completed for those patients who were fully insured. As Canadian patients are part of a universal healthcare system, it was necessary to restrict participation to only insured patients in the United States to insure similarity in drug coverage between the countries. We cannot extrapolate our results to non-insured patients in the United States.

Clinical practice guidelines in both Canada and the United States stress treatment intensification as an important component of any effective diabetes management program. Although the reasons are not fully known, compared to clinicians in Canada, those in the United States appear to be managing their patients more aggressively with respect to the intensification

of therapies for glycemic control. For important clinical outcomes, the potential impact of these treatment differences in Canada compared to the United States is uncertain.

Table 2-A: Baseline Characteristics for New Metformin Users by Observation Period and Country

	2004 to 2007 New Users			2008 to 2009 New Users		
	Mean (SD) or n (%)			Mean (SD) or n (%)		
	Canada N=2116	**United States N=2631**	**p-value**	**Canada N=23022**	**United States N=19318**	**p-value**
Age (years)	71.3 (4.7)	69.6 (3.9)	< 0.01	56.9 (14)	53.7 (9.4)	< 0.01
Male	956 (44.6)	1476 (56.1)	< 0.01	12110 (52.6)	9775 (50.6)	< 0.01
Medications						
ACE or ARB	1083 (51)	1743 (66)	< 0.01	6330 (28)	11270 (58)	< 0.01
Beta Blockers	575 (27)	950 (36)	< 0.01	2409 (11)	4624 (24)	< 0.01
Calcium Channel Blockers	595 (28)	537 (20)	< 0.01	2287 (10)	3005 (16)	< 0.01
Statins	651 (31)	1161 (61)	< 0.01	4530 (20)	11109 (58)	< 0.01
Nitrate	386 (18)	170 (7)	< 0.01	799 (4)	544 (3)	< 0.01
Elixhauser Comorbidity Score	1.55(1.20)	1.11 (0.51)	< 0.01	1.15 (0.65)	1.09 (0.46)	< 0.01
Duration of follow-up (days)	1153 (650)	981 (579)	< 0.01	578 (265)	649 (303)	< 0.01

Table 2-B: Baseline Characteristics for New Metformin Users with Laboratory Data

	2008 to 2009 New Users With Baseline A1c		
	Mean (SD) or n (%)		
	Canada N=593	**United States N=2748**	**p-value**
Age (years)	55.7 (13.5)	52.7 (9.6)	< 0.01
Male	339 (57.2)	1467 (53.4)	0.45
Medications			
ACE or ARB	199 (34)	1637 (60)	< 0.01
Beta blockers	89 (15)	600 (22)	0.01
Calcium Channel Blockers	77 (13)	396 (14)	0.22
Statins	131 (22)	1567 (57)	< 0.01
Nitrate	25 (4)	88 (3)	0.63
Baseline A1c (%)	8.15 (2.3)	7.97 (2.2)	0.95
Baseline LDL (mmol/L)	112.9 (39.2)	119.0 (39.2)	0.07
Baseline eGFR (mL/min	49.6 (15.8)	88.9 (19.4)	< 0.01
A1c at treatment intensification (%)	9.0 (2.0)	8.6 (2.2)	< 0.01
Elixhauser Comorbidity Score	1.18 (0.50)	1.11 (0.47)	0.05
Duration of follow-up (days)	444 (192)	623 (310)	0.01

References

4. Nathan, D.M., et al., *Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2009. **32**(1): p. 193-203.

7. Association, A.D., *American Diabetes Association Standards of Medical Care in Diabetes 2017.* Diabetes Care, 2017. **40 (suppl 1)**.

8. Cheng, A.Y.Y., *Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction.* Canadian Journal Of Diabetes, 2013. **37 Suppl 1**: p. S1-S3.

29. Silberman, G., et al., *Availability and Appropriateness of Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia in 10 Countries.* New England Journal of Medicine, 1994. **331**(16): p. 1063-1067.

30. Peter C, C., et al., *Waiting Times For Knee-Replacement Surgery In The United States And Ontario.* The New England Journal of Medicine, 1994(16): p. 1068.

31. Gorey, K.M., et al., *An International Comparison of Cancer Survival: Toronto, Ontario, and Detroit, Michigan, Metropolitan Areas.* American Journal of Public Health, 1997. **87**(7): p. 1156-1163.

32. Booth, G.L., B. Zinman, and D.A. Redelmeier, *Diabetes care in the U.S. and Canada.* Diabetes Care, 2002. **25**(7): p. 1149-1153.

33. Boccuzzi, S.J., et al., *Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population.* Diabetes Care, 2001. **24**(8): p. 1411.

34. Ulcickas Yood, M., *Time to pharmacotherapy change in response to elevated HbA(1c) test results.* CURRENT MEDICAL RESEARCH AND OPINION, 2006. **22**(8): p. 1567-1574.

35. Pantalone, K.M., et al., *Intensification of Diabetes Therapy and Time Until A1C Goal Attainment Among Patients With Newly Diagnosed Type 2 Diabetes Who Fail Metformin Monotherapy Within a Large Integrated Health System.* Diabetes Care, 2016. **39**(9): p. 1527-1534.

36. Fu, A.Z., et al., *Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.* DIABETES OBESITY & METABOLISM, 2011. **13**(8): p. 765-769.

37. Brown, J.B., C. Conner, and G.A. Nichols, *Secondary failure of metformin monotherapy in clinical practice.* DIABETES CARE -ALEXANDRIA VA-, 2010. **33**(3): p. 501-506.

41. Inzucchi, S.E., et al., *Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach.* Diabetes Care, 2012. **35**: p. 1364-1379.

42. Jackevicius, C.A., et al., *Use of fibrates in the united states and canada.* JAMA, 2011. **305**(12): p. 1217-1224.

43. Jackevicius, C.A., et al., *Use of Ezetimibe in the United States and Canada.* New England Journal of Medicine, 2008. **358**(17): p. 1819-1828.

44. Jack V, T., et al., *Use of Cardiac Procedures and Outcomes in Elderly Patients with Myocardial Infarction in the United States and Canada.* The New England Journal of Medicine, 1997(21): p. 1500.

45. John C. Hornberger, a., a. Alan M. Garber, and a. John R. Jeffery, *Mortality, Hospital Admissions, and Medical Costs of End-Stage Renal Disease in the United States and Manitoba, Canada.* Medical Care, 1997(7): p. 686.

46. FDA, *Sentinel Initiative.*

47. Padwal, R., M. Lin, and D.T. Eurich, *The Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients With Diabetes.* The Journal of Clinical Hypertension, 2016. **18**(3): p. 200-206.

48. Eurich, D.T., et al., *Risk of new-onset heart failure in patients using sitagliptin: A population-based cohort study.* Diabetic Medicine, 2016. **33**(5): p. 621-630.

49. Weir, D.L., et al., *Clinical Research: Sitagliptin Use in Patients With Diabetes and Heart Failure. A Population-Based Retrospective Cohort Study.* JACC: Heart Failure, 2014. **2**: p. 573-582.

50. Ray, W.A., *Evaluating Medication Effects Outside of Clinical Trials: New-User Designs.* American Journal of Epidemiology, 2003. **158**(9): p. 915-920.

51. Lashen, H., *Role of metformin in the management of polycystic ovary syndrome.* Therapeutic Advances in Endocrinology and Metabolism, 2010. **1**(3): p. 117-128.

52. Riedel, A.A., et al., *Loss of Glycemic Control in Patients with Type 2 Diabetes Mellitus Who Were Receiving Initial Metformin, Sulfonylurea, or Thiazolidinedione Monotherapy.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2007. **27**(8): p. 1102-1110.

