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Antihyperglycemic Medications and Hypoglycemia in Older Adults with Diabetes

Kristin K. Clemens, *The University of Western Ontario*

Supervisor: Dr. Amit Garg, *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Master of Science degree in Epidemiology and Biostatistics

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by

Kristin K. Clemens

Graduate Program in Epidemiology and Biostatistics

A thesis submitted in partial fulfillment
of the requirements for the degree of
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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

Abstract

Background: In the last decade, several new antihyperglycemic medications have been approved to treat people with diabetes. However, the hypoglycemia risk of these medications in older adults in routine clinical practice remains unclear. Further, there is limited understanding as to how these medications are being prescribed to older adults in our region.

Methods: We carried out retrospective, population-based studies of adults age 66 and older in Ontario, Canada using linked healthcare databases. We first investigated the real-world hypoglycemia risk of 2 antihyperglycemic medications – glyburide and modified-release gliclazide. In an ecological study, we then examined trends in antihyperglycemic medication prescriptions, and in this setting, investigated hospital encounters for hypoglycemia.

Results: Initiating glyburide vs gliclazide as monotherapy or in the presence of metformin was associated with a significantly higher risk of a hospital encounter with hypoglycemia. Over the last decade, newer and safer antihyperglycemic medications have been prescribed to older adults in our region. In this setting, the overall percentage of patients with a hospital encounter with hypoglycemia has declined.

Conclusions: Antihyperglycemic medications differ in their real-world hypoglycemia risk in older patients. In the setting of newer and safer antihyperglycemic medications, encounters for hypoglycemia have declined.

Keywords

Diabetes, hypoglycemia, older adults, antihyperglycemic medications, glyburide, modified-release gliclazide

Co-Authorship Statement

Under the supervision of Amit Garg, Kristin Clemens played a substantial role in the included manuscripts. Kristin was involved in the conception and design of the studies and she prepared their protocols. She also played a primary role in the interpretation of the results of both studies. Further, she drafted and revised both manuscripts for publication.

Several co-authors also made contributions to the included manuscripts. For the study "The hypoglycemic risk of glyburide (glibenclamide) compared with modified-release gliclazide", co-author Eric McArthur contributed to the design of study, acquired the data, carried out the statistical analysis and revised the manuscript critically for its content. Stephanie Dixon aided in the data acquisition and its analysis and she reviewed the manuscript. Jamie Fleet helped to design the study and she revised the manuscript critically. Irene Hramiak helped to develop the concept of the study, aided in its interpretation and she revised the article for its content.

For the included study, "Trends in antihyperglycemic medication prescriptions and hypoglycemia in older adults: 2002-2013", Salimah Shariff contributed to the design of study, acquired the data, and she revised the manuscript critically for its content. Kuan Liu contributed to the design of the study, acquired and analyzed the data, and she revised the manuscript critically for its content. Irene Hramiak helped to design the study, interpret the results and she critically reviewed the manuscript. Jeffrey Mahon helped to interpret the results of the study and he contributed to the drafting of the manuscript. Eric McArthur was involved in the conception of the study, result interpretation and he reviewed the manuscript critically.

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Dedication

This thesis is dedicated to my husband Mike, my son Cole, and to our little boy on the way. Thank you for your ongoing love, support, encouragement, and patience.

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Preface

I conducted all work for this thesis at the Kidney Clinical Research Unit at London Health Sciences Centre and at the Institute for Clinical Evaluative Sciences (Western Site).

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The included study "Trends in antihyperglycemic medication prescriptions and hypoglycemia in older adults: 2002-2013" authored by Kristin Clemens, Salimah Shariff, Kuan Liu, Irene Hramiak, Jeffrey Mahon, Eric McArthur and Amit Garg has been submitted for peer-reviewed publication.

Chapter 1

1 Introduction

1.1 What is diabetes?

Diabetes is a chronic metabolic condition characterized by insulin deficiency, impaired secretion and/or insulin resistance (ie poor utilization). As insulin aids in the storage and utilization of glucose,[1,2] patients with diabetes have elevated blood sugar or hyperglycemia. The Canadian Diabetes Association currently recommends that a diagnosis of diabetes be made in an individual with: 1) a fasting blood glucose ≥7 mmol/L, or 2) a 2 hour blood glucose ≥11.1 mmol/L following a 75 gram oral glucose tolerance test, or 3) a random blood glucose ≥11.1 mmol/L or 4) a glycosylated hemoglobin (HbA1c) greater than 6.5% (a test that reflects glycemic control over the previous 8-12 weeks).[3]

There are two main types of diabetes - type 1 diabetes and type 2 diabetes. Type 1 diabetes is the result of pancreatic beta-cell destruction, most commonly from an autoimmune process.[4] This leads to insulin deficiency and these patients require insulin replacement therapy.[1] Type 1 diabetes can occur at any age but is more common in childhood and adolescence. It accounts for approximately 5% of all patients with diabetes.[2]

Type 2 diabetes is characterized by insulin resistance and impaired insulin secretion.[2] Although genetic factors play a role in its development, it is closely related to obesity and decreased physical activity.[5] As such, these patients often have concomitant medical conditions including lipid disorders and high blood pressure (the “metabolic syndrome”).[1] Most people with type 2 diabetes do not need insulin initially, but with time, often require it to maintain adequate glycemic control.[1] Type 2 diabetes typically arises in adulthood, though it is increasing in onset in younger individuals. It accounts for about 95% of patients with diabetes.[2]

1.2 What is the burden of diabetes?

The number of people with type 1 and type 2 diabetes is increasing in North America and worldwide.[4,6] In 2013 there were almost 2 million people over the age of 12 with the condition in Canada, and almost 900,000 were age 65 and older.[7] Where sedentary habits and obesity are epidemic, this trend is expected to continue, especially in type 2 diabetes.[6]

Diabetes can lead to significant consequences for patients including structural complications, treatment related side effects, impaired quality of life, and premature death (detailed below). The disease is also associated with major economic burden, and has consumed an increasing proportion of provincial health care expenditures.[8] From 2000 until 2010, the economic burden of diabetes (direct and indirect costs) was estimated to double ($6.3 billion in 2000, $12.2 billion in 2010). By 2020, it has been projected that its associated costs will increase by another $4.7 billion.[8]

1.3 What are the consequences of diabetes?

Diabetes can have several significant consequences for patients. Acutely, hyperglycemia can lead to symptoms including frequent urination and blurred vision.[1] Weight loss may occur through the depletion of water and nutrient stores, and dizziness and weakness can result from lowered plasma volume.[1] In severe instances, diabetic ketoacidosis or hyperglycemic hyperosmolar state (ie. hyperglycemic emergencies) can arise which may lead to hospital presentation, morbidity and mortality.[9]

Over the longer term, hyperglycemia can also result in small and large blood vessel damage. Small vessel damage, termed microvascular disease, typically impacts the kidney (nephropathy), nerves (neuropathy), and eyes (retinopathy). Diabetic nephropathy initially manifests as protein loss in the urine (proteinuria) and eventually can lead to chronic kidney disease.[1] Neuropathy can involve the sensory, motor and autonomic nerves and can result in loss of vibration sense and temperature along with pain, impaired reflexes, joint and connective tissue changes, low blood pressure, impaired gastro-intestinal activity (ie. gastroparesis), and bladder and erectile dysfunction.[1] Diabetic

retinopathy can lead to vision loss as a result of hemorrhage, microaneurysms, exudates, retinal detachment and macular edema.[1]

Chronic hyperglycemia can also lead to large vessel or macrovascular disease which impacts the vessels of the heart (cardiovascular), brain (cerebrovascular) and periphery (peripheral vascular). Cardiovascular disease may lead to heart attack and heart failure. Peripheral vascular disease may cause ischemia of the lower extremities, erectile dysfunction, intestinal angina and gangrene.[1] Cerebrovascular disease may result in stroke or transient ischemic attack.

Other recognized complications of diabetes include bony fractures,[10] skin changes, and chronic infections.[1] In the elderly, depression, impaired cognition, urinary incontinence and chronic pain have also been identified.[11] Life expectancy is 3 to 6 years shorter in patients over the age of 65 with diabetes compared to those without the condition.[11]

1.4 How is diabetes managed?

The management of diabetes involves treating hyperglycemia and managing its related complications.[12]

1.4.1 Hyperglycemia

Central to the management of diabetes is controlling hyperglycemia. The target for glycemic control for most patients with diabetes is an HbA1c less than 7%. This is based upon studies which have indicated that an HbA1c less than 7% reduces the risk of microvascular complications, and in younger patients with a recent diagnosis of the disease, macrovascular complications.[13–17]

Glycemic control can be accomplished through lifestyle modification and/or the initiation of antihyperglycemic medications. Lifestyle modification (including exercise, healthy diet, and weight control), can have a significant impact on blood sugars. In fact, for type 2 diabetes, lifestyle changes are considered first line therapy. In a meta-analysis of the effects of exercise on glycemic control, it was found that aerobic, resistance and combination exercise programs improved glycemia.[18] Likewise, nutritional therapy with

a registered dietitian can lower HbA1c by 1 to 2%.[19] The impact of weight loss on glycemic control is supported by recent studies on the benefits of bariatric surgery in type 2 diabetes .[20] Physicians who treat diabetes usually aim for multi-factorial lifestyle intervention based upon the benefits reported by the Diabetes Prevention Program (DPP) Trial,[21] and the LOOKAHEAD trial which indicated that patients randomized to an intensive lifestyle (healthy diet and 175 minutes of physical activity per week to induce at least 7% weight loss) had a lower HbA1c after 4 years compared to those randomized to diabetes support and education alone (HbA1c -0.36% vs -0.09%, $p<0.001$).[22]

Beyond lifestyle modification, antihyperglycemic medications can help to improve glycemic control. These medications can include insulin (for both type 1 and 2 patients) or other oral/subcutaneous antihyperglycemic medications (for patients with type 2 diabetes). Where only sulphonylureas (eg. glyburide), biguanides (eg. metformin), insulin, and alpha glucosidase inhibitors (eg. acarbose) were available for the treatment of type 2 diabetes in Canada in the 1990's, there are now 20 different antihyperglycemic medications approved for use in our country, each with different benefits and side effect profiles (list of available drugs, potency, side effects presented in Table 1).

Table 1. Antihyperglycemic medications currently available in Canada

Class	Drug Names Available	Mechanism of Action	Glucose Lowering Effect	Weight Effect	Hypoglycemic Risk	Side Effects	Notes
Biguanides	Metformin	Decreases hepatic glucose output; enhances insulin effect at peripheral receptors [23]	Reduces HbA1c by 1.5% [24]	Weight loss reported [25]	Negligible risk as monotherapy [6]	Gastrointestinal upset, lactic acidosis (esp in those with renal, liver, heart failure) [6]	Considered first line therapy for type 2 diabetes by most clinical practice guidelines
Alpha glucosidase inhibitors	Acarbose	Inhibits the intestinal enzyme that breaks down polysaccharides and reduces carbohydrate re-absorption[1]	Reduces HbA1c by 0.5-0.8% [24]	Neutral	Negligible risk as monotherapy [23]	Gastrointestinal upset	
Insulin	Bolus: Aspart, Glulisine, Lispro, Regular Basal: NPH,	Binds to receptor on surface of target cell membrane leading to increased glycogen, lipid and protein	Reduces HbA1c by 1.5-2.5% [24]	Associated with weight gain [24]	Very high risk of hypoglycemia		For treatment of type 1 and type 2 diabetes. Need consideration of patient function,

	Detemir, Glargine Pre-mixed: Regular/NPH (30/70, 40/60, 50/50), Biphasic aspart (novomix 30), Lispro/protamine (Humalog mix 25, 50)[26]	synthesis; triggers genes involved in growth and metabolism; promotes the storage of ingested nutrients[1]					autonomy, cognition, vision, self-management ability. No dose ceiling and flexible regimens[27]
Sulphonylureas	Glyburide, Gliclazide, Glimepiride, Acetohexamide, Chlorpropamide, Tolbutamide	Bind to sulphonylurea receptor on the beta cell of the pancreas to inhibit potassium efflux; leads to depolarization of beta cell and insulin release [25]	Reduces HbA1c by 1.5%[24]	Associated with weight gain [25]	High risk of hypoglycemia		Often considered second line agent to metformin in type 2 diabetes
Thiazolidinediones	Pioglitazone, Rosiglitazone	Bind to perioxisome proliferator activated receptors; increase sensitivity of muscle fat, and liver to	Reduce HbA1c by 0.5 to 1.4%[24]	Weight neutral	Negligible risk of hypoglycemia as monotherapy	Edema, heart failure, fracture, hepatotoxicity. Rosiglitazone potentially linked	

		insulin[1]				to adverse cardiovascular events[6,25]	
Meglitinides	Repaglinide, Nateglinide	Bind to sulphonylurea receptor and induce the depolarization of pancreatic beta cells to secrete insulin[23]	Reduce HbA1c by 1-1.5%[24]	Associated with weight gain[6]	Risk of hypoglycemia (though less than with sulphonylureas)		Rapid onset of action so can be dosed prior to meals
Dipeptidyl peptidase-4 inhibitors	Sitagliptin, Saxagliptin, Linagliptin	Inhibit the enzyme degradation of glucagon like peptide-1; suppress glucose release, delays gastric emptying and stimulates insulin release from the pancreas in a glucose dependent fashion [25]	Reduce HbA1c by 0.5-1%[24]	Weight neutral	Negligible risk of hypoglycemia as monotherapy	Gastrointestinal upset, nasopharyngitis, headache	
Glucagon like peptide-1 agonists	Exenatide, Liraglutide	Glucagon like peptide-1 stimulates insulin release from the pancreas in a	Reduce HbA1c by 0.5 to 1%[24]	Associated with weight loss [24]	Negligible risk as monotherapy	Gastrointestinal discomfort	Subcutaneous injection

		glucose dependent fashion[23]					
Sodium glucose co-transporter 2 inhibitors	Canagliflozin, Dapagliflozin	Inhibit renal reabsorption of glucose [28]	Reduce HbA1c by about 0.7%	Associated with weight loss	Negligible risk as monotherapy	Genital mycotic infections, osmotic diuresis and volume depletion	

1.4.2 Diabetes-related complications

In addition to managing hyperglycemia, physicians who treat diabetes must also address its related complications.

Alongside tight glycemic control, kidney health can be optimized through control of blood pressure and the use of angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB' s).[29–32] Eye health can be promoted through blood pressure control and smoking cessation.[1] In those with advanced retinopathy, photocoagulation can reduce severe visual loss.[1,33] Neuropathy-associated conditions including gastroparesis can be managed with medications including dopamine antagonists (eg. metoclopramide, domperidone) and erythromycin. Erectile dysfunction can be treated with cyclic guanosine monophosphate-specific phosphodiesterase type 5 inhibitors.[1,34] Painful diabetic neuropathy can be treated with anticonvulsants, antidepressants, opioids, topical nitrates, and capsaicin.[34]

In addition to lifestyle modification, the cardiovascular health of patients can be optimized with smoking cessation,[35] the use of lipid-lowering medications,[36,37] the control of blood pressure,[38] antiplatelet therapy (in those with a previous cardiovascular event or at high risk of an event),[39] and ACE inhibitors or ARB's.[32,40,41] A multifactorial strategy to improve cardiovascular health is especially beneficial as illustrated by the STENO 2 trial. In this trial, patients randomized to intensive therapy (ie. tight glucose control, ACE inhibitors or ARB's, aspirin and lipid lowering therapy) had both a lower risk of death from cardiovascular causes (hazard ratio (HR) 0.43 [95% confidence interval (CI) 0.19 to 0.95], p=0.04] and a lower risk of cardiovascular events (HR 0.41 [95% CI 0.25 to 0.67], p<0.001) compared with those randomized to standard care.[42]

Finally foot health can be maintained through regular physical examination, education, the optimization of vascular health, the use of proper footwear, and early referral should foot complications occur.[43] For those with evidence of skin ulcers, local wound care, debridement and mechanical unloading are important interventions.[1,43]

1.5 What are the complications of diabetes management?

1.5.1 Hypoglycemia

Because antihyperglycemic medications by design lower blood glucose levels, a significant complication of diabetes management is hypoglycemia. Though definitions vary, the Canadian Diabetes Association defines hypoglycemia by 1) the development of symptoms (eg. shaking, tremor); 2) a low plasma glucose level (<4.0 mmol/L); and 3) the relief of symptoms with carbohydrate administration.[44] The severity of hypoglycemia is best defined by whether a patient can self-treat their episode with the ingestion of carbohydrate (mild) or if they need assistance for treatment from another person (severe).[45]

In addition to producing uncomfortable symptoms including tremor, lightheadedness, palpitations, sweating, anxiety, hunger, nausea, tingling, vision changes, and headaches, [44] hypoglycemia can have other significant consequences for patients.

Motor activities and coordination can be impacted leading to falls, injury and fracture.[45] Reaction times can also be prolonged and often do not return to baseline until 20-30 minutes after normal blood glucose levels are restored.[46] As a result, activities including driving performance can deteriorate.

Hypoglycemia can also lead to neurological dysfunction including decreased level of consciousness, coma, stroke, transient ischemic attack and seizures.[45] In the elderly there is additionally increasing evidence that recurrent exposure to severe episodes of hypoglycemia can have detrimental effects on cognitive function and may promote the development of dementia.[45] In a study of 16,667 older patients with type 2 diabetes, the age-adjusted incidence rates of dementia were elevated for those with at least 1 severe hypoglycemic episode compared with those with no episodes (567 cases per 10,000 person years [95% CI 497 to 637 per 10,000 person-years] vs 328 cases per 10,000 person years [95% CI 311 to 343 per 10,000 person years], adjusted HR 1.68 [95% CI 1.47 to 1.93]). In this study, the risk of dementia also increased with a greater number of hypoglycemic events.[47]

Additionally, the release of stress hormones in the setting of hypoglycemia can impact the cardiovascular system. In those with heart disease, hypoglycemia has been linked with heart attack, heart failure, and irregular heart rhythms.[45]

Further, it has been recognized that hypoglycemia has a significant impact on quality of life. Barnett et al found that hypoglycemia was independently associated with reduced quality of life and additionally noted that the magnitude of the quality of life reduction increased with the severity and frequency of hypoglycemia symptoms.[46] Events can also lead to adverse consequences in the work place, in social relationships and in the educational environment.[45]

Hypoglycemia has also been associated with death. “Dead in bed syndrome” has been described in case reports of patients with type 1 diabetes with documented nocturnal hypoglycemia (by real-time glucose monitoring) who died in their sleep.[46] In a case-control study of hospitalized patients, it has also been found that insulin-associated and spontaneous hypoglycemia was associated with increased mortality.[48]

Additional consequences of hypoglycemia include a fear of ongoing events which may prompt avoiding behaviour and poor adherence to diabetes treatment.[45,46] Chronic hypoglycemia can also impair defenses against subsequent falling plasma glucose concentrations and may lead to a cycle of recurrent hypoglycemia.[46]

1.5.2 Additional risk factors for hypoglycemia

Beyond the use of antihyperglycemic medications, several risk factors have been established for hypoglycemia. Those with type 1 diabetes [45] and advanced type 2 diabetes [46] are at increased risk along with those with either tightly controlled or poorly controlled blood sugar.[49,50] Compared with patients using thiazolidinediones, metformin, dipeptidyl peptidase-4 inhibitors (DPP-4), glucagon like peptide-1 agonists (GLP-1), and sodium glucose co-transporter 2 inhibitors (SGLT2), those using insulin, sulphonylureas and meglitinides are also at higher risk of hypoglycemia (Table 1).[45]

Several comorbidities also place patients at increased risk of hypoglycemia. These include nephropathy, cognitive dysfunction, alcohol use, neuropathy and hypoglycemia

unawareness (impaired awareness of hypoglycemia symptoms).[45] The elderly are at particular risk of hypoglycemia as they have impaired counter-regulatory responses,[51] tend to have few warning symptoms;[51,52] and recover more slowly from events.[45]

1.6 Special issues in older adults and the need for research

Glycemic control is a central issue in the management of patients with diabetes. However a significant practical problem for clinicians is finding a balance between control that is adequate to prevent symptoms and reduce the risk for structural complications, and the cost of unacceptable side effects including hypoglycemia. This risk to benefit ratio is particularly poorly understood in older patients - a heterogeneous population with different life expectancies, functionalities, comorbidities, levels of frailty (marker of vulnerability which identifies patients with a diminished capacity to compensate effectively for external stresses and disability)[53] and durations of disease.[6]

Further adding to their treatment complexity is the recent proliferation of antihyperglycemic medications that have become available to treat people with diabetes in the last decade. In the older adult population, there has been limited study into the efficacy of these medications,[10,54] their hypoglycemia risk (Table 2), and their use in this vulnerable population.

1.7 Research aims

In the current work we aimed to expand our knowledge of antihyperglycemic medication prescribing and safety in older adults with diabetes. Our specific aims were to:

1) Investigate the real-world risk of hypoglycemia for new users of glyburide vs modified-release gliclazide (2 sulphonylurea medications).

2) Investigate patterns in antihyperglycemic medication prescriptions in older adults from 2002 until 2013, and over the period of study, investigate hospital encounters for hypoglycemia.

Table 2. Real-world studies on the efficacy and safety of antihyperglycemic medications

Authors	Study Design	Results	Conclusions
Mathieu C et al [55]	Multicentre prospective observational cohort study of 45,868 adults with type 2 diabetes inadequately controlled on 1 antihyperglycemic medication. Examined treatment response and tolerability to vildagliptin vs. other oral agents (including risk of hypoglycemia).	Mean age 57.8± 11.8, 12, 917 (29.5%) over the age of 65. Noted better treatment response and tolerability with vildagliptin compared with other antihyperglycemic medications (adjusted odds ratio 1.49 [CI 1.42-1.55], p<0.001).	Compared with other medications, vildagliptin can lower HbA1c to target without side effects.
Al-Arouj M et al[56]	Multicentre prospective study from the Middle East and Asia of type 2 patients over the age of 18 treated with vildagliptin (n=684) or sulphonylurea (n=631) as add on to metformin. Primary outcome was the proportion with at least 1 hypoglycemia event during the fasting period in Ramadan.	Mean age 49.6 with 10% over the age of 65. Significantly fewer patients in the vildagliptin group experienced a hypoglycemia event compared with those receiving sulphonylureas (5.4% vs 19.8%, p<0.001).	Vildagliptin was associated with significantly fewer hypoglycemia episodes compared with sulphonylureas and was well-tolerated in this population.
Freemantle N et al [57]	Multicentre, prospective cohort study of type 2	Propensity score matches achieved for 686 starting premix vs basal insulin,	Less nocturnal hypoglycemia with

	patients over the age of 40 who started insulin within 12 months prior to study entry (n= 2374). Aimed to examine the performance of different insulin regimens on HbA1c reduction and hypoglycemia along with body weight change.	542 starting basal and mealtime vs premix, 400 starting basal and mealtime (ie bolus). Mean age was approximately 60 across groups. HbA1c reduction did not differ between the 3 insulin regimens. Relative risk of overall and nocturnal hypoglycemia lower ($p=0.010$ to $p<0.001$) with basal or basal plus mealtime compared with premix. Similar finding for nocturnal ($p=0.021$) hypoglycemia but not for overall hypoglycemia for basal compared with basal and mealtime regimens.	basal insulin than premix.
Gitt AK et al[58]	German prospective cohort study of 3810 patients with type 2 diabetes over the age of 40 on mono or dual combination therapy prior to study. Aimed to examine if DPP-4 inhibitor compared to sulphonylurea provided non-inferior glycemic control with reductions in body weight and lower risk of hypoglycemia.	884 received dual therapy with DPP-4 or sulphonylurea in setting of metformin (n=628 and n=256 respectively). Mean age 64.1 in DPP-4 group and 67.9 in SU group. No significant difference in change in HbA1c over the 12 months of treatment but hypoglycemia significantly less frequent in those receiving DPP-4 inhibitors (odds ratio 0.32 [95% CI 0.19 to 0.54]).	DPP-4 on top of metformin resulted in similar HbA1c reductions within 12 months with a significant reduction in hypoglycemia.
Holstein et al[59]	Prospective cohort study of 30,768 patients who attended the emergency room over a 4 year period.	Glimepiride produced fewer episodes of hypoglycemia than glyburide (0.86/1000 person-years vs. 5.6/1000 person years respectively).	In people with type 2 diabetes, glimepiride associated with fewer episodes of severe

	Aimed to evaluate the incidence of severe hypoglycemia associated with glimepiride and glyburide.		hypoglycemia than glyburide in routine care.

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Chapter 2

2 The hypoglycemic risk of glyburide (glibenclamide) compared with modified release gliclazide

Kristin K. Clemens, MD [1]; Eric McArthur, MSc [2]; Stephanie N. Dixon, PhD [2,3]; Jamie L. Fleet, BHSc [2,4]; Irene Hramiak, MD [5]; Amit X. Garg, MD [2,3,4]

1. Department of Medicine, Western University, London Ontario Canada

2. Institute for Clinical Evaluative Sciences, London Ontario Canada

3. Department of Epidemiology & Biostatistics, Western University, London Ontario Canada

4. Division of Nephrology, Department of Medicine, Western University, London Ontario Canada

5. Division of Endocrinology, Department of Medicine, Western University, London Ontario Canada

2.1 Introduction

Sulphonylureas are easy to administer, low in cost, and through their insulin secreting mechanism, are amongst the most potent of all oral hypoglycemic agents.[1,2] These drugs however, must be used very carefully in older adults to avoid hypoglycemia, given that this population frequently has medical comorbidities, takes multiple medications, and has altered drug metabolism.

In Canada, glyburide (glibenclamide) and gliclazide are 2 commonly prescribed sulphonylureas. Because of glyburide's high affinity for the sulphonylurea receptor,[3] its long duration of action, and its glucose lowering metabolites,[4] the hypoglycemia risk of glyburide is anticipated to be higher than other sulphonylureas.[5-7] Accordingly, diabetes guidelines have cautioned against the use of glyburide in the elderly in favor of other oral hypoglycemic agents.[8] However, to our knowledge, the risk of hypoglycemia with

glyburide compared with a long-acting alternative, modified-release gliclazide,[9] has not been examined in a large representative population of older adults in routine practice. For this reason we conducted 2 population-based cohort studies to examine the risk of hospital encounters with hypoglycemia after the initiation of glyburide vs once-daily modified-release gliclazide in the outpatient setting.

2.2 Methods

2.2.1 Study design and setting

We conducted 2 population-based matched retrospective cohort studies of older adults using linked health care databases in Ontario, Canada. Ontario has approximately 1.8 million adults aged 65 years or older who have comprehensive universal healthcare including coverage for outpatient prescription medications, physician services, hospitalizations and diagnostic testing.[10] The reporting of these studies follows guidelines for observational studies (Appendix B Table 1).[11]

The studies were conducted at the Institute for Clinical Evaluative Sciences (ICES) according to a pre-specified protocol which was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). Participant informed consent was not required.

2.2.2 Data sources

We obtained patient characteristics, drug use, covariate information, and outcome data using records from several databases. We ascertained vital statistics from the Registered Persons Database of Ontario, which contains demographic information on all Ontario residents who have been issued a health card. The Ontario Drug Benefit Program database was used to identify prescription drug use and contains accurate records of all formulary prescriptions dispensed to those aged 65 years or older, with an error rate of less than 1%.[12] Diagnostic and procedural information on hospital admissions and emergency room visits was abstracted from the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System database, respectively. Covariate information was also derived from the Ontario

Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We used the ICES Physician Database to abstract sulfonylurea prescriber information. In previous studies, we have used these databases to research adverse drug events and health outcomes.[13-18] A subpopulation of patients had laboratory creatinine or HbA1c values available in the year prior to the relevant sulphonylurea prescription.[19,20]

With the exception of sulfonylurea prescriber information (missing in approximately 13% of both studies), and income quintile (missing in approximately 0.5% of both studies) the databases were complete for all variables used. International Classification of Diseases 9th Revision (ICD-9) (pre-2002), International Classification of Diseases 10th Revision (ICD-10) (post-2002), Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures (CCP) (pre-2002) and Canadian Classification of Health Interventions (CCI) (post-2002) codes were utilized to assess baseline comorbidities and investigations in the 5 years prior to the relevant sulphonylurea prescription (Appendix B Table 2). Physician visits in the year prior to the sulphonylurea prescription were assessed through provincial fee for service codes. Codes used to assess outcomes are detailed in Appendix B Table 3, which lists only ICD-10 codes as all events would have occurred after the implementation of this coding system in Canada.

2.2.3 Patients

To mimic routine practice, we conducted 2 population-based studies of older adults newly prescribed glyburide or modified-release gliclazide from April 2002 to December 2011. In the first study we examined a sulphonylurea prescribed as monotherapy and in the second study we examined a sulphonylurea prescribed in the presence of metformin. In both studies, the date of the sulphonylurea prescription served as the index date (cohort entry date).

Monotherapy study

In this study, we excluded the following patients from analysis: 1) those in their first year of eligibility for prescription drug coverage (aged 65 years) to avoid incomplete

medication records, 2) those who had insulin or any other oral hypoglycemic agent dispensed in the year prior to the index date to ensure new oral hypoglycemic agent use, 3) those who had other medications commonly associated with hypoglycemia (ie. pentamidine, quinine, glucagon, indomethacin) dispensed in the year prior to the index date,[21] 4) those with a history of at least one hospital encounter (emergency room or hospitalization) with hypoglycemia in the 5 years prior to the index date as antecedent hypoglycemia can be associated with hypoglycemic unawareness and recurrent episodes,[22] 5) those with a history of end-stage renal disease in the 5 years prior to the index date as reduced renal function may decrease the clearance of drugs and their metabolites, 6) those who were discharged from hospital in the 2 days prior to or on the index date to ensure these were new outpatient sulphonylurea prescriptions (because in Ontario patients continuing a sulphonylurea initiated in hospital would have their medication dispensed on the same day or the day after hospital discharge). A patient could only enter the cohort once. Patient selection is presented in Figure 1 of Appendix B.

Metformin combination study

In this study, in addition to either glyburide or modified-release gliclazide, patients were required to have evidence of metformin therapy (dispensed on the index date or dispensed at least once in the 180 days prior to the index date with the day supply covering the index date). The exclusion criteria applied were as in the monotherapy study, with the exception of excluding patients with oral hypoglycemic agents other than metformin dispensed in the year prior to the index date (Appendix B Figure 2).

In each study, we restricted the analysis to comparable sulphonlyurea dosages - glyburide total doses of 5, 10, 15, and 20 mg per day, and modified release gliclazide total doses of 30, 60, 90 and 120 mg per day.

2.2.4 Outcomes

In both studies, outcomes were assessed 90 days after the index date for the primary analysis. We chose 90 days of follow-up to avoid crossover in drug therapy that could

occur with longer periods of follow up, and because prescriptions covered by Ontario's drug plan are prescribed at no more than 100-day intervals.

The primary outcome was a hospital encounter (emergency room visit or hospital admission) with hypoglycemia. The secondary outcome was all-cause mortality (any death in or outside of hospital). The validity of the diagnostic codes used to identify these outcomes is presented in Table 3 of Appendix B.

2.2.5 Statistical analysis

We used similar statistical methods in each of the 2 studies. Baseline characteristics were compared between glyburide and gliclazide users using standardized differences. This metric describes differences between group means relative to the pooled standard deviation and is considered a meaningful difference if greater than 10%.[23]

A propensity score for the potential receipt of gliclazide was derived from a logistic regression model where treatment status was regressed on a set of 19 and 21 baseline covariates in each study respectively.[24] Covariates were selected on the basis of their potential association with oral hypoglycemic agent use or the study outcome, and included comorbidities, medications, health care visits, investigations and laboratory testing. We then retained each glyburide user who could be matched with a gliclazide user (1:1 match). Groups were matched using a nearest neighbor "greedy" matching algorithm on the basis of the logit of their propensity score (with a caliper width of ± 0.6 standard deviations),[24] age (±2 years), the presence of chronic kidney disease, at least one endocrinologist visit in the year prior, and the prescribed equivalent dose of glyburide or gliclazide (5 mg of glyburide equivalent to 30 mg of modified release gliclazide).[9,25-28] Matching on characteristics apart from the propensity score was completed in order to ensure good balance on prognostically important characteristics,[24] and to facilitate potential subgroup analyses. We then assessed the degree of balance in measured covariates between groups by examining post-match standardized differences which were less than 10% for over 55 characteristics in both studies.

The referent group consisted of older adults who were prescribed gliclazide. We estimated absolute risk differences by directly examining the percentage of patients in each treatment group with an encounter for hypoglycemia within 90 days. Absolute risk was also expressed as the number needed to harm (NNH) which is the reciprocal of the risk difference (1 / absolute risk difference). To account for matching, we used conditional logistic regression to estimate unadjusted odds ratios (OR) and 95% confidence intervals (CI's). OR's can be interpreted as relative risks (RR) (appropriate given the incidences observed).

To assess the robustness of our primary outcome, we also carried out several additional secondary analyses. These analyses were carried out after knowledge of our primary results. First, we adjusted our conditional OR's for the year of study cohort entry. Further, we extended follow-up beyond 90 days, terminating the observation period for reasons of death, study sulphonylurea discontinuation, receipt of a non-study hypoglycemic agent, or the last date of available records (March 31, 2012) and used Cox regression analyses stratified on matched sets.

Additionally, we performed other analyses to put the results into context and to guide the types of physicians to target with educational initiatives. We examined the total 90-day cost of all prescription drugs to the provincial health care program in glyburide vs. gliclazide users and tested for a statistical difference between the cost distributions using a Kruskal-Wallis test. We also examined physician characteristics associated with glyburide (versus gliclazide) prescriptions in the last 3 years of study accrual using conditional logistic regression [covariates included year since medical school graduation, physician sex, and practicing in a rural setting (population less than 10,000)].

We conducted all analyses with SAS version 9.3 (SAS Institute, Cary, North Carolina). We interpreted 2-tailed p values lower than 0.05 as statistically significant.

2.3 Results

2.3.1 Monotherapy study baseline characteristics

We identified 18,804 patients prescribed glyburide (n = 13,550) or gliclazide (n = 5254). Baseline characteristics of the 2 groups before and after matching are presented in Table 3, and the characteristics of patients with and without laboratory values available in the year prior are illustrated in Appendix B Table 4. After matching, we retained 4374 patients in each group, and baseline characteristics were similar between the groups. Over the course of the study, there were 4288 unique health care prescribers of glyburide or gliclazide and approximately 78% of prescribers were primary care physicians. Prescriptions were filled across 464 pharmacies. Over the years of accrual, glyburide continued to be initiated in routine care. However, there was a trend to fewer initiations over time with 609 prescriptions in 2002 (34 per 100,000 older adults in the general population) and 132 prescriptions in 2011 (7 per 100,000 older adults). The initiation of gliclazide increased from 6 in 2002 (at a time when the medication was not covered under Ontario's universal prescription drug plan) to 839 prescriptions in 2011 (47 per 100,000 older adults).

2.3.2 Monotherapy study outcomes

Prescribing glyburide was associated with a higher risk of a hospital encounter with hypoglycemia compared with gliclazide (69 patients of 4374 taking glyburide [1.60%] vs 8 patients of 4374 taking gliclazide [0.18%], absolute risk increase 1.40% [95% CI 1.01% to 1.79%], OR 8.63 [95% CI 4.15 to 17.93], $p < 0.0001$). Prescribing glyburide was not associated with a significantly higher risk of all-cause mortality compared with gliclazide (100 patients of 4374 taking glyburide [2.29%] vs 84 patients of 4374 taking gliclazide [1.92%], absolute risk increase 0.37% [95% CI -0.21% to 0.95%], OR 1.21 [95% CI 0.89 to 1.63], p=0.22) (Table 4).

2.3.3 Metformin combination study baseline characteristics

We identified 26,598 patients prescribed glyburide (n= 16,631) or gliclazide (n= 9967) in the presence of metformin. Baseline characteristics of the 2 groups before and after

matching are presented in Table 5, and the characteristics of those with and without laboratory values available in the year prior are illustrated in Appendix B Table 4. After matching, we retained 8038 patients in each group, and baseline characteristics were similar between groups. Metformin continued to be used in follow-up in both groups, with evidence of repeat prescriptions after the index date in 6403 of 8038 (80%) glyburide users and 6660 of 8038 (83%) gliclazide users (standardized difference 8%).