53. Eurich, D.T., et al., *Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus.* Pharmacotherapy, 2005. **25**(6): p. 810-816.

54. Elixhauser, A., et al., *Comorbidity Measures for Use with Administrative Data.* Medical Care, 1998. **36**(1).

55. Quan, H., et al., *Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data.* Medical Care, 2005. **43**(11).

56. Huberman, M. and B. Langholz, *Application of the Missing-Indicator Method in Matched Case-Control Studies with Incomplete Data.* American Journal of Epidemiology, 1999. **150**(12): p. 1340-1345.

57. Maruthur, N.M., et al., *Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis.* Annals of Internal Medicine, 2016. **164**(11): p. 740-751.

58. McEwen, L.N., et al., *Predictors and Impact of Intensification of Antihyperglycemic Therapy in Type 2 Diabetes: Translating Research into Action for Diabetes (TRIAD).* Diabetes Care, 2009. **32**(6): p. 971-976.

59. Rodondi, N., et al., *Therapy Modifications in Response to Poorly Controlled Hypertension, Dyslipidemia, and Diabetes Mellitus.* Annals of internal medicine, 2006. **144**(7): p. 475-484.

60. Yu, S., et al., *Use of Add-on Treatment to Metformin Monotherapy for Patients with Type 2 Diabetes and Suboptimal Glycemic Control: A U.S. Database Study.* Journal of Managed Care & Specialty Pharmacy, 2016. **22**(3): p. 272-280.

61. Gomes, T., et al., *Progression through diabetes therapies among new elderly users of metformin: a population-based study.* Diabetic Medicine, 2013. **30**(2): p. e51-e55.

62. Meltser, Ś., *1998 clinical practice guidelines for the management of diabetes in Canada*. 1998: [Ottawa] : Canadian Diabetes Association : Canadian Medical Association, 1998.

3 CHAPTER 3: RATE OF COMPLICATIONS IN TYPE 2 DIABETES PATIENTS TREATED WITH METFORMIN MONOTHERAPY – A COMPARATIVE ANALYSIS BETWEEN CANADA AND THE UNITED STATES

3.1 Introduction

Canada and the United States share similar clinical practice guidelines (CPGs) which recommend maintaining good glycemic control for type 2 diabetes patients as well as stressing the importance of cardiovascular risk management [7, 8]. Patients with type 2 diabetes are well known to be at an increased risk of macrovascular and microvascular complications compared to non-diabetes patients [63]. As such, the CPGs take a multifactorial approach to diabetes care to prevent complications related to diabetes.

While intensive glycemic control with a variety of agents is associated with a reduction in some microvascular complications [5, 14-17], the evidence for reductions of cardiovascular (CV) complications is far less certain [64]. As it is important to maintain macrovascular health in type 2 diabetes patients, blood pressure and lipid control are seen as a cornerstone of type 2 diabetes management. Indeed, randomized controlled trials have shown tight blood pressure control in patients with type 2 diabetes significantly reduces diabetes mortality, stroke, heart failure, vision loss, and microvascular complications [14, 18-20]. Moreover, lipid control and the use of statin

therapy to reduce low-density lipoprotein (LDL) has also been shown to reduce the risk of cardiovascular complications [21-24].

Although proven efficacious therapies exist, diabetes care remains suboptimal in both the United States and Canada. Moreover, it is possible that significant differences in disease management approaches may also exist between Canada and the United States despite the similarity of CPGs for type 2 diabetes management. For example, within cardiovascular disease management, significant differences have been observed between Canada and the United States, with the utilization of fibrates and ezetimibe being higher in the United States relative to Canada [42, 43]. Additional studies have shown that the rates of myocardial infarctions, mortality, and the use of cardiac procedures and surgeries are different between Canada and the United States [65, 66]. Comparative studies between Canada and the United States in other diseases and procedures like kidney disease, cancer, orthopedics, and transplants have also shown major differences in the use of procedures, wait times, and mortality, but these differences have not consistently favored one country or the other [29-31, 45].

To date, to our knowledge, no one hasdirectly compared the risk of complications in newly treated type 2 diabetes patients in the United States and Canada. Although the CPGs are similar, considering the differing evidence in the treatment of cardiovascular disease and procedures, wait times and mortality, the potential exists for there to be different incidences of complications in newly treated type 2 diabetes patients in Canada and the United States. Accordingly, the objective of this study was to analyze and compare the time to, and incidence of, diabetes-related complications in newly treated type 2 diabetes patients in the United States and Canada.

3.2 Methods

Using administrative health claims, prescription data, and hospitalization data, we conducted a retrospective cohort study of newly treated type 2 diabetes patients over the age of 65 in Canada and the United States. The study period was 2004 to 2007. Patients were restricted to those over the age of 65 as medication use was not routinely available for patients under the age of 65 in Canada.

Data

For our United States patients, our research was conducted using a large de-identified United States claims-and-integrated-laboratory database which includes employed, commercially insured individuals from all 50 states (Clinformatics® Data Mart Database; OptumInsight, Eden Prairie, MN). Data included patient-level administrative and demographic information, and billable medical services claims including inpatient and outpatient visits and medical procedures, and pharmacy claims data. Clinformatics® Data Mart is one of the few data sources approved by the FDA's Mini-Sentinel Program to perform active surveillance of the safety of marketed medical products, including drugs and biologics [46]. This database has been used in research related to health outcomes in patients with diabetes [47-49].

Data for patients in Canada were obtained from the administrative databases of Alberta Health (AH) and Alberta Health Services (AHS). Similar to the Clinformatics® Data Mart, these databases maintain current demographic information and billable medical services claims including inpatient and outpatient visits and medical procedures for all patients within Alberta's universal, publicly funded healthcare system. In addition, prescription drug dispensations are routinely recorded by a provincial agency for all registrants ≥65 years of age.

Subjects

Our study group included patients who initiated therapy in Canada and the United States between 2004 and 2007 and were over 65 years of age. The study population was followed to December 31, 2010. A new user design was utilized for our study group [50]. Newly treated type 2 diabetes patients were identified from 2004 to 2007 as individuals who received their first prescription for an oral antihyperglycemic drug and did not have a history of insulin or any antihyperglycemic drug in the year before their new antihyperglycemic prescription (i.e., one-year wash-out).

All patients determined to be new users were further restricted to only metformin monotherapy users, in order to ensure that all patients included in this study were being managed in accordance with CPGs in each country [7, 8]. In order to ensure that metformin was being utilized truly as a monotherapy regimen, we excluded all patients who were prescribed another antihyperglycemic medication or insulin within two weeks of the initial metformin prescription. Additionally, female patients who had an International Classification of Diseases (ICD) code for polycystic ovary disease (ICD-9: 256.4 ICD-10: E28.2) were excluded to ensure that metformin was used for type 2 diabetes, as other studies have done [51].

Finally, patients who had an ICD-9-CM or ICD-10 hospitalization code before the date of their initial metformin prescription for any of the outcomes of concern in this study were excluded from both cohorts. This restriction was to ensure that the hospitalizations following metformin monotherapy would be unrelated to a preexisting condition. Hospitalization codes for all patients were available for a minimum of a year before antihyperglycemic treatment.

Outcome

The three primary outcomes were time to incident hospitalization for cardiovascular disease, hospitalization for nephrotic disease or end-stage renal disease, and time to either a coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). These events occur commonly in patients with type 2 diabetes [14, 17, 67-69], and previous studies have included them as outcomes of interest [15, 48, 49, 70]. As with other studies, the outcomes were identified using ICD-9-CM codes in the United States and ICD-10 codes in Canada from inpatient and emergency records [48, 49, 55, 71, 72] (Table 3-B). Patients were followed from their initial metformin prescription to their first date of any primary outcome, to end of coverage in the databases, or death, or until December 31, 2010, or until five years of follow-up.