Over the course of the study, there were 7913 unique health care prescribers of glyburide or gliclazide and about 78% of prescribers were primary care physicians. Prescriptions were filled across 477 pharmacies. Over the years of accrual, glyburide continued to be initiated in routine care. There were 411 prescriptions in 2002 (23 per 100,000 older adults in the general population) and 376 prescriptions in 2011 (21 per 100,000). The initiation of gliclazide increased from less than 5 prescriptions in 2002 (at a time when the medication was not covered under the universal prescription drug plan) to 1905 prescriptions in 2011 (106 per 100,000).

2.3.4 Metformin combination study outcomes

Prescribing glyburide was associated with a higher risk of a hospital encounter with hypoglycemia compared with prescribing gliclazide (110 patients of 8038 taking glyburide [1.37%] vs 19 patients of 8038 taking gliclazide [0.24%], absolute risk increase 1.13% [95% CI 0.86% to 1.40%], OR 6.06 [95% CI 3.68 to 9.97], p<0.0001). Prescribing glyburide was also associated with a higher risk of all-cause mortality compared with gliclazide (109 patients of 8038 taking glyburide [1.36%] vs 75 patients of 8038 taking gliclazide [0.9%], absolute risk increase 0.43% [95% CI 0.10% to 0.76%], OR 1.47 [95% CI 1.09 to 1.97], p=0.012) (Table 5).

2.3.5 Additional analyses

The primary outcome associations in each study proved robust in additional analyses. Prescribing glyburide remained associated with a 90-day higher risk of a hospital encounter with hypoglycemia compared with prescribing gliclazide after adjustment for the year of cohort entry (monotherapy study adjusted OR 4.47 [95% CI 1.66 to 12.05], p=0.003; metformin combination study adjusted OR 5.90 [95% CI 2.85 to 12.18],

p<0.0001). Additionally, in time to event analyses, prescribing glyburide remained associated with a higher risk of a hospital encounter with hypoglycemia (monotherapy study HR 6.71 [95% CI 3.04 to 14.85], p<0.0001); metformin combination study HR 5.78 [95% CI 3.50 to 9.52], p<0.0001) (Appendix B Table 5 and 6).

In further analyses, encounters with hypoglycemia decreased throughout the study period from 1.5% in 2002 to less than 0.5% in 2011. Encounters took place across 77 different emergency rooms or hospitals. In the emergency room setting, day time visits (between hours of 8AM and 8PM) were more frequent than night time visits (between hours of 8PM and 8AM) (39 vs 24 visits, respectively). Similar findings were observed in the metformin combination study (99 different emergency rooms or hospitals, 68 day time vs 31 night time visits). When we examined total 90-day prescription costs to the provincial drug program (in 2012 Canadian dollars), in both studies the median per patient 90-day cost of drugs for glyburide patients was slightly less than gliclazide patients (monotherapy study $474 vs $525, p=0.006; metformin combination study $499 vs $528, p=0.017). Finally, when we examined the characteristics of physicians who prescribed glyburide (vs. gliclazide), in both studies the year since medical school graduation, physician sex, and practicing in a rural setting were not associated with prescribing glyburide. In the monotherapy study, being a foreign (vs Canadian) trained physician was associated with a higher likelihood of prescribing glyburide (adjusted OR 1.38 [95% CI 1.03 to 1.83]), an association not observed in the metformin combination study (adjusted OR 1.01 [95% CI 0.87 to 1.18]).

2.4 Discussion

2.4.1 Principal findings and main implications

Despite cautionary guidelines, glyburide still continues to be initiated in older adults in routine care.[8] Yet, long-acting modified-release gliclazide is more convenient for patients to take (once a day) than many glyburide dosing regimens. When prescribed as monotherapy or in the presence of metformin, modified-release gliclazide is a safer sulfonylurea than glyburide and is associated with less hypoglycemia. Although

modified-release gliclazide has a long duration of action, its hypoglycemia risk might be lower as it has no known active drug metabolites.[27,29]

At the population level, it is possible that many hospital encounters and even some deaths may be prevented by avoiding glyburide in favor of modified-release gliclazide. Prescription costs for glyburide and gliclazide patients were similar, and avoiding the former could also reduce associated health care costs of hypoglycemia management.

2.4.2 Results in relation to other studies

Patients studied in randomized controlled trials typically have more regimented treatment and monitoring than those studied in routine practice and may not include vulnerable patient groups. In this way the findings from our population-based study extend the results of randomized controlled trials, where the increase in risk was greater than previous trials. In a systematic review and meta-analysis of randomized controlled trials, glyburide was associated with a 44% greater risk (RR 1.44 [95% CI 1.13 to 1.85]) of hypoglycemic episodes compared with other sulphonylureas (including immediate release gliclazide, glimepiride, and chlorpropamide) across 2 studies (n=1365).[30] Where studies (n=1365) examined the risk of severe hypoglycemic events (ie. events requiring assistance or a hospital presentation), there was no significant difference between those prescribed glyburide vs other sulphonlyureas (RR 4.69 [95% CI 0.78 to 28.08]). In contrast, in our population-based study the relative risk of a hospital encounter with hypoglycemia was over 500% greater with glyburide compared with modified release gliclazide.

Our results also extend the findings of a prior population-based study examining rates of hypoglycemia in adult sulphonylurea users, published over 10 years ago. When glyburide was compared with immediate release gliclazide (recognizing modified-release gliclazide was the comparator in our study), glyburide users had a higher risk of hypoglycemia, as assessed from the medical records of general practitioners (adjusted RR 1.35 [95% CI 1.09 to 1.69]).[31]

In our metformin-glyburide combination study we also noted that glyburide vs gliclazide was associated with a higher risk of all-cause mortality. Sulfonylurea induced hypoglycemia has been reported to have a case-fatality rate of 4-10%.[32] However, the increased mortality in the metformin-glyburide group could have been the result of unmeasured or incompletely quantified confounding variables.[33]

2.4.3 Strengths and limitations

To our knowledge our studies are the first to quantify the risk of hypoglycemia after initiating glyburide compared with modified-release gliclazide in older adults in a real practice setting. Compared with an older population-based study of sulphonylurea users (noted above),[31] we accounted for a number of baseline comorbidities, medications, and measures of health care utilization including physician visits, investigations and laboratory testing. We also excluded those on concomitant hypoglycemic agents to help reduce confounding (apart from metformin in our combination study). Additionally, we matched patients based on the dose equivalence of their prescription. Where a previous study included self-reported hypoglycemia,[31] in our studies, hypoglycemia was documented in hospital records by the treating health care team.

To raise awareness, target education and quality assurance, we also illustrated trends in glyburide use, characterized hypoglycemia encounters, explored the costs of prescriptions, and examined the characteristics of recent glyburide prescribers. Our research protocols, cohorts and outcomes were also prespecified, and the results were consistent with our a priori hypotheses. Additional strengths of our 2 studies include our examination of hypoglycemic episodes leading to hospital presentation, a more extreme outcome in the spectrum of hypoglycemia. Such an outcome may help convince clinicians, pharmacists and policy makers about the importance of this safety concern.

Our studies do have some limitations. Prospective data collection with independent outcome adjudication is a preferred methodology to a retrospective database study. Also, we assessed the outcome of a hospital encounter with hypoglycemia with administrative codes which have limited sensitivity and accuracy compared to laboratory plasma glucose measurements (although the latter is not the best reference standard as treatment

with glucose has frequently been initiated in many hypoglycemic episodes by the time plasma glucose is measured). Although episodes of hypoglycemia may be underrepresented in our studies, we had no reason to believe they were assessed differently in those prescribed glyburide vs gliclazide. We were also only able to accurately ascertain medications dispensed with no information on medication use. Additionally we were unable to capture hypoglycemic episodes experienced outside of hospital. Further, our cost analysis was a simple calculation of the 90-day cost of all medications to the Ontario government and we did not carry out more detailed economic analyses.

Residual confounding is an additional consideration in all observational studies, and in the current studies we had no information on factors such as nutrition, glucose monitoring and patient education which may have influenced the association between sulphonylurea type and outcome. However, using a matching technique we did obtain good balance on a large number of measured baseline characteristics between the two groups. As well, the magnitude of the relative risk of hypoglycemia was large in both studies and our results proved robust in additional statistical analyses, making it unlikely that the association can be explained entirely by confounding factors.

2.4.4 Conclusions

Although glyburide is effective in lowering blood glucose in patients with diabetes, its use in older adults is associated with a much higher risk of hypoglycemia than modified-release gliclazide. The results of our studies may help convince physicians, pharmacists and patients who still use glyburide to consider modified-release gliclazide as a more convenient and safer alternative.

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Table 3: Key Baseline characteristics of the monotherapy study

	Unmatched			Matched		
	Glyburide n=13,550	**Gliclazide n=5254**	**Standardized Difference [a]**	**Glyburide n=4374**	**Gliclazide n=4374**	**Standardized Difference**
Demographics						
Age, Years*	74.52	76.10	23%	75.66	75.66	0%
Female*	6414 (47.34)	2596 (49.41)	4%	2138 (48.88)	2138 (48.88)	0%
Income based socioeconomic status [b]						
Quintile 1 (lowest)	3189 (23.54)	1085 (20.65)	7%	994 (22.73)	881 (20.14)	6%
Rural Location	1654 (12.21)	635 (12.09)	0%	484 (11.07)	542 (12.39)	4%
Year of cohort entry [c]						
2002	2432 (17.95)	6 (0.11)	65%	609 (13.92)	6 (0.14)	56%
2003	2640 (19.48)	18 (0.34)	68%	724 (16.55)	18 (0.41)	61%
2004	2115 (15.61)	16 (0.30)	59%	643 (14.70)	16 (0.37)	56%
2005	1754 (12.94)	23 (0.44)	52%	569 (13.01)	21 (0.48)	52%
2006	1507 (11.12)	24 (0.46)	47%	551 (12.60)	23 (0.53)	50%
2007	1061 (7.83)	996 (18.96)	33%	423 (9.67)	852 (19.48)	28%
2008	731 (5.39)	821 (15.63)	34%	309 (7.06)	696 (15.91)	28%
2009	574 (4.24)	1168 (22.23)	55%	251 (5.74)	968 (22.13)	49%
2010	419 (3.09)	1163 (22.14)	60%	163 (3.73)	935 (21.38)	55%
2011	317 (2.34)	1019(19.39)	57%	132 (3.02)	839 (19.18)	53%
Long term care	443 (3.27)	239 (4.55)	7%	165 (3.77)	197 (4.50)	4%
Charlson Comorbidity Index [d]						
0 or no hospitalizations	8967 (66.18)	3088 (58.77)	15%	2648 (60.54)	2665 (60.93)	1%
1	1585 (11.70)	743 (14.14)	7%	576 (13.17)	589 (13.47)	1%
2	1344 (9.92)	594 (11.31)	5%	501 (11.45)	481 (11.00)	1%
≥3	1654 (12.21)	829 (15.78)	10%	649 (14.84)	639 (14.61)	1%
Health care visits in the prior year						

Cardiologist visit *	4476 (33.03)	2181 (41.51)	18%	1724 (39.41)	1739 (39.76)	1%
Ophthalmologist visit	3614 (26.67)	1588 (30.22)	8%	1331 (30.43)	1275 (29.15)	3%
Endocrinologist visit*	767 (5.66)	465 (8.85)	12%	363 (8.30)	363 (8.30)	0%
Internist visit	2936 (21.67)	1414 (26.91)	12%	1101 (25.17)	1150 (26.29)	3%
Sulphonylurea prescriber						
General practitioner	10,393 (76.70)	4152 (79.03)	6%	3398 (77.69)	3474 (79.42)	4%
Internist	208 (1.54)	144 (2.74)	8%	78 (1.78)	119 (2.72)	8%
Endocrinologist	149 (1.10)	161 (3.06)	14%	66 (1.51)	118 (2.70)	8%
Other	836 (6.17)	259 (4.93)	5%	272 (6.22)	221 (5.05)	5%
Missing	1961 (14.47)	535 (10.18)	13%	560 (12.80)	439 (10.04)	9%
Comorbidities [e]						
Chronic kidney disease* [f]	1010 (7.45)	886 (16.86)	29%	601 (13.74)	601 (13.74)	0%
Congestive heart failure*	2055 (15.17)	969 (18.44)	9%	722 (16.51)	758 (17.33)	2%
Thyroid disease [g]	1118 (8.25)	514 (9.78)	5%	431 (9.85)	420 (9.60)	1%
Investigations [h]						
Carotid ultrasound	1638 (12.09)	804 (15.30)	9%	655 (14.97)	650 (14.86)	0%
Coronary angiogram	885 (6.53)	498 (9.48)	11%	371 (8.48)	403 (9.21)	3%
Coronary revascularization	537 (3.96)	262 (4.99)	5%	240 (5.49)	210 (4.80)	3%
Echocardiography*	4379 (32.32)	2334 (44.42)	25%	1853 (42.36)	1851 (42.32)	0%
Holter monitoring*	1744 (12.87)	1025 (19.51)	18%	772 (17.65)	805 (18.40)	2%
Stress test	3753 (27.70)	1845 (35.12)	16%	1506 (34.43)	1491 (34.09)	1%
At least one HbA1c test*	10208 (75.34)	4738 (90.18)	40%	3895 (89.05)	3876 (88.61)	1%
Diabetes management * [i]	629 (4.64)	1122 (21.36)	51%	485 (11.09)	582 (13.31)	7%
Diabetes incentive* [j]	413 (3.05)	1028 (19.57)	54%	336 (7.68)	455 (10.40)	9%
Medications [k]						
ACE inhibitors	4287 (31.64)	1813 (34.51)	6%	1551 (35.46)	1503 (34.36)	2%
ARBs*	1482 (10.94)	1281 (24.38)	36%	891 (20.37)	904 (20.67)	1%
Antidepressants*	1466 (10.82)	815 (15.51)	14%	612 (13.99)	629 (14.38)	1%
Beta blockers	3428 (25.30)	1733 (32.98)	17%	1341 (30.66)	1346 (30.77)	0%

Corticosteroids*	2575 (19.00)	1000 (19.03)	0%	794 (18.15)	823 (18.82)	2%
Ezetimibe*	131 (0.97)	280 (5.33)	25%	100 (2.29)	122 (2.79)	3%
Glucose test strips*	20 (0.15)	164 (3.12)	24%	16 (0.37)	20 (0.46)	1%
H2 Receptor Antagonists*	1083 (7.99)	219 (4.17)	16%	207 (4.73)	238 (5.44)	3%
Loop diuretics	1790 (13.21)	913 (17.38)	12%	686 (15.68)	688 (15.73)	0%
Potassium sparing	867 (6.40)	350 (6.66)	1%	299 (6.84)	279 (6.38)	2%
Statins*	4155 (30.66)	2730 (51.96)	44%	2044 (46.73)	2094 (47.87)	2%
Thiazide diuretics	2040 (15.06)	939 (17.87)	8%	747 (17.08)	742 (16.96)	0%
Thyroid replacement*	1291 (9.53)	763 (14.52)	15%	553 (12.64)	582 (13.31)	2%
Drug Dosage [l]						
1	8496 (62.70)	3905 (74.32)	25%	3246 (74.21)	3246 (74.21)	0%
2	3649 (26.93)	982 (18.69)	20%	899 (20.55)	899 (20.55)	0%
3	343 (2.53)	123 (2.34)	1%	96 (2.19)	96 (2.19)	0%
4	857 (6.32)	152 (2.89)	16%	133 (3.04)	133 (3.04)	0%
Laboratory Data [m]						
Evidence of creatinine	2505 (18.49)	1373 (26.13)	18%	896 (20.48)	1108 (25.33)	12%
Mean creatinine (umol/L) (SD)	93.25 (38.55)	103.89 (47.14)	25%	97.54 (40.74)	100.71 (46.81)	7%
Median creatinine (umol/L) (IQR)	83.71 (69.32-105.76)	93.29 (74.12-123.02)	---	85.81 (72.20-111.51)	90.42 (72.20-117.13)	---
Mean GFR (mL/min/1.73 m^2) (SD)	67.78 (19.82)	60.33 (21.72)	36%	64.75 (20.49)	62.29 (20.61)	12%
Median GFR (mL/min/1.73 m^2) (IQR)	70.83 (54.49-83.91)	60.47 (43.86-78.40)	---	67.27 (48.85-82.04)	63.21 (46.46-80.61)	---
Evidence of HbA1c value	1639 (12.10)	1096 (20.86)	24%	641 (14.65)	877 (20.05)	14%
Mean HbA1c (SD)	0.079 (0.019)	0.075 (0.015)	22%	0.077 (0.018)	0.075 (0.015)	15%
Median HbA1c (IQR)	0.074 (0.066-0.086)	0.072 (0.066-0.080)	---	0.073 (0.066-0.083)	0.072 (0.065-0.080)	---

Data presented as number (percent) except where indicated.
Cell sizes less than six were not reported for reasons of privacy.
Abbreviations: ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, HbA1c glycosylated hemoglobin, IQR interquartile range, GFR glomerular filtration rate, SD standard deviation.
Variables marked * were included as covariates in the propensity score model.

[a] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
[b] Income was categorized into fifths of average neighborhood income on the index date.
[c] The year of cohort entry is also referred to as the index date.
[d] Charlson Comorbidity Index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0. [34]
[e] Comorbidities were assessed by administrative database codes in the previous five years.
Less than 5% had evidence of a nephrologist visit in the one year prior or evidence of alcoholism, chronic liver disease, peripheral vascular disease, sepsis or pancreatitis in the five years prior. Less than 1% had evidence of pituitary disease, adrenal disease, pancreatic cancer or diabetic retinopathy in the five years prior.
[f] We identified individuals with chronic kidney disease using a validated algorithm of diagnosis and physician claim codes. In Ontario, this algorithm identifies patients with a median estimated glomerular filtration rate (eGFR) of 38 mL/min per 1.73 m^2 (interquartile range 27 to 52). Its absence identifies patients with a median eGFR of 69 mL/min per 1.73 m^2 (interquartile range 56 to 82). [35]
[g] Thyroid disease includes hypothyroidism, thyroiditis, iodine deficiency related thyroid disorders, nontoxic goiter, thyrotoxicosis, and other disorders of the thyroid.
[h] Investigations were assessed by administrative codes in the previous five years.
[i] Diabetes management is an all-inclusive service payable to the most responsible physician for providing continuing management and support of a diabetic patient. The service must include assessments focusing on diabetic target organ systems, relevant counseling and maintenance of a diabetic flow sheet retained on the patient's permanent medical record. The flow sheet must track lipids, cholesterol, HbA1C, urinalysis, blood pressure, fundal examination, peripheral vascular examination, weight, body mass index and medication dosage. [36]
[j] Diabetes management incentive is a fee rendered to a general practitioner providing ongoing management of a diabetic patient consistent with the requirements of the Canadian Diabetes Association including a minimum of lipid, HbA1C, blood pressure, body mass index measurement, albumin:creatinine, preventative measures and health promotion, referral for dilated eye exam, foot and neurological exam over the previous 12 months.[36]
[k] Baseline medication use was assessed in the previous 120 days.
Less than 5% received prescriptions for atypical antipsychotics, amiodarone, clarithromycin, fibrates, gatifloxacin or sulphonamides. Less than 1% received prescriptions for valproic acid, protease inhibitors, monoamine oxidase inhibitors, danazol, isoniazid, disopyramine, tacrolimus/sirolimus, probenicid, rifampin, aliskerin, androgens, barbiturates, carbamazepine, clonidine, cyclosporine, fluconazole/voriconazole, tetracycline. There were no prescriptions for acetohexamide, chloramphenicol, pegvisimont, colesevelam, reserpine, guanethidine, ifosfamide, phenylbutazone, diazoxide, aprepitant and bosentan.
[l] Drug dose level 1=glyburide 5mg/modified release gliclazide 30mg, 2=glyburide 10mg/ modified release gliclazide 60mg, 3=glyburide 15mg/ modified release gliclazide 90 mg, 4=glyburide 20mg/modified release gliclazide 120 mg.
[m] Where available, laboratory data was collected in the one year previous.

Table 4: Key baseline characteristics the metformin combination study

	Unmatched			Matched		
	Glyburide n=16,631	**Gliclazide n=9967**	**Standardized Difference [a]**	**Glyburide n=8038**	**Gliclazide n=8038**	**Standardized Difference [a]**
Demographics						
Age, years*	73.12	73.58	8%	73.34	73.33	0%
Female*	7952 (47.81)	4572 (45.87)	4%	3707 (46.12)	3707 (46.12)	0%
Income based socioeconomic status [b]						
Quintile 1 (lowest)	3931 (23.64)	2080 (20.87)	7%	1793 (22.31)	1715 (21.34)	2%
Rural location	2036 (12.24)	1247 (12.51)	1%	1031 (12.83)	997 (12.40)	1%
Year of cohort entry [c]						
2002	1191 (7.16)	<=5 (0.05)	39%	411 (5.11)	<=5 (<=0.06)	--
2003	1910 (11.48)	8 (0.08)	50%	743 (9.24)	7 (0.09)	44%
2004	2202 (13.24)	15 (0.15)	54%	930 (11.57)	14 (0.17)	50%
2005	2280 (13.71)	18 (0.18)	55%	1050 (13.06)	18 (0.22)	53%
2006	2585 (15.54)	34 (0.34)	59%	1306 (16.25)	29 (0.36)	60%
2007	2070 (12.45)	1013 (10.16)	7%	1137 (14.15)	873 (10.86)	10%
2008	1460 (8.78)	1386 (13.91)	16%	777 (9.67)	1161 (14.44)	15%
2009	1218 (7.32)	2163 (21.70)	42%	722 (8.98)	1754 (21.82)	36%
2010	1036 (6.23)	2904 (29.14)	63%	586 (7.29)	2275 (28.30)	57%
2011	679 (4.08)	2424 (24.32)	61%	376 (4.68)	1905 (23.70)	57%
Long term care	268 (1.61)	173 (1.74)	1%	120 (1.49)	144 (1.79)	2%
Charlson Comorbidity Index [d]						
0 or no hospitalizations	11,164	5857 (58.76)	17%	5146 (64.02)	4902 (60.99)	6%
1	2150 (12.93)	1682 (16.88)	11%	1137 (14.15)	1281 (15.94)	5%
2	1575 (9.47)	1063 (10.67)	4%	844 (10.50)	808 (10.05)	1%
≥3	1742 (10.47)	1365 (13.70)	10%	911 (11.33)	1047 (13.03)	5%
Health care visits in the year prior						
Cardiologist visit *	5397 (32.45)	3685 (36.97)	10%	2849 (35.44)	2900 (36.08)	1%

Ophthalmologist visit	4469 (26.87)	2956 (29.66)	6%	2392 (29.76)	2298 (28.59)	3%
Endocrinologist visit *	1072 (6.45)	884 (8.87)	9%	696 (8.66)	696 (8.66)	0%
Internist visit *	3440 (20.68)	2564 (25.72)	12%	1972 (24.53)	1992 (24.78)	1%
Sulphonylurea prescriber						
General practitioner	12,894	7862 (78.88)	3%	6248 (77.73)	6343 (78.91)	3%
Endocrinologist	353 (2.12)	398 (3.99)	11%	181 (2.25)	294 (3.66)	8%
Internist	296 (1.78)	296 (2.97)	8%	154 (1.92)	244 (3.04)	7%
Other	771 (4.64)	384 (3.85)	4%	344 (4.28)	318 (3.96)	2%
Missing	2347 (14.11)	1024 (10.28)	12%	1111 (13.82)	837 (10.41)	10%
Comorbidities [e]						
Chronic kidney [f]	723 (4.35)	640 (6.42)	9%	420 (5.23)	420 (5.23)	0%
Congestive heart	1805 (10.85)	1026 (10.29)	2%	813 (10.11)	810 (10.08)	0%
Thyroid disease [g]	1193 (7.17)	711 (7.13)	0%	610 (7.59)	557 (6.93)	3%
Investigations [h]						
Carotid ultrasound	1924 (11.57)	1433 (14.38)	8%	1072 (13.34)	1114 (13.86)	2%
Coronary angiogram	1247 (7.50)	935 (9.38)	7%	763 (9.49)	714 (8.88)	2%
Coronary revascularization	737 (4.43)	540 (5.42)	5%	458 (5.70)	400 (4.98)	3%
Echocardiography*	5368 (32.28)	4150 (41.64)	19%	3172 (39.46)	3182 (39.59)	0%
Holter monitoring*	2063 (12.40)	1611 (16.16)	11%	1214 (15.10)	1238 (15.40)	1%
Stress test	4943 (29.72)	3625 (36.37)	14%	2832 (35.23)	2805 (34.90)	1%
At least 1 HbA1c test *	14431	9317 (93.48)	23%	7474 (92.98)	7416 (92.62)	3%
Diabetes management [i]	2023 (12.16)	3275 (32.86)	51%	1698 (21.12)	1905 (23.70)	6%
Diabetes incentive* [j]	1382 (8.30)	2952 (29.60)	60%	1245 (15.49)	1496 (18.61)	8%
Medications [k]						
ACE inhibitors	6403 (38.50)	4085 (40.99)	5%	3464 (43.10)	3225 (40.12)	6%
ARBs*	2644 (15.90)	2641 (26.50)	26%	1854 (23.07)	1876 (23.34)	1%
Antidepressants*	1778 (10.69)	1289 (12.93)	7%	971 (12.08)	1002 (12.47)	1%
Beta blockers	4166 (25.05)	2951 (29.61)	10%	2405 (29.92)	2244 (27.92)	4%
Corticosteroids*	2583 (15.53)	1582 (15.87)	1%	1264 (15.73)	1272 (15.82)	0%

Clonidine	38 (0.23)	20 (0.20)	1%	22 (0.27)	14 (0.17)	2%
Ezetimibe*	243 (1.46)	563 (5.65)	23%	218 (2.71)	266 (3.31)	3%
Glucose test strips*	78 (0.47)	223 (2.24)	15%	74 (0.92)	99 (1.23)	3%
H2 receptor blockers*	992 (5.96)	357 (3.58)	11%	318 (3.96)	355 (4.42)	2%
Loop diuretics	1486 (8.94)	885 (8.88)	0%	745 (9.27)	677 (8.42)	3%
Potassium sparing diuretics	734 (4.41)	414 (4.15)	1%	362 (4.50)	318 (3.96)	3%
Statins*	7089 (42.63)	6112 (61.32)	38%	4635 (57.66)	4589 (57.09)	1%
Thiazide diuretics*	2865 (17.23)	1868 (18.74)	4%	1484 (18.46)	1473 (18.33)	0%
Thyroid replacement*	1597 (9.60)	1154 (11.58)	6%	866 (10.77)	866 (10.77)	0%
Drug Dosage [l]						
1	8430 (50.69)	7212 (72.36)	46%	5620 (69.92)	5620 (69.92)	0%
2	5707 (34.32)	2038 (20.45)	31%	1908 (23.74)	1908 (23.74)	0%
3	459 (2.76)	217 (2.18)	4%	169 (2.10)	169 (2.10)	0%
4	1895 (11.39)	377 (3.78)	29%	341 (4.24)	341 (4.24)	0%
Laboratory Data [m]						
Serum creatinine value available	3645 (21.92)	2688 (26.97)	12%	1954 (24.31)	2138 (26.60)	5%
Mean creatinine (umol/L) (SD)	84.83 (27.58)	87.22 (30.53)	8%	85.34 (27.31)	86.57 (29.74)	4%
Median creatinine (umol/L) (IQR)	79.87 (67.41-95.21)	81.79 (68.37-97.13)	---	79.87 (67.41-95.21)	80.83 (68.00-96.17)	---
Mean GFR (mL/min/1.73 m^2)	72.23 (17.73)	70.99 (18.48)	7%	71.87 (17.71)	71.53 (18.37)	2%
Median (mL/min/1.73 m^2) (IQR)	74.93 (60.41-86.96)	74.08 (59.13-86.19)	---	74.13 (59.85-86.78)	74.92 (59.91-86.43)	---
HbA1c value available	3333 (20.04)	2484 (24.92)	12%	1836 (22.84)	1960 (24.38)	4%
Mean HbA1c (SD)	0.083 (0.020)	0.080 (0.018)	14%	0.081 (0.018)	0.081 (0.019)	2%
Median HbA1c (IQR)	0.078 (0.070-0.092)	0.076 (0.070-0.085)		0.076 (0.069-0.087)	0.076 (0.070-0.087)	

Data presented as number (percent) except where indicated.
Cell sizes less than 6 were not reported for reasons of privacy.
Abbreviations: ACE angiotensin converting enzyme, ARB angiotensin receptor blocker, HbA1c glycosylated hemoglobin, IQR interquartile range, GFR glomerular filtration rate, SD standard deviation.
Variables marked * were included as covariates in the propensity score.

[a] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
[b] Income was categorized into fifths of average neighborhood income on the index date.
[c] The year of cohort entry is also referred to as the index date.
[d] Charlson Comorbidity Index was calculated using five years of hospitalization data. "No hospitalizations" received a score of 0. [34]
[e] Comorbidities were assessed by administrative database codes in the previous five years.
Less than 5% had evidence of a nephrologist visit in the one year prior or evidence of chronic liver disease, peripheral vascular disease or sepsis in the five years prior. Less than 1% had evidence of alcoholism, diabetic retinopathy, pituitary disease, adrenal disease, pancreatitis, pancreatectomy or pancreatic cancer in the five years prior.
[f] We identified individuals with chronic kidney disease using a validated algorithm of diagnosis and physician claim codes. In Ontario, this algorithm identifies patients with a median estimated glomerular filtration rate (eGFR) of 38 mL/min per 1.73 m^2 (interquartile range 27 to 52). Its absence identifies patients with a median eGFR of 69 mL/min per 1.73 m^2 (interquartile range 56 to 82). [35]
[g] Thyroid disease includes hypothyroidism, thyroiditis, iodine deficiency related thyroid disorders, nontoxic goiter, thyrotoxicosis, and other disorders of the thyroid.
[h] Investigations were assessed by administrative codes in the previous five years.
[i] Diabetes management is an all-inclusive service payable to the most responsible physician for providing continuing management and support of a diabetic patient. The service must include assessments focusing on diabetic target organ systems, relevant counseling and maintenance of a diabetic flow sheet retained on the patient's permanent medical record. The flow sheet must track lipids, cholesterol, HbA1C, urinalysis, blood pressure, fundal examination, peripheral vascular examination, weight, body mass index and medication dosage.[36]
[j] Diabetes management incentive is a fee rendered to a general practitioner providing ongoing management of a diabetic patient consistent with the requirements of the Canadian Diabetes Association including a minimum of lipid, HbA1C, blood pressure, body mass index measurement, albumin:creatinine, preventative measures and health promotion, referral for dilated eye exam, foot and neurological exam over the previous 12 months.[36]
[k] Baseline medication use was assessed in the previous 120 days.
Less than 5% received prescriptions for atypical antipsychotics, clarithyromycin, fibrates, gatifloxacin or sulphonamides. Less than 1% received prescriptions for tacrolimus/sirolimus chloramphenicol, cyclosporine, disopyramine, isoniazid, probenicid, rifampin, aprepitant, protease inhibitors, danazol, valproic acid, monoamine oxidase inhibitors, aliskerin, amiodarone, androgens, barbiturates, carbamazepine, clonidine, fluconazole/voriconazole or tetracycline. There were no prescriptions for acetohexamide, pegvisimont, colesevelam, reserpine, guanethidine, ifosfamide, phenylbutazone, diazoxide or bosentan.
[l] Drug dose level 1=glyburide 5mg/modified release gliclazide 30mg, 2=glyburide 10mg/ modified release gliclazide 60mg, 3=glyburide 15mg/ modified release gliclazide 90 mg, 4=glyburide 20mg/modified release gliclazide 120 mg.
[m] Where available, laboratory data was collected in the 1 year previous.

Table 5: Ninety-day outcomes in the monotherapy study

	Number of Events (%)		**Risk Difference (%) (95% CI)**	**NNH (95% CI)**	**Conditional OR (95% CI)**	**p-value**
	Glyburide n=4374	**Gliclazide n=4374**				
Hospital encounter with hypoglycemia	69 (1.58%)	8 (0.18%)	1.40% (1.01% to 1.79%)	71 (55 to 99)	8.63 (4.15 to 17.93)	<0.0001
All-cause mortality	100 (2.29%)	84 (1.92%)	0.37% (-0.21% to 0.95%)	(…)	1.21 (0.89 to 1.63)	0.22

Patients prescribed gliclazide served as the referent group.
Abbreviations: NNH Number needed to harm
(…) NNH not significant.

Table 6: Ninety-day outcomes in the metformin combination study

	Number of Events (%)		Risk Difference (%) (95% CI)	NNH (95% CI)	Conditional OR (95% CI)	p-value
	Glyburide n=8038	Gliclazide n=8038				
Hospital encounter with hypoglycemia	110 (1.37%)	19 (0.24%)	1.13% (0.86% to 1.40%)	77 (71 to 116)	6.06 (3.68 to 9.97)	<0.0001
All-cause mortality	109 (1.36%)	75 (0.93%)	0.43% (0.10% to 0.76%)	233 (131 to 1000)	1.47 (1.09 to 1.97)	0.012

Patients prescribed gliclazide served as the referent group
Abbreviations: NNH Number needed to harm

Chapter 3

3 Trends in antihyperglycemic medication prescriptions and hypoglycemia in older adults: 2002-2013

Kristin K Clemens, MD [1]; Salimah Shariff, PhD [2]; Kuan Liu, MMath [2]; Irene Hramiak, MD [3]; Jeffrey L Mahon, MD [3,4]; Eric McArthur, MSc [2] ; Amit X. Garg, MD PhD [1,2,4]

1. Department of Medicine, Western University, London Ontario Canada

2. Institute for Clinical Evaluative Sciences, London Ontario Canada

3. Department of Medicine, Division of Endocrinology, Western University, London Ontario Canada

4. Department of Epidemiology and Biostatistics, Western University, London Ontario Canada

3.1 Introduction

The management of glycemic control in older patients with type 2 diabetes has become increasingly complex over the last decade.[1] First, where only sulfonylureas (eg. glyburide), insulin, alpha glucosidase inhibitors (eg. acarbose), and biguanides (eg. metformin) were accessible in Canada in the 1990's, there are now 9 classes of medications and at least 20 unique drugs and their combinations available to control hyperglycemia. Second, while all drugs by design lower glucose levels, there are important differences among them with respect to their other known or suspected advantages and risks. Of particular importance in older patients are differences among the medications in risk for hypoglycemia.[2–4] Third, while randomized trials have established the benefit of intensified glycemic control in reducing risk for microvascular complications, it remains unclear as to whether this also leads to an important reduction in risk for macrovascular complications and, if so, whether such benefit exceeds the risks of tighter control in all cases.[5,6]

Given that there are limited data on how antihyperglycemic medications are being used in older patients with diabetes, in the current study we aimed to examine patterns in antihyperglycemic

medication prescriptions in this population from 2002 until 2013. As the hypoglycemia risk of these medications differ, we also examined their hospital encounters for hypoglycemia over the period of study.

3.2 Methods

3.2.1 Study design and setting

We conducted population-based cross sectional analyses of older adults with diabetes from April 1, 2002 until March 31, 2013, using linked health care databases in Ontario Canada. Ontario currently has a population of over 13 million people, of which 2 million are age 65 years or older.[7] In our province, people over the age of 65 have universal coverage for outpatient prescription medications, physician services, hospitalizations and investigations.[8]

Databases were linked using unique, encoded identifiers and were analyzed at the Institute for Clinical Evaluative Sciences according to a pre-specified protocol. The study was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). Participant informed consent was not required.

We divided our study timeframe into 3-month intervals (study quarters). We report this study using guidelines for observational studies (checklist of recommendations presented in Appendix D Table 1).[9]

3.2.2 Data sources

We used 6 databases to examine patient characteristics, drug use, covariate information, and outcomes. To identify patients with diabetes, we used the Ontario Diabetes Database (ODD), a previously validated electronic registry with 86% sensitivity and 97% specificity to detect diabetes.[10] The Registered Persons Database of Ontario was used to collect vital statistics. It contains demographic information for all Ontario residents who have ever been issued a health card. We used the Ontario Drug Benefit Program database to examine prescription medications as in our province, adults age 65 and older are eligible for drug coverage, and the information on these prescribed medications is accurately contained within this database (error rate of less than 1%).[11] Diagnostic and procedural information on hospitalizations and emergency room visits was obtained from the Canadian Institute for Health Information's Discharge Abstract Database and

the National Ambulatory Care Reporting System database. We obtained additional covariate information from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. A subpopulation had outpatient glycosylated hemoglobin (HbA1c) values available in the 1 year prior to the relevant study quarter.