To further examine processes of care, we also specifically evaluated the proportion of patients prescribed statin therapy, the proportion of patients actively receiving blood pressure medication, and specifically agents affecting the renin angiotensin aldosterone system prior to the onset of the first major outcome or censoring in those who did not have an outcome.

Statistical Analysis

Cox proportional hazard models were used to evaluate the time to incident complications. Separate models were constructed for each of the primary outcomes, as well as for the use of preventative medications. The index date was the date of the initial metformin prescription. Canada was used as the reference population in all analyses. The Cox regression models included the following: a dummy variable for Canada; other confounding variables including age, sex, use of additional drugs commonly prescribed to diabetes patients in the year prior to the first metformin prescription (angiotensin converting enzyme (ACE) inhibitors, other blood pressure medications (e.g. beta blockers), and statins); the year of therapy initiation; and the well-validated Elixhauser comorbidity score. The Elixhauser comorbidity score was calculated

using hospital and physician ICD codes in the year prior to the initial metformin prescription [54, 55]. The score included in the analysis was a total of all comorbid conditions. All data are presented as hazard ratios (HR) and 95 percent confidence intervals (95% CI) with $p<0.05$ considered statistically significant.

3.3 Results

We identified 1510 and 2333 type 2 diabetes patients newly treated with metformin monotherapy between 2004 and 2007 in Canada and the United States, respectively. In Canada, the average age was slightly higher, and there was a higher proportion of females (Table 3-A). Patients in Canada had a higher proportion of nitrate use, and higher proportion of calcium channel blocker use in the year prior to the initiation of metformin. Patients in the United States had a higher proportion of the use of beta blockers, ACE inhibitors and statins in the year prior to metformin initiation.

From the newly treated patients in 2004 to 2007, 202 patients (13.4%) in Canada and 37 patients (1.6%) in the United States experienced a cardiovascular-related hospitalization with the median time from metformin to cardiovascular event of 645 days for Canada and 799 days for the United States (unadjusted HR 1.13, 95%CI 0.79 to 1.62). Secondly, 140 patients (9.3%) in Canada and 10 patients (0.4%) in the United States experienced a hospitalization for nephropathy or end-stage renal disease with a median time from metformin to hospitalization of 838 days for patients in Canada and 1071 days for patients in the United States (unadjusted HR 0.73, 95% CI 0.36-1.50). Finally, 30 patients (2.0%) in Canada and 29 patients (1.2%) in the United States experienced a CABG or PCI procedure with a median time from metformin to the procedure of

767 days for Canada and 413 days for the United States (unadjusted HR 2.160, 95%CI 1.23-3.79).

After fully adjusting for demographics, use of other medications and comorbidities, newly treated type 2 diabetes patients in the United States were more likely to experience a CABG or PCI procedure than Canadian patients (aHR 2.39; 95% CI 1.09 to 5.22). No difference in cardiovascular-related hospitalizations, and nephropathy or end-stage renal disease was observed in the adjusted analyses (Figure 3-A).

With respect to process of care, after adjustments were made we observed no difference in the time between when the statins were initiated in Canada and the United States (200 (9%) patients in the United States vs 301 (20%) patients in Canada, aHR 1.081, 95%CI 0.920-1.271). Similarly, we observed no difference in the time between when blood pressure agents were initiated with (169 (7.2%) patients in the United States vs 322 (21%) patients in Canada, aHR 1.151, 95%CI 0.970-1.365).

3.4 Discussion

This study shows that the time to incidences of diabetes-related complications is mostly similar between Canada and the United States, though patients in the United States appear to be experiencing procedures of CABG and PCI sooner than patients in Canada. This may be an expected result, as CPGs in Canada and the United States make similar recommendations to help reduce complications. However, there are significant differences in the way that healthcare is delivered in Canada and the United States. Surprisingly, our results suggest that despite these different factors, the risk of complications is similar in the United States and Canada.

Other studies that have looked at cardiovascular complications or mortality have shown inconsistent results. In a study of elderly patients in the year following a myocardial infarction, Tu et al. found that mortality rates did not vary between patients in Canada and the United States, with mortality rates being 34.4% and 34.3% respectively [65]. Eisenberg et al. showed that in a population of patients from Canada and the United States who underwent a CABG procedure, similar in-hospital mortality was reported (1.4% in Canada compared to 2.2% in the United States [66]). Tu et al. also reported that elderly patients in the United States were more likely to undergo expensive and invasive treatments such as coronary angiography (34.9% United States, 6.7% Canada), percutaneous transluminal coronary angioplasty (11.7% United States, 1.5% Canada), and coronary-artery bypass surgery (10.6% United States, 1.4% Canada) [65]. The latter findings by Tu et al are consistent with our results, as we also observed that diabetes patients in the United States had a shorter time to CABG or PCI procedures than their counterparts in Canada.

Previous studies have been conducted comparing complications, outcomes and mortality in other diseases and procedures between Canada and the United States, but this is the first study we are aware of to directly compare the risk and incidence of diabetes-related complications between the two countries. In a population-based study, Jackevicius et al. found that fibrate use increased by 117.1% in the United States compared to an increase of only 18.1% in Canada from 2002 to 2009 [42]. Jackevicius et al. also reported in another population-based study that of the prescribed lipid-lowering drugs in both countries, the proportion of ezetimibe increased from 0.2% to 3.4% in Canada from 2003-2006 and from 0.1% to 15.2% in the United States from 2002 to 2006 [43]. Given a higher usage of fibrates in the United States compared to Canada, and the proportional difference in the prescribing of lipid-lowering agents, the effects of these medications could influence the incidence of complications in our similar population-based

study. However, in our study we observed no appreciable difference in the time it took to initiate statins in the two countries.

We did not observe any significant differences in the risk of nephropathy or end-stage renal disease. Although the health systems in Canada and the United States are fundamentally different in the majority of situations, in the case of end-stage renal disease, both health systems are more comparable. The United States has a system similar to the single-payer system in Canada for financing care for almost all end-stage renal disease treatment. This funding approach reduces the system-level differences between countries [73]. However, in a population of patients treated for end-stage renal disease in Canada and the United States, Hornberger et al. found that mortality was 47% higher in the United States [45]. Although our study does not investigate mortality following hospitalizations for nephropathy or end-stage renal disease among our diabetes cohort, we did not observe any significant differences between Canada and the United States with respect to time to first hospitalization for end-stage renal disease. Thus, these inconsistencies in mortality and use of procedures shown in the previous comparisons of Canada and the United States, as well as our own data, demonstrate that any differences between the countries are likely disease-specific and no overarching assumptions can be made.

The similarity between diabetes CPGs in Canada and the United States is a strength of this comparison, as newly treated type 2 diabetes patients should be managed similarily in both countries. Our study is not without limitations. First, we have excluded from our analysis any patient with a ICD-9-CM or ICD-10 code for any of the major outcomes in this study before metformin monotherapy. While it is reasonable to assume that our analyses would hold true for those with existing cardiac disease, the possibility exists that the prevalence of a major outcome of this study would affect future risk and decrease the generalizability of the study and

potentially introduce confounding to the results. Second, although numerous studies have relied on ICD-9/ICD-10 billing data in both the United States and Canada, it is possible that slight differences in the coding of outcomes may have affected our results. Last, our data only pertains to those people ≥65 years of age and we can make no assumptions in regard to younger patients.

Canada and the US share similar CPGs: in both countries, the cornerstones of effective managment for diabetes patients are good glycemic control and the management of lipds and blood pressure. Patients in the United States are requiring some diabete treatment-related procedures sooner than their counterparts in Canada. The explanation for this is not completely understood. Further research into incident complications in new type 2 diabetes patients is required to determine the potential causes of or influences on the differences observed between patients in Canada and the United States.

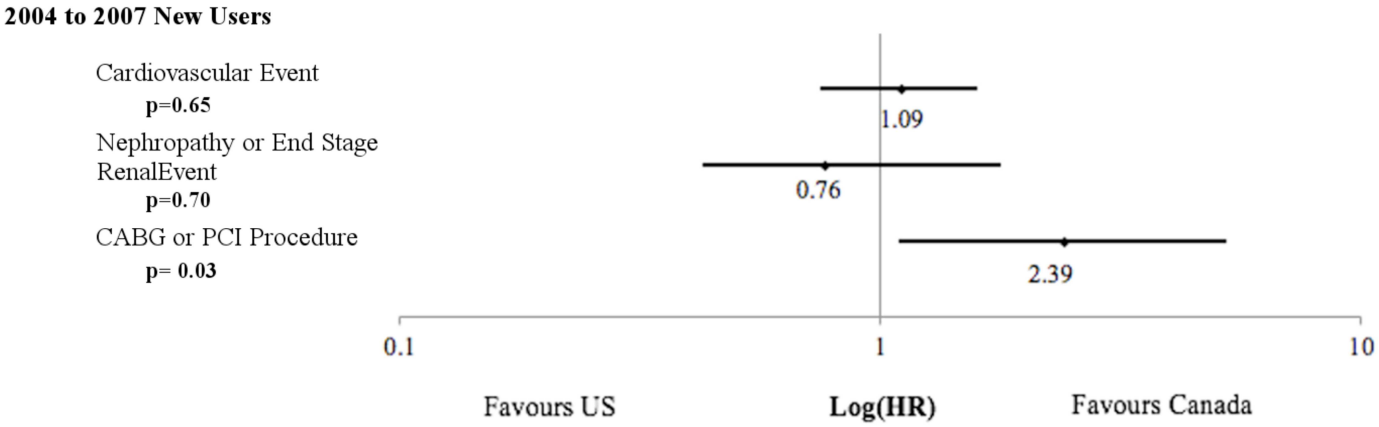
Table 3-A: Baseline Characteristics for New Metformin Users by Country

	2004 to 2007 New Users		
	Mean (SD) or n (%)		
	Canada N=1510	**United States N=2333**	**p-value**
Age (years)	71.2 (4.7)	69.5 (3.9)	< 0.01
Male	661 (43.8)	1275 (54.7)	< 0.01
Medication use in previous year:			
ACE or ARB	741 (49)	1515 (65)	< 0.01
Beta blockers	366 (24)	745 (32)	< 0.01
Calcium Channel Blockers	422 (28)	464 (20)	< 0.01
Statins	465 (31)	1410 (60)	< 0.01
Nitrate	224 (15)	102 (4)	< 0.01
Thiazide	284 (19)	398 (17)	< 0.01
Elixhauser Comorbidity Score	1.41 (1.02)	1.07 (0.34)	< 0.01
Duration of follow-up	1150 (638)	971 (577)	< 0.01

Table 3-B: ICD-9 and ICD-10 Codes for Incident Complications

	ICD-9-CM Code	**ICD-10 Code**
Cardiovascular Events	410, 411.1, 428, 362.3, 430, 431, 432, 433, 434, 435, 436, 437, 438	I21.09, I21.19, I21.11, I21.19, I21.29, I21.4, I21.3, I20.0, I50.9, I50.1, I50.20-I50.23, I50.30-I50.33, I50.40-I50.43, I50.9
Nephropathy	250.4, 581.1, 581.8, 583.8, 582.1, 593.9, 584.5, 584.6, 584.7, 584.8, 586.0, 587.0, 796.0	E11.29, E10.29, E11.21, E11.65, E10.21, E10.65, N02.2, N0.8, N04.8, N05.8, N03.3, N28.9, N17.0, N17.1, N17.2, N17.8, N19, N26.9, R82.5, R82.6, R89.2, R89.3
End Stage Renal Disease	403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.5, 585.6, 586	I12.0, I13.11, I13.2, N18.5, N18.6, N19
CABG Procedure	36.1	1IJ76
PCI Procedure	36.06, 36.07, 00.66	1IJ50

Figure 3-A: Log Adjusted Hazard Ratio Endpoints of interest



3.5 References

5. *Effects of Intensive Glucose Lowering in Type 2 Diabetes.* New England Journal of Medicine, 2008. **358**(24): p. 2545-2559.

7. Association, A.D., *American Diabetes Association Standards of Medical Care in Diabetes 2017.* Diabetes Care, 2017. **40 (suppl 1)**.

8. Cheng, A.Y.Y., *Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction.* Canadian Journal Of Diabetes, 2013. **37 Suppl 1**: p. S1-S3.

14. Association, A.D., *Implications of the United Kingdom Prospective Diabetes Study.* Diabetes Care, 2002. **25**(suppl 1): p. s28.

15. Duckworth, W., et al., *Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes.* New England Journal of Medicine, 2009. **360**(2): p. 129-139.

16. M, S., et al., - *Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients.* Diabetes Care, 2000. **23**(2): p. B21-9.

17. Heller, S.R., *A Summary of the ADVANCE Trial.* Diabetes Care, 2009. **32**(suppl 2): p. S357.

18. BMJ, *Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.* BMJ, 1998. **317**(7160): p. 703.

19. Adler, A.I., et al., *Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study.* BMJ : British Medical Journal, 2000. **321**(7258): p. 412-419.

20. Hansson, L., et al., *Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.* The Lancet, 1998. **351**(9118): p. 1755-1762.

21. Jaiswal, M., A. Schinske, and R. Pop-Busui, *Lipids and lipid management in diabetes.* Best Practice & Research Clinical Endocrinology & Metabolism, 2014. **28**(3): p. 325-338.

22. Chahil, T.J. and H.N. Ginsberg, *Diabetic Dyslipidemia.* Endocrinology and Metabolism Clinics of North America, 2006. **35**(3): p. 491-510.

23. *MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.* The Lancet, 2003. **361**(9374): p. 2005-2016.

24. Colhoun, H.M., et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial.* The Lancet, 2004. **364**(9435): p. 685-696.

29. Silberman, G., et al., *Availability and Appropriateness of Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia in 10 Countries.* New England Journal of Medicine, 1994. **331**(16): p. 1063-1067.

30. Peter C, C., et al., *Waiting Times For Knee-Replacement Surgery In The United States And Ontario.* The New England Journal of Medicine, 1994(16): p. 1068.

31. Gorey, K.M., et al., *An International Comparison of Cancer Survival: Toronto, Ontario, and Detroit, Michigan, Metropolitan Areas.* American Journal of Public Health, 1997. **87**(7): p. 1156-1163.

42. Jackevicius, C.A., et al., *Use of fibrates in the united states and canada.* JAMA, 2011. **305**(12): p. 1217-1224.

43. Jackevicius, C.A., et al., *Use of Ezetimibe in the United States and Canada.* New England Journal of Medicine, 2008. **358**(17): p. 1819-1828.

45. John C. Hornberger, a., a. Alan M. Garber, and a. John R. Jeffery, *Mortality, Hospital Admissions, and Medical Costs of End-Stage Renal Disease in the United States and Manitoba, Canada.* Medical Care, 1997(7): p. 686.

46. FDA, *Sentinel Initiative.*

47. Padwal, R., M. Lin, and D.T. Eurich, *The Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients With Diabetes.* The Journal of Clinical Hypertension, 2016. **18**(3): p. 200-206.