International Classification of Diseases 9th revision (ICD-9, pre-2002), 10th Revision (ICD-10, post-2002), Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures (CCP, pre-2002) and Canadian Classification of Health Interventions (CCI, post-2002) codes were used to assess baseline comorbidities in the 5 years prior to 3 study quarters (administrative codes listed in Appendix D Table 2). Codes utilized to ascertain hypoglycemia encounters are detailed in Appendix D Table 3, which lists only ICD-10 codes as all events would have occurred after the implementation of this coding system in Canada.

3.2.3 Patients

During each quarter, we identified all adults with diabetes as defined by the ODD. We then excluded the following patients from analysis: 1) those with a missing age or sex, invalid age (over 105 years) or death recorded on or before the beginning of the quarter (for data cleaning purposes), 2) non-Ontarian residents at the beginning of each quarter (to allow for adequate patient follow-up), and 3) those under the age of 66 (as the province's drug formulary provides prescription coverage to those over the age of 65 and to avoid incomplete medication records in their first year of eligibility).

We defined patients with treated diabetes as those who had evidence of at least 1 antihyperglycemic prescription (including insulin or an oral antihyperglycemic medication) during the study quarter, insulin users as those with evidence of at least 1 prescription for insulin during the study quarter, and patients with newly treated diabetes as those who had evidence of at least 1 antihyperglycemic medication prescription during the quarter with no evidence of a previous prescription for any agent in the 1 year prior. Monotherapy users had evidence of only 1 antihyperglycemic medication prescription during the relevant quarter and combination users had evidence of more than 1 prescription.

3.2.4 Outcomes

For the primary outcome, we examined the percentage of treated and newly treated patients with a prescription for insulin, sulphonylureas, alpha-glucosidase inhibitors, metformin, thiazolidinediones, meglitinides, and dipeptidyl peptidase-4 inhibitors (DPP-4). These antihyperglycemic medications are the only agents currently covered by our provincial drug formulary. For our secondary outcome we examined the percentage of treated patients with a hospital encounter with hypoglycemia (emergency room visit or inpatient admission) during each quarter of study.

3.2.5 Statistical analysis

We used descriptive statistics to summarize the baseline characteristics of patients with treated and newly treated diabetes at the beginning of three study quarters (April 1 2002, April 1, 2007, April 1, 2012). The percentage of patients prescribed each antihyperglycemic medication during the relevant quarter was calculated by dividing the total number with a prescription (numerator) by the total number of treated patients (or newly treated patients) (denominator) during the quarter. The percentage of patients with a hypoglycemia encounter during each quarter was determined by dividing the total number of patients with at least 1 encounter (numerator) by the total number of treated patients (denominator). We conducted all analyses with SAS version 9.3 (SAS Institute, Cary, North Carolina).

3.3 Results

Over the decade from April 2002 until March 2013, the number of patients with treated diabetes almost doubled from 148,021 to 289,312 individuals (Figure 1). The baseline characteristics of treated and newly treated patients are presented in Table 7 and Appendix D Table 4 respectively. In both groups, their mean age remained stable over the study quarters as did the proportion that were female. With the exception of chronic kidney disease, the percentage with a diabetes-related comorbidity appeared to decline. Where available for a sub-population of included patients, HbA1c values appeared to increase slightly (Table 7 and Appendix D Table 4).

3.3.1 Patients with treated diabetes

Figure 2 shows the percentage of patients with treated diabetes with a prescription for insulin, sulphonylureas, alpha-glucosidase inhibitors, metformin, meglitinides, thiazolidinediones and DPP-4 inhibitors from 2002 until 2013.

The percentage prescribed metformin increased over the study period (56.17% in first quarter, 76.51% in last quarter), as did prescriptions for the DPP-4 inhibitors saxagliptin (prescriptions increased from 0% to 1.79% following its formulary introduction in 2012) and sitagliptin (prescriptions increased from 0% to 18.09% following its formulary introduction in 2010). A decline in glyburide prescriptions was evident (56.43% in the first quarter, 10.65% in the last quarter), while gliclazide prescriptions increased (prescriptions increased from 0.40% to 24.30% following the formulary introduction of modified-release gliclazide in 2007). Over the last 10 years about 20% of treated patients have been prescribed insulin. Further, after an initial increase following their introduction to the provincial formulary in 2006/2007, thiazolidinedione prescriptions declined, although pioglitazone did so less steeply than rosiglitazone. Prescriptions for acarbose, acetohexamide, glimepiride, repaglinide, tolbutamide, nateglinide, and chlorpropamide have remained low (less than 5% of patients had evidence of a prescription during each study quarter).

Antihyperglycemic mono and combination therapy is illustrated in Appendix D Figure 1 and 2. Over the last decade, there was a small decrease in the percentage of patients prescribed monotherapy (including insulin monotherapy), and a small increase in those prescribed three or more agents (including in insulin users). The oral antihyperglycemic medications prescribed in insulin users are illustrated in Appendix D Figure 3.

3.3.2 Patients with newly treated diabetes

New antihyperglycemic medication prescriptions are illustrated in Appendix D Figure 4. The majority of patients were prescribed metformin (approximately 80%), with a small percentage decrease noted from July 2006 until April 2008. The percentage of patients prescribed the DPP-4 inhibitors increased (prescriptions for sitagliptin increased from 0% to 10.10% following its introduction to the formulary; saxagliptin prescriptions increased from 0% to 2.08% following its introduction to the formulary). We also note that fewer of these patients were initiated on

glyburide over time, (38.99% in the first quarter and 2.90% in the last quarter) with an increasing number initiated on gliclazide (prescriptions increased from 0.26% to 11.69% following the introduction of modified-release gliclazide to the formulary). Insulin use remained relatively stable (approximately 7%). Further, although thiazolidinedione prescriptions initially rose in 2006/2007, they have since decreased. Prescriptions for acarbose, acetohexamide, glimepiride, repaglinide, tolbutamide, nateglinide, and chlorpropamide remained low (less than 5% of patients had evidence of a prescription during each study quarter).

Where mono- and combination therapy was examined in newly treated patients, there was a slight decrease in monotherapy (including insulin monotherapy) and an increase in combination therapy over time (including insulin combination therapy) (Appendix D Figure 5 and 6).

3.3.3 Hypoglycemia

In the setting of these prescription trends, the absolute number of treated patients with a hypoglycemia encounter increased until mid-2006 and then declined. However, when the increasing prevalence of treated diabetes was accounted for, the percentage with a hospital encounter with hypoglycemia declined by 50% over the decade (0.79% with an event in the first quarter, 0.41% with an event in the last quarter). (Figure 3)

3.4 Discussion

3.4.1 Principal findings and main implications

In this study we have identified several trends in antihyperglycemic medication prescriptions in patients with diabetes age 66 and older in Ontario.

First, over the last decade there has been a substantial increase in the number of older adults using antihyperglycemic medications in our province. Whether this increase is due to an increased detection of diabetes, an aging population, or a higher number of individuals with obesity and sedentary lifestyle remains to be determined.

Second, consistent with guidelines which recommend metformin as a first line agent for its efficacy, safety, weight effects, and possible cardiovascular benefit,[12,13] metformin remains the

most commonly prescribed antihyperglycemic medication among older adults in Ontario. This result is consistent with high rates of metformin use in other jurisdictions.[14–18]

Third, we found that prescriptions for glyburide steadily declined over the last decade whereas those for gliclazide have increased. This change is consistent with clinical practice guidelines which have endorsed avoiding glyburide in older patients in favour of sulphonylureas including gliclazide that have a lower risk for hypoglycemia. [19]

Fourth, since their addition to the drug formulary, prescriptions for both pioglitazone and rosiglitazone have declined. These findings may reflect safety concerns that have arisen with these medications,[20–23] regulatory advisories (Appendix D Table 5), and funding status changes in our province (thiazolidinediones transferred from the unrestricted formulary to the exceptional access program in in June 2009). [24,25] Pioglitazone currently remains more commonly prescribed than rosiglitazone perhaps reflecting evidence of its better safety profile compared with its counterpart.[26–28] Consistent with the findings of research in other regions, we also note that there has been an uptake of new medications including the DPP-4 inhibitors.[14,17,18]

Fifth, we found that that combination therapy has increased over time, including in newly treated patients. It is possible that clinical trials that have suggested the benefit of intensive glycemic control in the prevention of microvascular complications have been contributory,[5,6] along with the possibility of personalizing therapy with several drugs in order to achieve better control.[16] Further, published reports have noted that combination therapy at submaximal doses may help to improve glycemic control more rapidly and with fewer side effects than monotherapy,[13,29–31] and practice guidelines suggest that combination therapy be initiated in patients with higher HbA1c's.[13]

Finally, in the setting of these prescription trends, the overall percentage of treated patients with a hospital encounter for hypoglycemia has declined in our region. Our findings are consistent with a recent study of United States Medicare beneficiaries (1999 to 2011). When the changing prevalence of diabetes was accounted for by the authors, admissions for hypoglycemia decreased by 9.5%.[32] Although a decline in the use of glyburide and the uptake of agents associated with a lower hypoglycemic risk may have contributed to this trend, other factors including changes in the accuracy of diagnostic coding, diabetes screening, quality of patient care and education, [33]

secular trends in glycemic control, and the characteristics of patients with the disease (comorbidities, functional limitations, self-management behavior), may have also played a role.[32,34]

3.4.2 Strengths and limitations

Compared with previous drug trend studies, our report has several strengths.[18,24,25,27] First, we comprehensively examined all 15 antihyperglycemic medications currently covered by the provincial drug formulary and ascertained prescription trends in a variety of antihyperglycemic medication users (including those with treated and newly treated diabetes). Our decade of study also allowed for an assessment of medication trends during an era of changing diabetes care. Where previous studies have been limited to younger patients with diabetes, ours provided a perspective on prescribing practices in a more vulnerable population of older adults. We also detailed the demographic characteristics, comorbidities, and HbA1c values of included patients to help put prescribing practices into context. Finally, in the setting of changing prescription trends, we quantified both inpatient and emergency room hospital encounters with hypoglycemia – a serious adverse event in older patients.

Our study has limitations. We were unable to capture antihyperglycemic medication prescriptions not covered by our provincial formulary (including glucagon like peptide-1 agonists and sodium glucose co-transporter 2 inhibitors). Although we expect our results to be generalizable to the elderly with publically funded healthcare, we cannot extend our results to those under the age of 65 or on other drug funding schemes where variations in drug prescribing have been noted.

Our databases also did not allow us to evaluate diabetes type, although given their age and the prevalence of type 2 diabetes, the majority of patients may have had type 2 diabetes. Further, we could not capture their duration of diabetes which can influence treatment choices and diabetes-related complications.[34]

For our outcome of hypoglycemia, we were unable to assess events experienced outside of the hospital, including emergency medical service contacts or home events that did not lead to hospital presentation. Additionally, we assessed the outcome of hypoglycemia with

administrative codes which have limited sensitivity when compared to laboratory plasma glucose measurements (although the latter is not the best reference standard as treatment with glucose may have been initiated by the time plasma glucose is measured). Further, although we do note a decline in the use of glyburide and the uptake of safer medications, these data do not prove that prescription changes led to a decline in the rates of hypoglycemia. Although we did measure comorbidities and demographic characteristics that are associated with hypoglycemia, we were also unable to account for changes in health literacy, attitudes, and social support which could cause differences in the likelihood of seeking medical care.[33]

3.4.3 Conclusions

Antihyperglycemic medication prescribing practices have changed significantly in Ontario over the last 11 years. In the setting of a decline in the use of glyburide, and the uptake of drugs with a lower hypoglycemia risk, there has been a decrease in the percentage of treated patients with a hospital encounter for hypoglycemia in our region. The extent to which this reduction is related to the use of safer medication or to other factors remains to be established.

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The opinions, results, and conclusions are those of the authors, and no endorsement by ICES, AMOSO, SSMD, LHRI or the MOHLTC is intended or should be inferred.

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Table 7. Baseline characteristics of patients with treated diabetes

	April 1, 2002		April 1, 2007		April 1, 2012	
	N= 148,021	%	N=212,538	%	N=288,866	%
Age (yr)						
Mean (SD)	74.74 (6.28)		75.13 (6.48)		75.40 (6.80)	
Median (IQR)	74 (70-79)		74(70-80)		74 (70-80)	
66-69	35,472	23.96%	49,710	23.39%	69,073	23.91%
70-74	44,063	29.77%	59,111	27.81%	76,954	26.64%
75-79	35,821	24.20%	50,384	23.71%	63,877	22.11%
80-84	20,465	13.83%	33,387	15.71%	45,993	15.92%
85-89	9105	6.15%	14,839	6.98%	24,064	8.33%
90+	3095	2.09%	5107	2.40%	8905	3.08%
Sex - Female	76,456	51.65%	107,187	50.43%	140,884	48.77%
Income quintile						
Missing	465	0.31%	809	0.38%	1188	0.41%
1 (lowest)	35,308	23.85%	49,607	23.34%	62,975	21.80%
2	34,709	23.45%	47,862	22.52%	63,610	22.02%
3	29,639	20.02%	41,770	19.65%	57,919	20.05%
4	25,418	17.17%	38,819	18.26%	55,395	19.18%
5 (highest)	22,482	15.19%	33,671	15.84%	47,779	16.54%
Rural						
Missing	72	0.05%	72	0.03%	122	0.04%
No	125,609	84.86%	183,482	86.33%	250,090	86.58%
Yes	22,340	15.09%	28,984	13.64%	38,654	13.38%

	April 1, 2002		April 1, 2007		April 1, 2012	
	N= 148,021	%	N=212,538	%	N=288,866	%
Comorbidities[a]						
Chronic kidney disease	15,277	10.32%	24,665	11.60%	41,473	14.36%
Chronic liver disease	5650	3.82%	7963	3.75%	10,577	3.66%
Any cancer	37,955	25.64%	55,425	26.08%	79,749	27.61%
Coronary heart disease (excluding angina)	55,221	37.31%	73,074	34.38%	86,904	30.08%
Congestive heart failure	30,419	20.55%	36,450	17.15%	43,059	14.91%
Peripheral vascular disease	6000	4.05%	5666	2.67%	4706	1.63%
Dementia	14,096	9.52%	23,644	11.12%	35,577	12.32%
Stroke/TIA	8182	5.53%	8478	3.99%	9329	3.23%
Neuropathy	1640	1.11%	2683	1.26%	4085	1.41%
Retinopathy	5172	3.49%	4964	2.34%	4563	1.58%
Investigations[b]						
Mean (SD) number cholesterol tests	1.06 (1.26)	---	1.31 (1.26)	---	1.40 (1.19)	---
Median (IQR) cholesterol tests	1 (0-2)	---	1 (0-2)	---	1 (1-2)	---
Mean (SD) HbA1c tests	1.88 (1.9)	---	2.04 (1.73)	---	2.21 (1.56)	---

	April 1, 2002		April 1, 2007		April 1, 2012	
	N= 148,021	%	N=212,538	%	N=288,866	%
Median (IQR) HbA1c tests	2 (0-3)	---	2 (1-3)	---	2 (1-3)	---
Mean (SD) creatinine tests	1.93 (2.32)	---	2.23 (2.33)	---	2.41 (2.25)	---
Median (IQR) creatinine tests	1 (0-3)	---	2 (1-3)	---	2 (1-3)	---
Mean (SD) glucose tests	2.68 (3.25)	---	2.34 (2.46)	---	2.18 (1.95)	---
Median (IQR) glucose tests	2 (1-4)	---	2 (1-3)	---	2 (1-3)	---
At least 1 eye exam	61,157	41.32%	81,240	38.22%	97,025	33.59%
Laboratory Data[c]						
At least 1 HbA1c outpatient lab value	---	---	53,239	25.05%	75,311	26.07%
Mean (SD) HbA1c (%)	---	---	7.0% (1.2%)	---	7.2% (1.2%)	---
Mean (SD) HbA1c (mmol/mol)			53 (13.1)		55 (13.1)	
Median (IQR) HbA1c	---	---	6.8% (6.2%-7.5%)	---	7.0% (6.5%-7.7%)	---
Mean (SD) HbA1c (mmol/mol)			51 (44-58)		53 (48-61)	

Abbreviations: TIA transient ischemic attack, SD standard deviation, IQR interquartile range, HbA1c hemoglobin A1c

[a]Comorbidities were examined in the 5 years prior.

[b]Investigations were examined in the 1 year prior.

[c]Lab values were available in the 1 year prior.

Figure 1. The number of patients with treated diabetes has nearly doubled over the last decade (2002-2013)

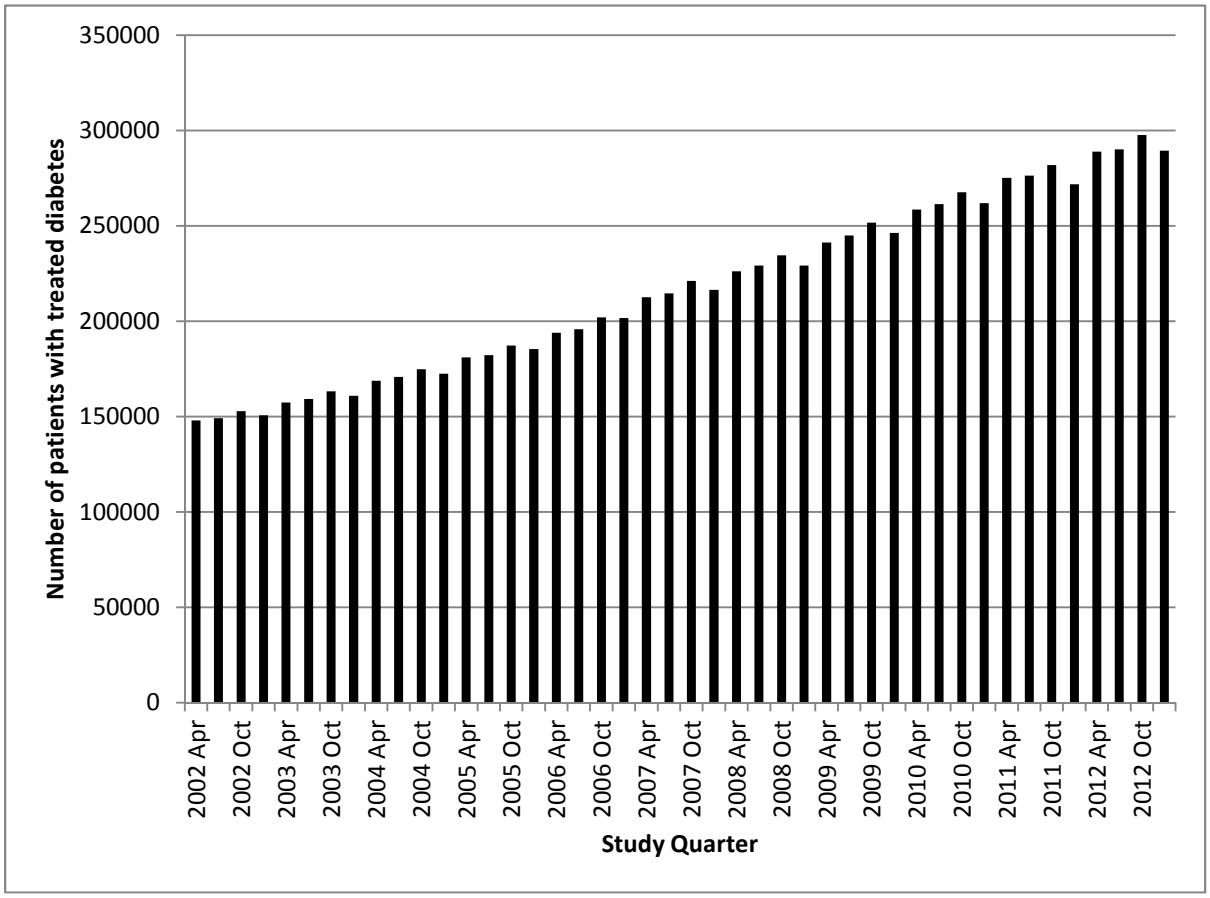
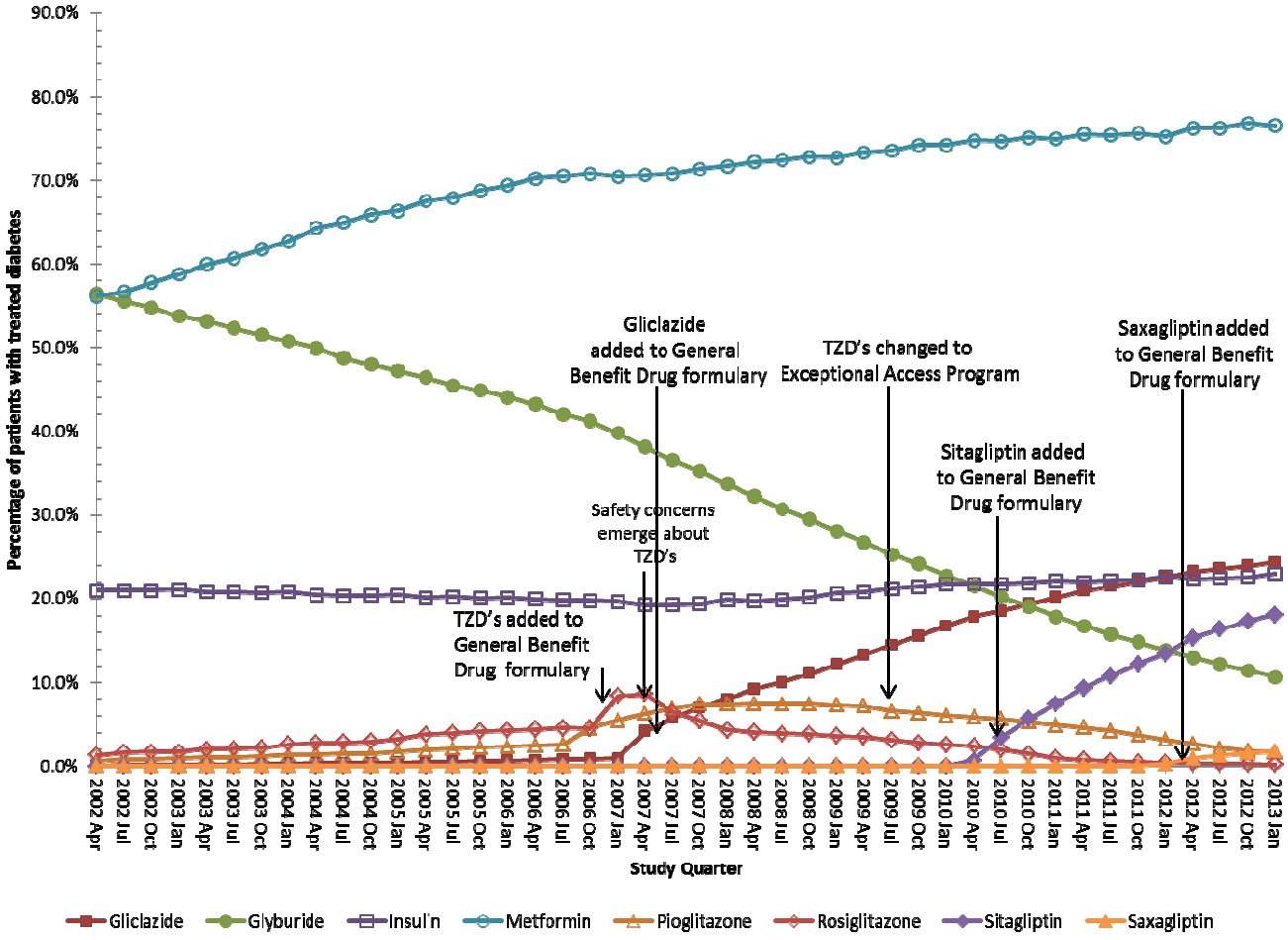


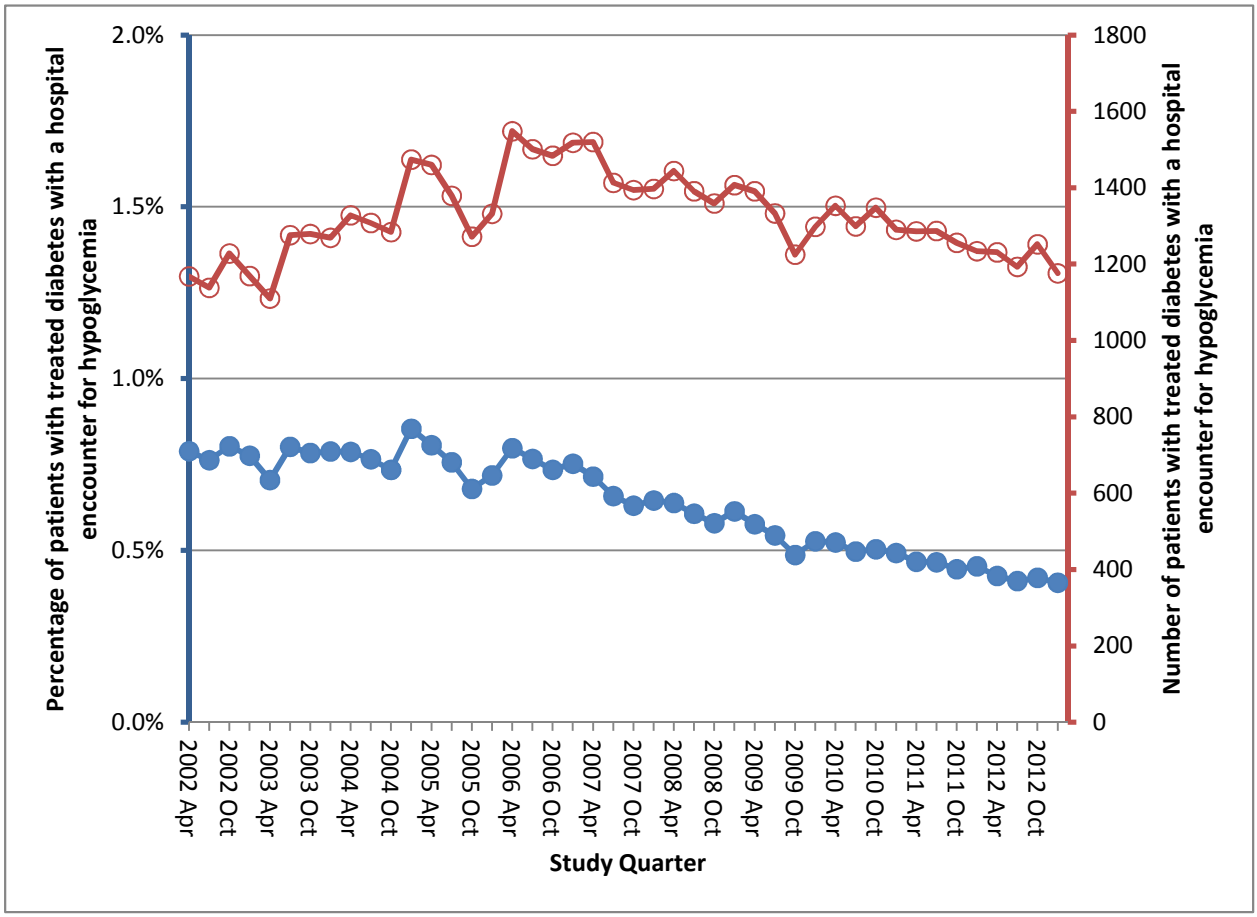
Figure 2. Antihyperglycemic medication prescriptions 2002-2013



*Drugs prescribed to less than 5% not illustrated (acarbose, acetohexamide, chlorpropamide, glimepiride, nateglinide, repaglinide, tolbutamide)

Abbreviations: TZD thiazolidinediones

Figure 3. Hospital encounters for hypoglycemia in treated patients 2002-2013



Chapter 4

4 Discussion

4.1 Main findings

In the current work we investigated antihyperglycemic medication prescribing and safety in older adults with diabetes.

We first note that even within the same drug class (sulphonylureas), the hypoglycemia risk of antihyperglycemic medications differ significantly in routine care. In 2 matched retrospective cohort studies of older adults newly prescribed glyburide or modified-release gliclazide as monotherapy or in the presence of metformin, we found that the hypoglycemia risk of glyburide was over 500% greater than modified-release gliclazide.

Given the increasing availability of antihyperglycemic medications with different safety profiles, we then carried out an ecological study to examine patterns in antihyperglycemic medication prescriptions in older adults from 2002 until 2013. Here we note that there has been increasing uptake of safer medications (including gliclazide) in our region. In this setting, there has been a decline in the overall percentage of treated patients with an encounter for hypoglycemia. Although the decline in hypoglycemia observed in recent years may relate to the use of medications with a lower hypoglycemia risk, additional factors may have also contributed including changing quality of care, the accuracy of administrative codes, or the characteristics of patients with the diabetes (ie. their duration of disease, comorbidities etc.).

4.2 General strengths and limitations

There are several strengths to our current work. First, as our studies were observational in design, we were able to examine a population of older adults with comorbidities who are frequently excluded from randomized controlled trials. This makes our work generalizable to a larger population.[1,2] Where clinical trials are often limited in their sample size, we were also able to efficiently study a large sample of these individuals (up to 289,312 in the last quarter of our antihyperglycemic medication trends investigation).[1]

Second we were able to draw upon the rich data contained within Ontario's health administrative databases. Ontario's health administrative databases are a unique combination of the province's large population and Canada's universal health care coverage. The data is recognized for its comprehensiveness (includes all Ontario residents, vital statistics, physician claims, hospitalizations and medical procedures), retention (loss to follow-up from emigration is <0.5%/year), and accuracy (validity of key elements such outpatient drug claims prescribed to older people).

There are some weaknesses of our work that warrant attention. First, for our glyburide vs gliclazide drug study, prospective data collection with independent outcome adjudication would have been a preferred methodology to a retrospective database study. Our trends study was additionally a general descriptive study and we collected data on groups and not for each individual within the population. We thus could not determine whether the individuals in whom hypoglycemia developed were on the agents associated with a higher hypoglycemia risk. As a result, we could not establish a causal association between drug use and hypoglycemia.[3]

Second, the potential biases in our studies warrant attention. In our glyburide vs gliclazide study, our non-random exposure allocation may have led to "indication bias", a bias frequently encountered in pharmacoepidemiologic studies. We did however did try to minimize this bias by using propensity score matching to help ensure that the distribution of measured baseline characteristics were similar between treated and untreated patients. [2,4]

Third, as in all observation studies, residual confounding is an additional consideration. This occurs where adjustment does not completely remove the confounding effect due to a given variable or a set of variables.[5] In our glyburide vs gliclazide study we had no information on unmeasured factors such as nutrition, glucose monitoring, patient education, health literacy, attitudes, and social support which may have influenced the association between sulphonylurea type and outcome. However, using a matching technique we did obtain good balance on a large number of measured baseline characteristics between the two groups. As well, the magnitude of the relative risk of hypoglycemia in these studies were large making it unlikely the association can be entirely explained by confounding factors.

Fourth, although we used rich administrative databases to obtain our data, the variables captured within these databases may not be complete. For example, we were unable to assess medical conditions that did not result in hospital presentation or physician billing including hypoglycemia encounters that were self-treated in the home or by emergency medical service personnel. We were also unable to identify comorbidities, outcomes, and procedures that are not associated with a specific ICD or billing codes, and were only able to examine procedures covered by the universal health care system.[1] The possibility of information bias thus arises, although we anticipate that this bias led to non-differential misclassification (ie. that not related to exposure status but due to a problem inherent in the data sources).[2]

Fifth, although we could accurately ascertain medications dispensed, we had no information on medication use. We further could not assess over the counter medications or medications covered by private drug-funding schemes.

Finally, we assessed the outcome of a hospital encounter with hypoglycemia with administrative codes which have limited sensitivity and accuracy compared to laboratory plasma glucose measurements (although the latter is not the best reference standard as treatment with glucose has frequently been initiated in many hypoglycemic episodes by the time plasma glucose is measured).

4.3 Conclusions

Antihyperglycemic medications are central to the management of patients with diabetes. These medications however have very different side effects including risks for hypoglycemia.

In Ontario, there has been an uptake of newer and safer medications in older adults including gliclazide. In this setting, over the past decade there has been a decrease in the percentage of treated patients with a hospital encounter with hypoglycemia. The extent to which this finding relates to the use of safer prescription medications or to other factors remains to be determined.

4.4 Future research

A closer examination of drug prescribing and safety in older adults with medical comorbidities is needed. This is especially important for those with chronic kidney disease (CKD).

CKD is a common comorbidity in people with diabetes.[6] Patients with CKD are often on multiple medications, have concomitant comorbidities, and have differences in drug metabolism and clearance. In this population, hypoglycemia is also a major concern due to diminished renal gluconeogenesis, and impaired clearance of antihyperglycemic medications.[6,7]

Given their vulnerabilities, patients with CKD and diabetes need to be treated cautiously.[8] Unfortunately, there have been few clinical studies that have been published to assess or guide the management of this patient population. Our future research efforts then will focus on antihyperglycemic medication prescribing, safety and efficacy in patients with impaired renal function.

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Appendix A

Definitions of Key Terminology

Angiotensin converting enzyme inhibitor – a medication that helps to relax blood vessels and decrease blood pressure.

Angiotensin receptor blockers – a medication that helps to relax blood vessels and decrease blood pressure.

Antihyperglycemic medications – medications that work to lower blood sugar.

Antiplatelet therapy – medications that help to prevent the formation of blood clots.

Autoimmune disease – disease where one's immune system inappropriately attacks healthy body cells/tissues.

Autonomic nerves – nerves that help to control involuntary actions such as digestion, heart rate, and vessel tone.

Bariatric surgery – weight-reduction surgery.

Chronic kidney disease – chronic loss of kidney function.

Cognitive function – involves one's memory, language, thinking and judgment.

Combination therapy – the use of 2 or more medications.

Counter-regulatory response – body's stress response to hypoglycemia, mediated by the release of hormones and neurotransmitters.

Debridement – the removal of dead or damaged body tissue.

Diabetic ketoacidosis – diabetes emergency that leads to hyperglycemia and the accumulation of ketones (breakdown product of fat).

Diagnostic – concerned with the identification of an illness/process.

Dopamine antagonists – drugs which block the body's dopamine receptors.

Drug formulary – a collection of drugs funded by the province's drug benefit program.

Exceptional access program – program which facilitates the funding of medications that are not covered by the province's drug benefit program.

Exudate – fluid which escapes from the body's blood vessels.

Gangrene – condition which occurs when body tissue dies.

Gastroparesis – impaired motility of the stomach.

Glycemic control – control of blood sugar.

Glycosylated hemoglobin (HbA1c)– laboratory measure which reflects blood sugar control over the previous 8-12 weeks.

Health literacy - the ability to access, comprehend, evaluate and communicate health information.

Hyperglycemia – high blood sugar.

Hyperglycemic hyperosmolar state – diabetes emergency that leads to extremely high blood sugar and dehydration, without the accumulation of ketones.

Hypoglycemia – low blood sugar.

Hypoglycemia unawareness – occurs when one has greater tolerance to low blood sugar and does not feel its associated symptoms.

Insulin – hormone responsible for the storage and utilization of glucose in the body.

Insulin deficiency – lack of insulin.

Insulin resistance – poor utilization of insulin.

Intensive glycemic control – blood sugar control that targets a glycosylated hemoglobin less than 7%.

Ischemia – lack of oxygen to a tissue.

Lipid disorder – abnormality of cholesterol and triglycerides.

Lipid lowering medications – medications that work to lower cholesterol and triglycerides.

Macrovascular disease – disease of the large blood vessels of the body (ie. heart, brain, periphery).

Macular edema – occurs when fluid leaks from the blood vessels in the eyes.

Metabolic condition – disease caused by a disruption in the chemical reactions in the body.

Microvascular disease – disease of the small blood vessels of the body (ie. eyes, kidney, nerves).

Microaneurysms – small aneurysm or swelling of the blood vessels in the eye.

Monotherapy – the use of 1 medication.

Motor nerves – nerves that act on the muscles.

Nephropathy – damage to the kidneys.

Neuropathy – damage to the nerves of the body.

Number needed to harm - estimate of how many people need to receive a treatment before one more person would experience a harmful outcome.

Odds ratio – the ratio of odds of the development of disease in exposed people to the odds of the development of disease in unexposed people.

Oral glucose tolerance test – a test which measures how well the body breaks down sugar.

Pancreatic beta cell – cell of the pancreas that is responsible for the production of insulin.

Photocoagulation- a surgical procedure which involves the clotting of eye tissue with a laser.

Procedural – refers to a task or operation.