48. Eurich, D.T., et al., *Risk of new-onset heart failure in patients using sitagliptin: A population-based cohort study.* Diabetic Medicine, 2016. **33**(5): p. 621-630.

49. Weir, D.L., et al., *Clinical Research: Sitagliptin Use in Patients With Diabetes and Heart Failure. A Population-Based Retrospective Cohort Study.* JACC: Heart Failure, 2014. **2**: p. 573-582.

50. Ray, W.A., *Evaluating Medication Effects Outside of Clinical Trials: New-User Designs.* American Journal of Epidemiology, 2003. **158**(9): p. 915-920.

51. Lashen, H., *Role of metformin in the management of polycystic ovary syndrome.* Therapeutic Advances in Endocrinology and Metabolism, 2010. **1**(3): p. 117-128.

54. Elixhauser, A., et al., *Comorbidity Measures for Use with Administrative Data.* Medical Care, 1998. **36**(1).

55. Quan, H., et al., *Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data.* Medical Care, 2005. **43**(11).

63. Booth, G.L., et al., *Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study.* The Lancet, 2006. **368**(9529): p. 29-36.

64. Turnbull, F.M., et al., *Intensive glucose control and macrovascular outcomes in type 2 diabetes.* Diabetologia, 2009. **52**(11): p. 2288-2298.

65. Tu, J.V., et al., *Use of Cardiac Procedures and Outcomes in Elderly Patients with Myocardial Infarction in the United States and Canada.* New England Journal of Medicine, 1997. **336**(21): p. 1500-1505.

66. Eisenberg, M.J., et al., *Outcomes and cost of coronary artery bypass graft surgery in the United States and Canada.* Arch Intern Med, 2005. **165**(13): p. 1506-13.

67. Pirart, J., *Diabetes Mellitus and Its Degenerative Complications: A Prospective Study of 4,400 Patients Observed Between 1947 and 1973.* Diabetes Care, 1978. **1**(3): p. 168.

68. Cowie CC, C.S., Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, Eds. Bethesda, *Diabetes in America, 3rd Edition.* 2016.

69. Luciani, N., et al., *Coronary artery bypass grafting in type II diabetic patients: a comparison between insulin-dependent and non-insulin-dependent patients at short- and mid-term follow-up.* The Annals of Thoracic Surgery, 2003. **76**(4): p. 1149-1154.

70. Dormandy, J.A., et al., *Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial.* The Lancet, 2005. **366**(9493): p. 1279-1289.

71. Quan, H., et al., *Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database.* Health Services Research, 2008. **43**(4): p. 1424-1441.

72. Quan, H., G.A. Parsons, and W.A. Ghali, *Validity of Information on Comorbidity Derived From ICD-9-CCM Administrative Data.* Medical Care, 2002. **40**(8).

73. Services, C.f.M.M., *End Stage Renal Disease*. 2013.

4 CHAPTER 4: SUMMARY

4.1 Summary of Research

Clinical practice guidelines (CPGs) in Canada and the United States both recommend metformin as first-line therapy for newly diagnosed type 2 diabetes patients, unless contraindicated [7]. Treatment should be intensified if metformin monotherapy is unable to achieve or maintain a glycemic target; however, it is unclear how aggressively physicians intensify treatments in real-world practice. Moreover, given the similarity in CPGs between Canada and the United States one could assume that the timing of intensification would be similar between the countries. However, there are fundamental health system differences between Canada and the United States and we hypothesized that those differences would exist between these countries with respect to type 2 diabetes treatment. This research project has shown that the timing of treatment intensification occurs earlier and at lower blood glucose levels for patients in the United States compared to Canada. One factor which may be driving the differences in time to intensification between Canada and the United States is that Canada is overall less aggressive with its approach to diabetes [12]. This is also supported by other research that has indicated that Canadian physicians tend to have "clinical inertia" with respect to blood glucose management [39]. Clinical inertia has also been noted in diabetes therapy in the United States, so it is unclear whether it is the sole driver in differences observed in this research [35]. Part of the delay in treatment may be due to a patient or physician feeling a lack of urgency in the early stages of this disease, which may manifest in a lack of follow-up visits to a physician, delays in undergoing blood testing for A1c values, or other as-yet unidentified factors. Unfortunately, these factors are difficult to account for in our study, and would require a study with much more qualitative measures, measures that are unavailable in administrative data.

Although this research has shown that intensification of type 2 diabetes therapy occurs earlier in the United States than in Canada, evidence that tighter glycemic control leads to improved outcomes is tenuous [74]. Thus, although treatment intensification was indeed more common in the United States, we also observed that overall use of cardiovascular protective agents was high in both countries. As a result of this similarity, it may not be surprising that overall outcomes were similar in both countries.

The early use of coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) in the United States compared to Canada is not unexpected; research has shown that in the United States, historical rates of cardiac procedures in patients with previous myocardial infarction (MI) are strikingly higher than in Canada [65]. In recent times, the rate of CABG procedures in the United States has been decreasing, but the rate of PCI has remained unchanged [75]. The majority of patients who receive and benefit from CABG and PCI procedures are elderly [76]. However, in our research, patients in Canada were older on average, so age may not be a deciding factor in what is driving this difference in procedures in each country. Notably, a trial of Canadian and United States patients with MI found that coronary revascularization and angiography occurred sooner in the United States than in Canada [77]. Thus, the United States seems to be much more aggressive in revascularization in the elderly, which is consistent with our results. Yet, despite the increased utilization of these procedures, we did not observe significant differences between the two countries in terms of other macrovascular complications.

4.2 Implications for Future Policy/Clinical Practice

This research highlights specific areas in Canada where newly treated type 2 diabetes patients' outcomes are varying substantially from predicted outcomes under recommended treatment in Canada's CPGs [8]. We recommend that type 2 diabetes treatment be escalated in a timely manner when a patient's A1c level is no longer within reasonable limits. Escalating drug therapy when a major indicator of a patient's health (specifically hemoglobin A1c) is no longer at target is a keystone of diabetes treatment. However, this research has shown that physicians in Canada are not escalating diabetes therapy in response to elevated A1c levels. Indeed, an average A1c of 9% among patients in Canada prior to intensification would be considered by the majority of clinicians as too high, irrespective of the patient's target A1c. This delay in response is indicative of clinical inertia in type 2 diabetes treatment, which has been studied [39].

However, interventions and polices to counter clinical inertia are less well known. A decrease in clinical inertia in type 2 diabetes patients was observed in a study which focused on involving patients in their own care through a telehealth intervention. In this study, Greenwood et al. observed that compared to a non-intervention group, patients given an intervention showed improved adherence and self-care activities which were sustained over time, as well as consistently reduced A1c levels over time [78]. An intervention as simple as reporting to a patient about his or her health status or keeping a patient involved in his or her care may be extremely beneficial. Explaining the importance of glycemic control as well as the downstream sequalae of type 2 diabetes and the associated complications may motivate patients to become more involved in maintaining the best health possible throughout the duration of diabetes. Although in theory this approach seems reasonable, the Look-AHEAD study suggests that more is need to truly improve outcomes in patients with type 2 diabetes [79]. In the Look-AHEAD

trial, the trial was stopped early on the basis of futility. After a median follow-up of 9.6 years, intervention patients had greater weight loss compared to the control group (6.0% vs. 3.5% at study end), greater reductions in A1c, and greater initial improvements in fitness and all cardiovascular risk factors except for low-density-lipoprotein cholesterol levels. However, no benefit in cardiovascular-related events was observed (1.83 and 1.92 events per 100 person-years, respectively; hazard ratio in the intervention group, 0.95; 95% confidence interval, 0.83 to 1.09; P=0.51). Thus, improving cardiovascular outcomes even among very motivated clinicians and patients continues to prove difficult in type 2 diabetes treatment.