Relative risk – describes disease risk in exposed people relative to the disease risk in unexposed people.

Retinopathy – disease of the eyes.

Retinal detachment – occurs when the retina (eye tissue) separates from the back of the eye.

Risk difference – difference in observed risks between groups.

Sensory nerves – nerves that transmit sensation information.

Structural complications – refer to the microvascular and macrovascular complications of diabetes.

Urinary incontinence- the loss of bladder control.

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Appendix B

Supplementary Materials for "The Hypoglycemic Risk of Glyburide Compared with Modified-Release Gliclazide"

Table 1: Checklist of recommendations for reporting of observational studies using the STROBE guidelines

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Methods
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Appendix B Table 2 and 3
Bias	9	Describe any efforts to address potential sources of bias	Discussion
Study size	10	Explain how the study size was arrived at	Methods, based on availability of the data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	Not Applicable

		(d) If applicable, explain how loss to follow-up was addressed	Not Applicable
		(e) Describe any sensitivity analyses	Methods
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Results, Appendix B Figure 1 and 2
		(b) Give reasons for non-participation at each stage	Appendix B Figure 1 and 2
		(c) Consider use of a flow diagram	Appendix B Figure 1 and 2
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results, Table 3 and 4
		(b) Indicate number of participants with missing data for each variable of interest	Results
		(c) Summarize follow-up time (e.g. average and total amount)	Results
Outcome data	15	Report numbers of outcome events or summary measures over time	Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results, Table 5 and 6
		(b) Report category boundaries when continuous variables were categorized	Table 3 and 4
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, Table 5 and 6
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion

Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Cover page, Disclosures

Table 2: Coding definitions for demographic and comorbid conditions

Characteristics/Condition	Database	Codes
Age	RPDB	
Sex	RPDB	
Socioeconomic Status	Statistics Canada	
Rural Location	Statistics Canada	
Long Term Care Utilization	ODB	
Charlson Comorbidity Index	CIHI-DAD	
Health Care Visits	OHIP IPDB	
Prescribing Physician	IPDB	
Alcoholism	CIHI-DAD	ICD 9: 303, 3050 ICD 10: E24, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510, X45, X65, Y15, Y573, Z502, Z714, Z721
Chronic Kidney Disease	CIHI-DAD OHIP	ICD 9: 4030, 4031, 4039, 4040, 4041, 4049, 585, 586, 5888, 5889, 25040 ICD 10: E102, E112, E132, E142, I12, I13, N08, N18, N19 OHIP DX: 403, 585
Chronic Liver Disease	CIHI-DAD OHIP	ICD 9: 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 2750, 2751, 7891, 7895, 571 ICD 10: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77 OHIP DX: 571, 573, 070 OHIP FEE: Z551, Z554
Carotid Ultrasound	CIHI-DAD OHIP	CCP: 0281 CCI: 3JE30 OHIP FEE: J201, J501, J189, J489, J190, J191, J490, J491, J492

Coronary Angiogram	CIHI-DAD OHIP	CCP: 4892, 4893, 4894, 4895, 4896, 4897, 4898, 4996, 4997 CCI: 3IP10 OHIP FEE: G297, Z442
Coronary Revascularization	CIHI-DAD OHIP	CCP: 481, 482, 483, 480 CCI: 1IJ50, 1IJ26, IIJ27, 1IJ57, 1IJ76 OHIP FEE: R741, R742, R743, E651, E652, E654, E646, G298, Z434, G262
Echocardiography	CIHI-DAD OHIP	CCP: 0282 CCI: 3IP30 OHIP FEE: G560, G561, G562, G566, G567, G568, G570, G571, G572, G574, G575, G576, G577, G578, G579, G580, G581
Holter Monitoring	CIHI-DAD OHIP	CCI: 2HZ24JAKH OHIP FEE: G650, G651, G652, G653, G654, G655, G656, G657, G658, GG59, G660, G661, G682, G683, G684, G685, G686, G687, G688, G689, G690, G692, G693
Stress Test	CIHI-DAD OHIP	CCP: 0341, 0342, 0343, 0344 CCI: 2HZ08, 3IP70 OHIP FEE: G315, G174, G111, G112, G319, J604, J606, J607, J608, J611, J612, J613, J667, J807, J808, J809, J804, J811, J812, J813, J867, J609, J666, J866
Glycosylated Hemoglobin Test	OHIP	OHIP FEE: L093
Diabetic Retinopathy	CIHI-DAD	ICD 9: 3602, 2505 ICD 10: E1030, E1031, E1032, E1033, E1130, E1131, E1132, E1133, E1330, E1331, E1332, E1333, E1430, E1431, E1432, E1433, H360
Diabetes Management	OHIP	OHIP FEE: K030
Diabetes Incentive	OHIP	OHIP FEE: Q040

Coronary Artery Bypass Graft	CIHI-DAD	CCI: 1IJ50, 1IJ76 CCP: 4802, 4803, 4809, 4811, 4812, 4813, 4814, 4815, 4816, 4817, 4819 OHIP FEE: Z434, R742, R743
Peripheral Vascular Disease	CIHI-DAD OHIP	ICD 9: 4402, 4408, 4409, 5571, 4439, 444 ICD 10: I700, I702, I708, I709, I731, I738, I739, K551 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038 CCI: 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87 OHIP FEE: R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649
Heart Failure	CIHI-DAD OHIP	ICD 9: 425, 5184, 514, 428 ICD 10: I500, I501, I509, I255, J81 CCP: 4961, 4962, 4963, 4964 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR OHIP FEE: R701, R702, Z429 OHIP DX: 428
Sepsis	CIHI-DAD OHIP	ICD 9: 0031, 0380, 0381, 0382, 0384, 0388, 0389, 0545 ICD 10: A40, A41, R572 OHIP DX: 038
Pituitary Disease	CIHI-DAD OHIP	ICD 9: 253, 2550 ICD10: E22, E23, E24 OHIP DX: 253
Adrenal Disease	CIHI-DAD	ICD9: 2552, 2553, 2554, 2555, 2556, 2558, 2559, 7591, 0363

	OHIP	ICD10: E25, E27, E351, Q891 OHIP DX: 255
Thyroid Disease	CIHI-DAD OHIP	ICD 9: 243, 244, 245, 246 ICD 10: E01, E03, E04, E05, E06, E07 OHIP DX: 242, 243, 244, 245
Pancreatitis	CIHI-DAD	ICD 9: 5770, 5771, 0723 ICD 10: K85, B252, B263, K860, K861
Pancreatectomy	CIHI-DAD	CCI: 1OJ87, 1OJ89, 1OK87, 1OK89, 1OK91 CCP: 6440, 6441,6442, 6443, 6449, 6450, 6460
Pancreatic Cancer	CIHI-DAD	ICD 9: 1570, 1571, 1572, 1573, 1574, 1578, 1579 ICD10: C250, C251, C252, C253, C254, C257, C258, C259 OHIP DX: 157

Abbreviations: CCI, Canadian Classification of Health Interventions; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; ICD9, International Classification of Diseases, 9th revision; ICD10, International Classification of Diseases, 10th revision; IPDB, Institute for Clinical Evaluative Sciences Physician Database; OHIP DX, Ontario Health Insurance Plan Diagnostic Code; OHIP FEE, Ontario Health Insurance Plan Fee Code; RPDB, Registered Persons Database of Ontario.

Table 3: Coding definitions for hospital presentation with hypoglycemia and all-cause mortality

Condition	Database	Codes
Hypoglycemia [a]	CIHI-DAD NACRS	ICD10: E15, E160, E161, E162, E1063, E1163, E1363, E1463
Mortality [b]	RPDB	Vital status field

[a] We established a validation study of hypoglycemia codes in an emergency room or inpatient setting using linked laboratory plasma glucose values in Ontario. In a cohort of 69,382 patients in the emergency room setting, hypoglycemia codes (ICD10: E15, E160, E161, E162, E1063, E1163, E1363, E1463) had a sensitivity of 21.8%, specificity of 99.5%, PPV 28.7%, NPV 99.2% for glucose values <3.9 mmol/L. For glucose values <3.0 mmol/L, hypoglycemia codes had a sensitivity of 33.3%, specificity 99.4%, PPV 18.1%, NPV 99.7%. In a cohort of 47,377 patients admitted to hospital, hypoglycemia codes had a sensitivity of 7.3%, specificity 99.5%, PPV 46.0%, NPV 94.9% for glucose values <3.9 mmol/L at the time of hospital presentation. For glucose values <3.0 mmol/L at the time of hospital presentation, hypoglycemia codes had a sensitivity 11.5%, specificity 99.4%, PPV 30.2%, and NPV 98.0%. We recognize laboratory plasma glucose values are not an ideal reference standard since in some instances hypoglycemia may have been treated by paramedics or the patient themselves prior to presenting to a hospital setting. Furthermore, hypoglycemia may have been detected and treated based upon point of care capillary testing which may not have been documented in the laboratory setting.

[b] Mortality has a sensitivity of 94% and a positive predictive value of 100%. See Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population based comparison . *J Am Coll Cardiol* 1996; 27:1335-42

Abbreviations: CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD10, International Classification of Diseases, 9th revision; NACRS, National Ambulatory Care Reporting System Database; RPDB, Registered Persons Database of Ontario.

Table 4: Characteristics of patients with and without baseline laboratory values (serum creatinine or HbA1c) in the monotherapy and metformin combination study

	Monotherapy Study			Metformin Combination Study		
	No lab values	Lab values	Standardized Difference	No lab values	Lab values	Standardized Difference[a]
Total	6744	2004		11,663	4413	
Age at Index Date						
Mean (SD)	75.79 (7.10)	75.21 (6.82)		73.40 (6.09)	73.16 (5.84)	
Median (IQR)	75 (70-81)	74 (69-80)		72 (68-77)	72 (68-77)	
66-70 years	1978 (29.33)	615 (30.69)	3%	4669 (40.03)	1804 (40.88)	2%
71-75 years	1600 (23.72)	510 (25.45)	4%	3161 (27.10)	1212 (27.46)	1%
76-80 years	1371 (20.33)	427 (21.31)	2%	2142 (18.37)	829 (18.79)	1%
81-85 years	1072 (15.90)	271 (13.52)	7%	1198 (10.27)	406 (9.20)	4%
86-90 years	544 (8.07)	138 (6.89)	4%	387 (3.32)	141 (3.20)	1%
>90	179 (2.65)	43 (2.15)	3%	106 (0.91)	21 (0.48)	5%
Female	3331 (49.39)	945 (47.16)	4%	5397 (46.27)	2017 (45.71)	1%
Income based socioeconomic status [b]						
Quintile 1 (lowest)	1444 (21.41)	431 (21.51)	0%	2569 (22.03)	939 (21.28)	2%
Quintile 2	1479 (21.93)	492 (24.55)	6%	2574 (22.07)	1012 (22.93)	2%
Quintile 3 (middle)	1352 (20.05)	391 (19.51)	1%	2379 (20.40)	919 (20.82)	1%
Quintile 4	1315 (19.50)	378 (18.86)	2%	2219 (19.03)	821 (18.60)	1%
Quintile 5 (highest)	1154 (17.11)	312 (15.57)	4%	1922 (16.48)	722 (16.36)	0%
Rural Location	851 (12.62)	175 (8.73)	13%	1550 (13.29)	478 (10.83)	8%

Data presented as number (percent) except where indicated.
Abbreviations: HbA1c glycosylated hemoglobin, IQR interquartile range, SD standard deviation

[a] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% is interpreted as a meaningful difference between groups.
[b] Income was categorized into fifths of average neighborhood income on the index date.

Table 5: Events in monotherapy study time to event analysis

Censoring events	Glyburide n=4374 3115.5 person years of follow-up Median (IQR) days of follow-up, 79.5 (30 to 230)	Gliclazide n=4374 4355.2 person years of follow-up Median (IQR) days of follow-up, 150 (48 to 520)
Hospital encounters with hypoglycemia		
Number of events	94 (2.2%)	20 (0.5%)
Event rate per 1000 person years	30.2	4.6
Censoring events		
Death	7 (0.2%)	12 (0.3%)
Study sulphonylurea discontinued	3529 (80.7%)	3605 (82.4%)
Prescription for a non-study oral hypoglycemic agent or insulin	744 (17.0%)	737 (16.9%)

Table 6: Events in metformin combination study time to event analysis

Censoring events	Glyburide n=8038 6973.4 person years of follow-up Median (IQR) days of follow-up, 90 (30 to 323)	Gliclazide n=8038 9101.6 person years of follow-up Median (IQR) days of follow-up, 192.5 (49 to 669)
Hospital encounters with hypoglycemia		
Number of events	205 (2.6%)	41 (0.5%)
Event rate per 1000 person years	29.4	4.5
Censoring events		
Death	11 (0.1%)	7 (0.1%)
Study sulphonylurea discontinued	6843 (85.1%)	6948 (86.4%)
Prescription for non-study oral hypoglycemic agent or insulin	979 (12.2%)	1042 (13.0%)

Figure 1: Flow diagram representing monotherapy study inclusions and exclusions

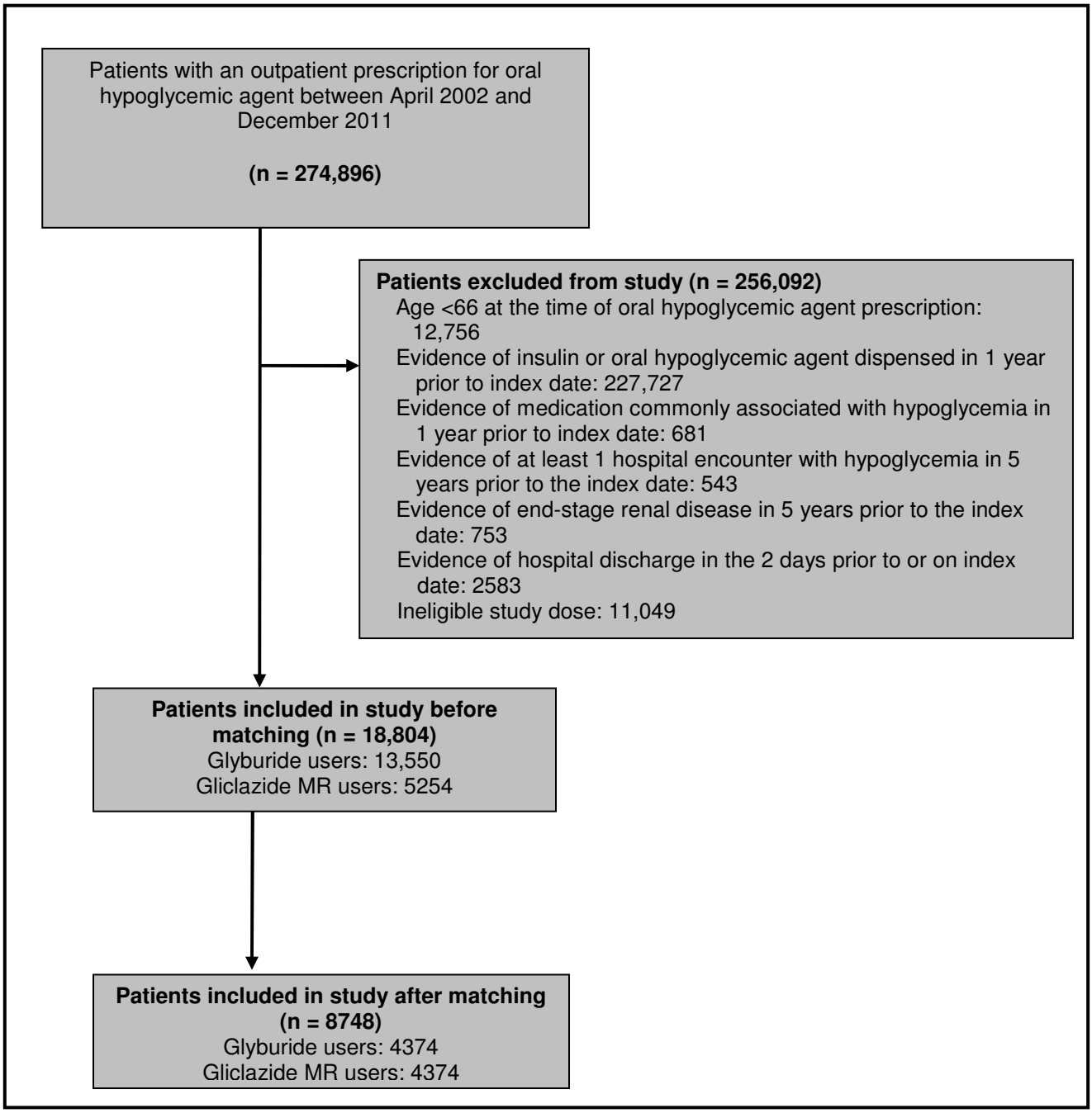
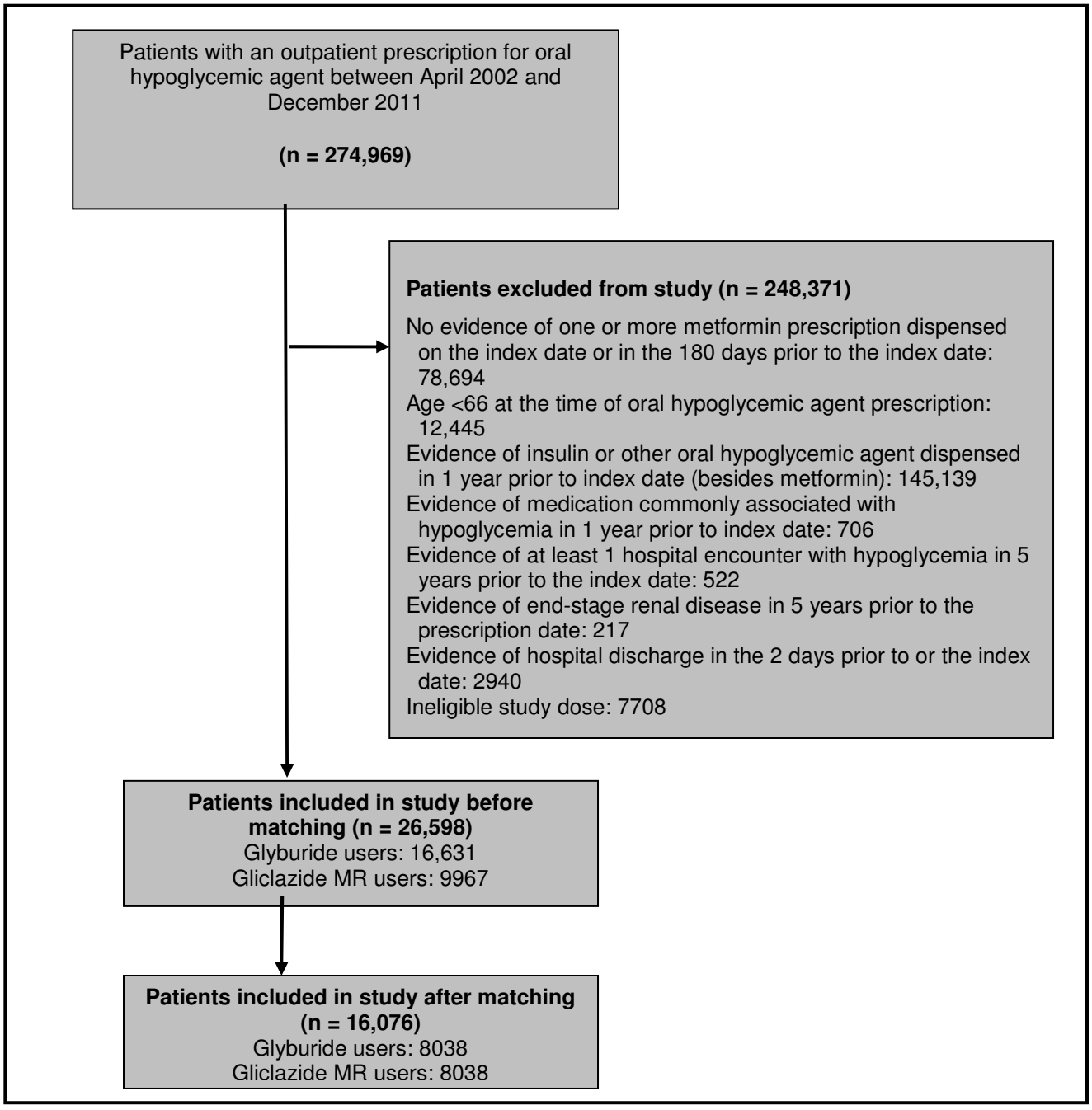