The potential reasons that physicians delay intensification of therapy may be multifactorial. Clinicians may tend to promote lifestyle changes in hopes that newly treated diabetes patients may improve their condition and the physician will not have to intensify treatment too soon [12]. However, the potential negative impacts of maintaining a patient in a hyperglycemic state for any period of time far outweighs the impact of an additional antihyperglycemic medication. Clinicians need to address patients who are not quickly responding well to lifestyle changes and/or medication regimens. Indeed, Pantalone et al. reported that in 20 patients treated with metformin monotherapy, 11 were noncompliant or missed appointments, while for nine, clinicians failed to intensify the treatment [35]. Clinicians must be prepared to intensify diabetes treatment, as research has shown diabetes patients are often not adhering to treatment plans which may adversely affect their diabetes care [80]. Clinicians must also ensure that they are outfitted with the most up-to-date therapies and treatment consensus regarding type 2 diabetes in order to create the most effective treatment plan [81]. Indeed, staying on-top-of the best available evidence is a daunting task for most primary care clinicians. It is also important for both patients and clinicians to work together to tackle the issue of proper intensification of treatment. Research on electronic devices and reminder systems

for type 2 diabetes patients has shown that simple reminder text messages help increase patient self-care, and in some cases help reduce a patient's A1c [82]. There are many simple ways to attempt to tackle the problem of clinical inertia ranging from small reminders for patients, to better communication from physicians to patients. Most of these are low cost and potentially extremely beneficial for type 2 diabetes patients. Unfortunately, few are put into real-world practice.

4.3 Implications for Future Research

Extensions of this research project are important to generate a complete understanding of the differences observed between Canada and the United States in newly treated type 2 diabetes patients. One major limiting factor of this research was the small sample size of newly treated type 2 diabetes patients who experienced a diabetes-related complication. Replicating the second study from this thesis with a larger sample size would reduce the chance of confounding in the results due to a small sample size.

Limitations in this research also come from the lack of comprehensive patient data in the databases used. Administrative data is useful, but can only go so far in determining conditions for or influences on a patient around the time of escalation in drug therapy or at the time of hospitalization [83, 84]. In order to analyze potential causes for the differences observed, further research should increase the scope of data used in analysis. Booth et al. noted that type 1 diabetes patients in Canada had more physician visits and higher hospitalizations for other conditions compared to type 1 diabetes patients in the United States [32]. Controlling for physician visits or visits to a specialist, as well as factors such as socioeconomic status and other patient level characteristics, may reduce confounding in future studies.

Another limitation introduced to this research is that patient data included from 2004 to 2007 were age-restricted to over 65 years of age. Including patients of all ages and not just elderly patients may help to reduce any potential biases introduced from an elderly population, specifically in extensions of this research on complications to young populations. Elderly patients have higher comorbidities and increased risks of macrovascular and microvascular disease. Although this would not introduce any confounding with respect to the international comparisons (as all patients were elderly), extrapolation of these findings to a younger, lower risk population may be difficult. Replication of this research with a younger population would be beneficial to improve the generalizability of the findings. Additionally, the data used from the United States in these studies comes from only insured patients, and is not generalizable to the entire population. Further research utilizing more general populations of both insured and non-insured patients would increase generalizability and be reflective of a broader population of patients with type 2 diabetes.

Finally, due to the date ranges of data available for this research beginning from over a decade ago, it must be noted that clinical practice guidelines and methods of treatment have evolved since that time. Most importantly, recent innovations in drug therapy have produced more treatment options for type 2 diabetes, such as glucagon-like peptide 1 receptor agonists (GLP-1), dipeptidyl peptidase-4 inhibitors (DPP-4), and sodium glucose co-transporter2 inhibitors (SGLT-2). Some of these new agents show beneficial or protective effects on the cardiovascular system and should be considered in future research in more modern populations [27, 28, 57]. There are many important avenues for future research to examine when making comparisons between type 2 diabetes patients in Canada and the United States.

4.4 References

7. Association, A.D., *American Diabetes Association Standards of Medical Care in Diabetes 2017.* Diabetes Care, 2017. **40 (suppl 1)**.

8. Cheng, A.Y.Y., *Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction.* Canadian Journal Of Diabetes, 2013. **37 Suppl 1**: p. S1-S3.

12. Harris, S.B., et al., *Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study).* Diabetes Research and Clinical Practice, 2005. **70**(1): p. 90-97.

27. Neal, B., et al., *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.* New England Journal of Medicine, 2017. **377**(7): p. 644-657.

28. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* New England Journal of Medicine, 2015. **373**(22): p. 2117-2128.

32. Booth, G.L., B. Zinman, and D.A. Redelmeier, *Diabetes care in the U.S. and Canada.* Diabetes Care, 2002. **25**(7): p. 1149-1153.

35. Pantalone, K.M., et al., *Intensification of Diabetes Therapy and Time Until A1C Goal Attainment Among Patients With Newly Diagnosed Type 2 Diabetes Who Fail Metformin Monotherapy Within a Large Integrated Health System.* Diabetes Care, 2016. **39**(9): p. 1527-1534.

39. Shah, B.R., et al., *Clinical Inertia in Response to Inadequate Glycemic Control.* Diabetes Care, 2005. **28**(3): p. 600.

57. Maruthur, N.M., et al., *Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis.* Annals of Internal Medicine, 2016. **164**(11): p. 740-751.

65. Tu, J.V., et al., *Use of Cardiac Procedures and Outcomes in Elderly Patients with Myocardial Infarction in the United States and Canada.* New England Journal of Medicine, 1997. **336**(21): p. 1500-1505.

74. Stolar, M., *Glycemic Control and Complications in Type 2 Diabetes Mellitus.* The American Journal of Medicine, 2010. **123**(3, Supplement): p. S3-S11.

75. Epstein, A.J., et al., *Coronary Revascularization Trends in the United States: 2001–2008.* JAMA : the journal of the American Medical Association, 2011. **305**(17): p. 1769-1776.

76. Raja, S.G., *Myocardial Revascularization for the Elderly: Current Options, Role of Off-pump Coronary Artery Bypass Grafting and Outcomes.* Current Cardiology Reviews, 2012. **8**(1): p. 26-36.

77. Fu, Y., et al., *Canadian-American Differences in the Management of Acute Coronary Syndromes in the GUSTO IIb Trial.* Circulation, 2000. **102**(12): p. 1375.

78. Greenwood, D.A., et al., *Overcoming Clinical Inertia: A Randomized Clinical Trial of a Telehealth Remote Monitoring Intervention Using Paired Glucose Testing in Adults With Type 2 Diabetes.* J Med Internet Res, 2015. **17**(7): p. e178.

79. *Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes.* New England Journal of Medicine, 2013. **369**(2): p. 145-154.

80. Cramer, J.A., *A Systematic Review of Adherence With Medications for Diabetes.* Diabetes Care, 2004. **27**(5): p. 1218.

81. Ross, S.A., *Breaking Down Patient and Physician Barriers to Optimize Glycemic Control in Type 2 Diabetes.* The American Journal of Medicine, 2013. **126**(9): p. S38-S48.

82. Russell-Minda, E., et al., *Health Technologies for Monitoring and Managing Diabetes: A Systematic Review.* Journal of Diabetes Science and Technology, 2009. **3**(6): p. 1460-1471.

83. Haut, E.R., P.J. Pronovost, and E.B. Schneider, *Limitations of administrative databases.* JAMA, 2012. **307**(24): p. 2589-2590.

84. Sarrazin, M. and G.E. Rosenthal, *Finding pure and simple truths with administrative data.* JAMA, 2012. **307**(13): p. 1433-1435.

Bibliography

1. American Diabetes, A., *Diagnosis and Classification of Diabetes Mellitus.* Diabetes Care, 2013. **36**(Suppl 1): p. S67-S74.

2. Canada, P.H.A.o., *Highlights from the Canadian Chronic Disease Surveillance System*. 2017.

3. Prevention, C.f.D.C.a., *National Diabetes Statistics Report 2017*. 2017.

4. Nathan, D.M., et al., *Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy: A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes Care, 2009. **32**(1): p. 193-203.

5. *Effects of Intensive Glucose Lowering in Type 2 Diabetes.* New England Journal of Medicine, 2008. **358**(24): p. 2545-2559.

6. Gregg, E.W., et al., *Changes in Diabetes-Related Complications in the United States, 1990–2010.* New England Journal of Medicine, 2014. **370**(16): p. 1514-1523.

7. Association, A.D., *American Diabetes Association Standards of Medical Care in Diabetes 2017.* Diabetes Care, 2017. **40 (suppl 1)**.

8. Cheng, A.Y.Y., *Canadian Diabetes Association 2013 clinical practice guidelines for the prevention and management of diabetes in Canada. Introduction.* Canadian Journal Of Diabetes, 2013. **37 Suppl 1**: p. S1-S3.

9. Sherifali, D., et al., *The Effect of Oral Antidiabetic Agents on A1C Levels: A systematic review and meta-analysis.* Diabetes Care, 2010. **33**(8): p. 1859-1864.

10. Libby, G., et al., *New users of metformin are at low risk of incident cancer: A cohort study among people with type 2 diabetes.* Diabetes Care, 2009.

11. Evans, J.M.M., et al., *Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin.* Diabetologia, 2006. **49**(5): p. 930.

12. Harris, S.B., et al., *Glycemic control and morbidity in the Canadian primary care setting (results of the diabetes in Canada evaluation study).* Diabetes Research and Clinical Practice, 2005. **70**(1): p. 90-97.

13. Sarwar, N., et al., *Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies.* Lancet, 2010. **375**(9733): p. 2215-22.

14. Association, A.D., *Implications of the United Kingdom Prospective Diabetes Study.* Diabetes Care, 2002. **25**(suppl 1): p. s28.

15. Duckworth, W., et al., *Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes.* New England Journal of Medicine, 2009. **360**(2): p. 129-139.

16. M, S., et al., - *Long-term results of the Kumamoto Study on optimal diabetes control in type 2 diabetic patients.* Diabetes Care, 2000. **23**(2): p. B21-9.

17. Heller, S.R., *A Summary of the ADVANCE Trial.* Diabetes Care, 2009. **32**(suppl 2): p. S357.

18. BMJ, *Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38.* BMJ, 1998. **317**(7160): p. 703.

19. Adler, A.I., et al., *Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study.* BMJ : British Medical Journal, 2000. **321**(7258): p. 412-419.

20. Hansson, L., et al., *Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial.* The Lancet, 1998. **351**(9118): p. 1755-1762.

21. Jaiswal, M., A. Schinske, and R. Pop-Busui, *Lipids and lipid management in diabetes.* Best Practice & Research Clinical Endocrinology & Metabolism, 2014. **28**(3): p. 325-338.

22. Chahil, T.J. and H.N. Ginsberg, *Diabetic Dyslipidemia.* Endocrinology and Metabolism Clinics of North America, 2006. **35**(3): p. 491-510.

23. *MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial.* The Lancet, 2003. **361**(9374): p. 2005-2016.

24. Colhoun, H.M., et al., *Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial.* The Lancet, 2004. **364**(9435): p. 685-696.

25. Stark Casagrande, S., et al., *The Prevalence of Meeting A1C, Blood Pressure, and LDL Goals Among People With Diabetes, 1988–2010.* Diabetes Care, 2013. **36**(8): p. 2271-2279.

26. Marso, S.P., et al., *Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes.* New England Journal of Medicine, 2016. **375**(4): p. 311-322.

27. Neal, B., et al., *Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.* New England Journal of Medicine, 2017. **377**(7): p. 644-657.

28. Zinman, B., et al., *Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.* New England Journal of Medicine, 2015. **373**(22): p. 2117-2128.

29. Silberman, G., et al., *Availability and Appropriateness of Allogeneic Bone Marrow Transplantation for Chronic Myeloid Leukemia in 10 Countries.* New England Journal of Medicine, 1994. **331**(16): p. 1063-1067.

30. Peter C, C., et al., *Waiting Times For Knee-Replacement Surgery In The United States And Ontario.* The New England Journal of Medicine, 1994(16): p. 1068.

31. Gorey, K.M., et al., *An International Comparison of Cancer Survival: Toronto, Ontario, and Detroit, Michigan, Metropolitan Areas.* American Journal of Public Health, 1997. **87**(7): p. 1156-1163.

32. Booth, G.L., B. Zinman, and D.A. Redelmeier, *Diabetes care in the U.S. and Canada.* Diabetes Care, 2002. **25**(7): p. 1149-1153.

33. Boccuzzi, S.J., et al., *Utilization of Oral Hypoglycemic Agents in a Drug-Insured U.S. Population.* Diabetes Care, 2001. **24**(8): p. 1411.

34. Ulcickas Yood, M., *Time to pharmacotherapy change in response to elevated HbA(1c) test results.* CURRENT MEDICAL RESEARCH AND OPINION, 2006. **22**(8): p. 1567-1574.

35. Pantalone, K.M., et al., *Intensification of Diabetes Therapy and Time Until A1C Goal Attainment Among Patients With Newly Diagnosed Type 2 Diabetes Who Fail Metformin Monotherapy Within a Large Integrated Health System.* Diabetes Care, 2016. **39**(9): p. 1527-1534.

36. Fu, A.Z., et al., *Treatment intensification in patients with type 2 diabetes who failed metformin monotherapy.* DIABETES OBESITY & METABOLISM, 2011. **13**(8): p. 765-769.

37. Brown, J.B., C. Conner, and G.A. Nichols, *Secondary failure of metformin monotherapy in clinical practice.* DIABETES CARE -ALEXANDRIA VA-, 2010. **33**(3): p. 501-506.

38. Bajaj, H.S., et al., *The Need Associated with Diabetes Primary Care and the Impact of Referral to a Specialist-Centered Multidisciplinary Diabetes Program (the NADIR Study).* Can J Diabetes, 2016. **40**(2): p. 120-5.

39. Shah, B.R., et al., *Clinical Inertia in Response to Inadequate Glycemic Control.* Diabetes Care, 2005. **28**(3): p. 600.

40. McAlister, F.A., et al., *The effect of specialist care within the first year on subsequent outcomes in 24 232 adults with new-onset diabetes mellitus: population-based cohort study.* Quality & Safety in Health Care, 2007. **16**(1): p. 6-11.

41. Inzucchi, S.E., et al., *Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach.* Diabetes Care, 2012. **35**: p. 1364-1379.

42. Jackevicius, C.A., et al., *Use of fibrates in the united states and canada.* JAMA, 2011. **305**(12): p. 1217-1224.

43. Jackevicius, C.A., et al., *Use of Ezetimibe in the United States and Canada.* New England Journal of Medicine, 2008. **358**(17): p. 1819-1828.

44. Jack V, T., et al., *Use of Cardiac Procedures and Outcomes in Elderly Patients with Myocardial Infarction in the United States and Canada.* The New England Journal of Medicine, 1997(21): p. 1500.

45. John C. Hornberger, a., a. Alan M. Garber, and a. John R. Jeffery, *Mortality, Hospital Admissions, and Medical Costs of End-Stage Renal Disease in the United States and Manitoba, Canada.* Medical Care, 1997(7): p. 686.

46. FDA, *Sentinel Initiative.*

47. Padwal, R., M. Lin, and D.T. Eurich, *The Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Patients With Diabetes.* The Journal of Clinical Hypertension, 2016. **18**(3): p. 200-206.

48. Eurich, D.T., et al., *Risk of new-onset heart failure in patients using sitagliptin: A population-based cohort study.* Diabetic Medicine, 2016. **33**(5): p. 621-630.

49. Weir, D.L., et al., *Clinical Research: Sitagliptin Use in Patients With Diabetes and Heart Failure. A Population-Based Retrospective Cohort Study.* JACC: Heart Failure, 2014. **2**: p. 573-582.

50. Ray, W.A., *Evaluating Medication Effects Outside of Clinical Trials: New-User Designs.* American Journal of Epidemiology, 2003. **158**(9): p. 915-920.

51. Lashen, H., *Role of metformin in the management of polycystic ovary syndrome.* Therapeutic Advances in Endocrinology and Metabolism, 2010. **1**(3): p. 117-128.

52. Riedel, A.A., et al., *Loss of Glycemic Control in Patients with Type 2 Diabetes Mellitus Who Were Receiving Initial Metformin, Sulfonylurea, or Thiazolidinedione Monotherapy.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2007. **27**(8): p. 1102-1110.

53. Eurich, D.T., et al., *Secondary failure rates associated with metformin and sulfonylurea therapy for type 2 diabetes mellitus.* Pharmacotherapy, 2005. **25**(6): p. 810-816.

54. Elixhauser, A., et al., *Comorbidity Measures for Use with Administrative Data.* Medical Care, 1998. **36**(1).

55. Quan, H., et al., *Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data.* Medical Care, 2005. **43**(11).

56. Huberman, M. and B. Langholz, *Application of the Missing-Indicator Method in Matched Case-Control Studies with Incomplete Data.* American Journal of Epidemiology, 1999. **150**(12): p. 1340-1345.

57. Maruthur, N.M., et al., *Diabetes medications as monotherapy or metformin-based combination therapy for type 2 diabetes: A systematic review and meta-analysis.* Annals of Internal Medicine, 2016. **164**(11): p. 740-751.

58. McEwen, L.N., et al., *Predictors and Impact of Intensification of Antihyperglycemic Therapy in Type 2 Diabetes: Translating Research into Action for Diabetes (TRIAD).* Diabetes Care, 2009. **32**(6): p. 971-976.

59. Rodondi, N., et al., *Therapy Modifications in Response to Poorly Controlled Hypertension, Dyslipidemia, and Diabetes Mellitus.* Annals of internal medicine, 2006. **144**(7): p. 475-484.

60. Yu, S., et al., *Use of Add-on Treatment to Metformin Monotherapy for Patients with Type 2 Diabetes and Suboptimal Glycemic Control: A U.S. Database Study.* Journal of Managed Care & Specialty Pharmacy, 2016. **22**(3): p. 272-280.

61. Gomes, T., et al., *Progression through diabetes therapies among new elderly users of metformin: a population-based study.* Diabetic Medicine, 2013. **30**(2): p. e51-e55.

62. Meltser, Ś., *1998 clinical practice guidelines for the management of diabetes in Canada*. 1998: [Ottawa] : Canadian Diabetes Association : Canadian Medical Association, 1998.

63. Booth, G.L., et al., *Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study.* The Lancet, 2006. **368**(9529): p. 29-36.

64. Turnbull, F.M., et al., *Intensive glucose control and macrovascular outcomes in type 2 diabetes.* Diabetologia, 2009. **52**(11): p. 2288-2298.

65. Tu, J.V., et al., *Use of Cardiac Procedures and Outcomes in Elderly Patients with Myocardial Infarction in the United States and Canada.* New England Journal of Medicine, 1997. **336**(21): p. 1500-1505.

66. Eisenberg, M.J., et al., *Outcomes and cost of coronary artery bypass graft surgery in the United States and Canada.* Arch Intern Med, 2005. **165**(13): p. 1506-13.

67. Pirart, J., *Diabetes Mellitus and Its Degenerative Complications: A Prospective Study of 4,400 Patients Observed Between 1947 and 1973.* Diabetes Care, 1978. **1**(3): p. 168.

68. Cowie CC, C.S., Menke A, Cissell MA, Eberhardt MS, Meigs JB, Gregg EW, Knowler WC, Barrett-Connor E, Becker DJ, Brancati FL, Boyko EJ, Herman WH, Howard BV, Narayan KMV, Rewers M, Fradkin JE, Eds. Bethesda, *Diabetes in America, 3rd Edition.* 2016.

69. Luciani, N., et al., *Coronary artery bypass grafting in type II diabetic patients: a comparison between insulin-dependent and non-insulin-dependent patients at short- and mid-term follow-up.* The Annals of Thoracic Surgery, 2003. **76**(4): p. 1149-1154.

70. Dormandy, J.A., et al., *Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial.* The Lancet, 2005. **366**(9493): p. 1279-1289.

71. Quan, H., et al., *Assessing Validity of ICD-9-CM and ICD-10 Administrative Data in Recording Clinical Conditions in a Unique Dually Coded Database.* Health Services Research, 2008. **43**(4): p. 1424-1441.

72. Quan, H., G.A. Parsons, and W.A. Ghali, *Validity of Information on Comorbidity Derived From ICD-9-CCM Administrative Data.* Medical Care, 2002. **40**(8).

73. Services, C.f.M.M., *End Stage Renal Disease*. 2013.

74. Stolar, M., *Glycemic Control and Complications in Type 2 Diabetes Mellitus.* The American Journal of Medicine, 2010. **123**(3, Supplement): p. S3-S11.

75. Epstein, A.J., et al., *Coronary Revascularization Trends in the United States: 2001–2008.* JAMA : the journal of the American Medical Association, 2011. **305**(17): p. 1769-1776.

76. Raja, S.G., *Myocardial Revascularization for the Elderly: Current Options, Role of Off-pump Coronary Artery Bypass Grafting and Outcomes.* Current Cardiology Reviews, 2012. **8**(1): p. 26-36.

77. Fu, Y., et al., *Canadian-American Differences in the Management of Acute Coronary Syndromes in the GUSTO IIb Trial.* Circulation, 2000. **102**(12): p. 1375.

78. Greenwood, D.A., et al., *Overcoming Clinical Inertia: A Randomized Clinical Trial of a Telehealth Remote Monitoring Intervention Using Paired Glucose Testing in Adults With Type 2 Diabetes.* J Med Internet Res, 2015. **17**(7): p. e178.

79. *Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes.* New England Journal of Medicine, 2013. **369**(2): p. 145-154.

80. Cramer, J.A., *A Systematic Review of Adherence With Medications for Diabetes.* Diabetes Care, 2004. **27**(5): p. 1218.

81. Ross, S.A., *Breaking Down Patient and Physician Barriers to Optimize Glycemic Control in Type 2 Diabetes.* The American Journal of Medicine, 2013. **126**(9): p. S38-S48.

82. Russell-Minda, E., et al., *Health Technologies for Monitoring and Managing Diabetes: A Systematic Review.* Journal of Diabetes Science and Technology, 2009. **3**(6): p. 1460-1471.

83. Haut, E.R., P.J. Pronovost, and E.B. Schneider, *Limitations of administrative databases.* JAMA, 2012. **307**(24): p. 2589-2590.

84. Sarrazin, M. and G.E. Rosenthal, *Finding pure and simple truths with administrative data.* JAMA, 2012. **307**(13): p. 1433-1435.