Figure 2: Flow diagram representing metformin combination study inclusions and exclusions



Appendix C

Dataset Creation Plan for "The Hypoglycemic Risk of Glyburide Compared with Modified Release Gliclazide"

Number of Study	2014 0906 038 000
Contacts	Jamie Fleet Amit Garg Stephanie Dixon Kristin Clemens
PIA Approved?	Yes
DCP update history	Version 0 – May 21st 2013 (JF) Version 1 – July 8th 2013 (JF after comments from AG and EM)  Update History.doc Version 2 – July 22nd 2013 (JF after meeting with KC, AG, EM) Version 3 – Aug 15, 2013 (KC after meeting with AG, EM) Version 4 – December 20, 2013 (KC) Version 5 – December 31, 2013 (KC after comments from AG) Version 6 – November 26th, 2014 (based on the recommendations of CJD)
Short Description of Research Question	Oral hypoglycemic agents are used to help control diabetes mellitus. We will explore the risk of a hospital encounter with hypoglycemia in new, older adult users of these medications – specifically in users of glyburide vs modified-release gliclazide.
List of Datasets Used	RPDB ODB Population ☒ Age 65+ CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Diagnosis Type (dxtype) ☒ All (alldx) OHIP Claim Type ☒ Nonlab NACRS Source

☒ Emergency Department visits
Include planned visits
☒No
Include suspected/questionable diagnoses?
☒ No

Gamma-Dynacare

Type of test

☒ Serum creatinine '/home/sdixon/data/GD/fullSCr'
☒ Hemoglobin A1C – test number 093D
☒ Glucose serum fasting – test number 111G
☒ Glucose serum random – test number 111H

Cerner

File name: /ices/CDP/cerner/cerner_apr99_dec10.sas7bdat

Hospital Stay
☒ Inpatient (Disposition = "Inpatient")
☒ Outpatient (Disposition = "Outpatient")
☒ Emergency Room (Disposition = "Emergency Room")

Type of test
☒ Serum creatinine in µmol/L (Test_Done = "A")
☒ Serum glucose in mmol/L (Test_Done = "B")

Defining the Cohort

Index Event	Prescription for new sulphonylurea medication
Inclusion – Cohorts A	Patients with an outpatient prescription for a study oral hypoglycemic agent (OHA) from ODB from April 1st 2002 to Dec 31st 2011 in one of the following DCLASSes:, S_GLY, S_GLC, This date will be the OHA prescription date
Exclusions – Cohorts A	1. Data cleaning a. Invalid IKN b. Missing age/sex c. Non-Ontario resident (CIHI variable prdcddablk does not begin with "35") d. Death on or before OHA prescription date 2. Age <66 on OHA prescription date 3. Evidence of any previous OHA in the 1 year prior (DCLASS: S_MET, S_GLY, S_GLC, S_GLM, S_REP, S_ROS, S_PIO, S_SIT, S_SAX, S_LIN, S_ACB, S_INS, S_MES) or more than 1 DCLASS type on the prescription date 4. Evidence of the following drugs in the 1 year prior to prescription date that have been linked to hypoglycemia (DCLASS = EX) 5. Evidence of hypoglycemia in ER or hospital in 5 years prior to prescription date CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT')

Diagnosis Type (dxtype)
☒ All (alldx)

NACRS
Source
☒ Emergency Department visits
Include planned visits
☒No
Include suspected/questionable diagnoses?
☒ No


hypoglycemia.txt

6. Evidence of any dialysis in the 1 year prior, or renal transplant in the 5 years prior (one or more of the codes below)


dialysis exclusion with pre 2002 codes.t


renal transplant.txt

7. Evidence of hospital discharge up to 2 days prior to or on OHA prescription date
8. Restrict to study doses as follows:

Dose	Gliclazide Modified Release	Glyburide
1	30mg	5mg
2	60mg	10mg
3	90g	15mg
4	120mg	20mg

Note: This also requires exclusion of gliclazide non-modified release: DCLASS = NS

9. If more than one eligible prescription is available, restrict to first

Inclusion – Cohorts B

Patients with an outpatient prescription for a study oral hypoglycemic agent (OHA) from ODB from April 1st 2002 to Dec 31st 2011 in one of the following DCLASSes: S_GLY, S_GLC,

This date will be the OHA prescription date

Exclusions – Cohorts B

1. Look back 180 days from OHA prescription date for at least 1 prescription for metformin (DCLASS = S_MET). This includes evidence of S_MET first prescribed on the index date. Exclude if does not meet this criteria (i.e. exclude if no evidence of prior metformin use, either in the preceding days or co-prescribed with the oral hypoglycemic of interest on the index date)
   - See drug list in Appendix A
   - Note: The day supply of the most recent metformin prescription [i.e. the most recent metformin prescription prior to OHA prescription date] must cross the OHA prescription date (if co-prescribed on the same day then not an issue).
2. Data cleaning
   a. Invalid IKN
   b. Missing age/sex

c. Non-Ontario resident (CIHI variable prdcddablk does not begin with "35")
d. Death on or before OHA prescription date

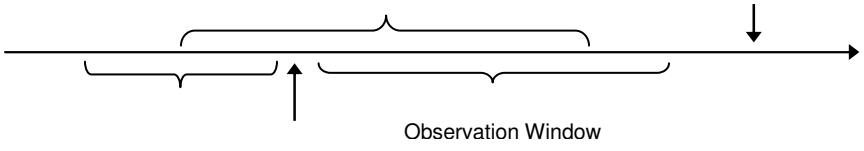
3. Age <66 on OHA prescription date
4. Evidence of any previous OHA other than metformin in the 1 year prior (DCLASS: S_GLY, S_GLC, S_GLM, S_REP, S_ROS, S_PIO, S_SIT, S_SAX, S_LIN, S_ACB, S_INS) or more than 1 DCLASS (except S_MET) type on the prescription date
5. Evidence of the following drugs that have been linked to hypoglycemia (DCLASS = EX)
6. Evidence of hypoglycemia in ER or hospital in 5 years prior to prescription date (see cohort A for codes)
7. Evidence of any dialysis in the 1 year prior, or renal transplant in the 5 years prior (one or more of the codes in Cohort A and B exclusions)
8. Evidence of hospital discharge up to 2 days prior to or on OHA prescription date
10. Restrict to study doses as follows:

Dose	Gliclazide Modified Release	Glyburide
1	30mg	5mg
2	60mg	10mg
3	90g	15mg
4	120mg	20mg

Note: This also requires exclusion of gliclazide non-modified release: DCLASS = NS

9. If more than one eligible prescription is available, restrict to first

Time Frame Definitions



Accrual Start/End Dates	April 1st 2002 to December 31st 2011
Max Follow-up Date	March 31st 2012
When does the observation window terminate?	1. 90 days after index 2. Death 3. Max follow-up (March 31, 2012)
Lookback Window	120 days for baseline medications 5 years for comorbidities 1 year for OHA's 1 year for labs
Exposure	New sulphonylurea prescription – glyburide vs modified-release gliclazide

Variable Definitions

Outcome Definitions

NACRS
Source
☒ Emergency Department visits
Include planned visits
☒No
Include suspected/questionable diagnoses?
☒ No

CIHI-DAD
Source
☒ Inpatient
Institution types
☒ Acute care (insttype = 'AP' or 'AT')

Diagnosis Type (dxtype)
☒ All (alldx)

RPDB

90 day outcomes

below)

1. Emergency room visit or Hospitalization with hypoglycemia

hypoglycemia.txt

2. All-cause mortality

Propensity Score Definition

See Appendix A (Drug list) and D for baseline codes, drug list and additional details

- The propensity score is defined as the probability of exposure (E) conditional on the covariates (See variables below): Pr (E=1IX$_1$, X$_2$, X$_3$, …, X$_n$)
- We will obtain a propensity score per patient (in both the gliclazide and glyburide groups) by fitting a logistic model (proc logistic) that estimates the probability of an OHA prescription given the covariates below and extracting the predicted probabilities
- Consider the following variables in the derivation of the propensity score using multivariable logistic regression model:

Demographics

Age at index year (per year)

Sex (men or women; referent = women)

Location of residence (urban or rural; referent = urban; include patients with 'missing' in the referent group for the purpose of developing propensity score)

	Socioeconomic status (neighbourhood income quintile) (quintiles 1,2,3,4 or t; include patients with 'missing' in quintile 3 for the purpose of developing the propensity score)
	Residential status (community-dwelling or long-term care; referent=community dwelling)
	Charlson score (0, 1, 2, or ≥3; include patients with 'missing' as score of 0 for the purpose of developing the propensity score)
	Comorbidities
	Alcoholism (yes/no; referent=no)
	Chronic kidney disease (yes/no; referent=no)
	Chronic liver disease (yes/no; referent = no)
	Diabetic retinopathy (yes/no; referent=no)
	PVD (yes/no; referent=no)
	Heart failure (yes/no; referent=no)
	Sepsis (yes/no; referent=no)
	Pituitary disease (yes/no; referent=no)
	Adrenal issues (yes/no; referent=no)
	Thyroid disease (yes/no;referent=no)
	Pancreatitis (yes/no; referent=no)
	Cystic fibrosis (yes/no; referent = no)
	Pancreatectomy (yes/no; referent=no)
	Pancreatic cancer (yes/no; referent=no)
	Diabetic neuropathy (yes/no; referent=no)
	Dementia (yes/no; referent = no)
	Health Care Utilization
	Nephrologist visit (0, 1, 2, ≥3; referent = no)

Cardiologist visit (0, 1, 2, ≥3; referent = no)

Ophthalmologist visit (0, 1, 2, ≥3; referent = no)

Endocrinologist visit (0, 1, 2, ≥3; referent = no)

Internist visit (0, 1, 2, ≥3; referent = no)

Carotid ultrasound (yes/no; referent=no)

Coronary angiogram (yes/no; referent=no)

Coronary revascularization (yes/no; referent=no)

Echocardiography (yes/no; referent=no)

Holter monitoring (yes/no; referent =no)

Stress test (yes/no; referent = no)

CABG (yes/no; referent=no)

Glycosylated hemoglobin (yes/no; referent=no)

Diabetes management (yes/no; referent = no)

Diabetes incentive (yes/no; referent=no)

Diabetes management by a specialist (yes/no; referent = no)

Diabetes management by a specialist team (yes/no; referent=no)

Prescribed Medication use (120 day look-back)

Acetohexamide (yes/no; referent=no)

ACE inhibitors (yes/no; referent=no)

ARBs (yes/no; referent=no)

Aliskiren (yes/no; referent=no)

Beta blockers (yes/no;referent=no)

Ezetimibe (yes/no; referent=no)

Fibrates (yes/no; referent = no)

Glucose test strips (yes/no; referent = no)

Loop diuretics (yes/no; referent = no)

Potassium sparing diuretics (yes/no; referent = no)

Statins (yes/no; referent = no)

Thiazide diuretics (yes/no; referent = no)

Gatifloxacin/Levofloxacin (yes/no; referent = no)

Pentamidine (yes/no; referent = no)

Quinine (yes/no; referent = no)

Indomethacin (yes/no; referent = no)

Tacrolimus/sirolimus (yes/no; referent=no)

Clonidine (yes/no; referent = no)

Chloramphenicol (yes/no; referent = no)

H2 Receptor Antagonist (yes/no; referent = no)

Clarithromycin (yes/no; referent = no)

Cyclosporine (yes/no; referent=no)

Fluconazole/voriconazole/miconazole (yes/no;referent =no)

Pegvisimont (yes/no; referent=no)

Probenecid (yes/no; referent=no)

Rifampin (yes/no; referent =no)

Amiodarone (yes/no; referent = no)

Valproic acid (yes/no; referent=no)

Aprepitant (yes/no; referent=no)

Bosentan (yes/no; referent = no)

Carbamazepine (yes/no; referent = no)

Antidepressants (yes/no; referent = no)

Protease inhibitors (yes/no; referent = no)

Atypical antipsychotics (yes/no; referent = no)

Corticosteroids (yes/no; referent = no)

Sulfonamide (yes/no; referent = no)

MAOI inhibitor (yes/no; referent = no)

Barbiturate (yes/no; referent = no)

Tetracycline (yes/no;referent = no)

Danazol (yes/no; referent = no)

Thyroid replacement (yes/no; referent =no)

Androgen (yes/no; referent = no)

Disopyramine (yes/no; referent = no)

Guanethidine (yes/no; referent = no)

Ifosfamide (yes/no; referent = no)

Phenylbutazone (yes/no; referent = no)

Diazoxide (yes/no; referent = no)

Isoniazid (yes/no; referent = no)

Colesevelam (yes/no; referent = no)

Reserpine (yes/no; referent = no)

Laboratory Testing (baseline characteristic only - not to be included in the propensity score):

For Cohorts A and B (both pre and post matching), where available, provide:

-Number (%) with creatinine in the 1 year prior

-Mean (SD) creatinine

-Median (IQR) creatinine

-Mean (SD) eGFR

-Median (IQR) eGFR

-Number (%) with hemoglobin A1c in the 1 year prior

-Mean (SD) hemoglobin A1c

-Median (IQR) hemoglobin A1c

Hard and Propensity Score Matching

- We will use greedy matching with specified caliper width of (plus/minus) 0.6 x the standard deviation of the logit of the propensity score
- The difference in the logit of the propensity score between the gliclazide and the glyburide groups in the matched set is required to be less than the pre-specified maximum caliper wide
- We will match without replacement. Matching gliclazide patients can no longer serve as a candidate for being matched to another glyburide patient

Matching Ratio: We will match 1 gliclazide patient with 1 glyburide patient on:

- The logit of the propensity score
- Age at the index date (plus/minus 2 years)
- Sex (men or women; referent=women)
- CKD status (yes/no; referent = no)
- Medication dose
- At least 1 endocrinologist visit

Dose	Gliclazide Modified Release	Glyburide
1	30mg	5mg
2	60mg	10mg
3	90g	15mg
4	120mg	20mg

Outline of Analysis Plan

1. Cohort Creation

- Show prescriptions and unique IKNs that are included at each stage
- Table 1A – Cohort A creation
- Table 1B – Cohort B creation

2. Aggregate Event Rate

- Show total number of patients, and broken down by CKD and no-CKD by codes
- Show number and proportion of patients with events in each category
- Table 2A – Cohort A
- Table 2B – Cohort B

3. Prescription Breakdown

- Show number with each prescription type
- Show min, max, median, IQR average daily dose for each prescription
- Table 3A – Cohort A
- Table 3B – Cohort B
- Note: For cohort B show how many prescriptions for metformin in 120 days prior to OHA prescription date (min # prescriptions, max # prescriptions, median # prescriptions, 25th percentile # of prescriptions, 75th percentile # of prescriptions). See Table 3D, 3E, 3F

4. Continuous Usage

- Show only for patients who have at least one year of prescriptions (those accrued no later than March 31st 2011; have done this to allow for the possibility of at least one full year of follow-up data)
- Look forward to end of day supply for last eligible prescription to assess continuous usage in number of days.
- If index script is the only prescription, look to the end of its day supply.
- Eligible prescriptions are those in the same DCLASS and with a subsequent prescription a max of 10 days following the end of day supply of the previous prescription (ie. could be before 10 days for next prescription)
- Person is no longer the continuous user if:
  - No more evidence of the DCLASS 10 days after end of prior prescription day supply
  - switch to a different DCLASS
  - die
  - end of follow up (March 31st 2012)

5. Metformin Usage After Index – Cohort A and B

- Show number of patients with ≥1 S_MET prescription within 180 days following the index date (not including the index date)

6. Baseline characteristics

- Show number and proportion with standardized differences comparing S_GLY and S_GLC for each characteristic listed in Appendix D
- Look back 5 years for comorbidities, 1 year for lab values (where available), and 120

days for medications unless otherwise specified

- Table 6a is for COHORT A prior to matching and includes laboratory values
- Table 6c is for COHORT A post-matching and includes laboratory values
- Table 6b is for COHORT B prior to matching and includes laboratory values
- Table 6d is for COHORT B post-matching and includes laboratory values

7. Primary Analysis

- Conditional logistic regression model looking at S_GLY vs. S_GLC with a 90 day follow up
- Table 7 are for COHORT A – total cohort (all outcomes)
- Table 8 are for COHORT B – metformin (all outcomes)

9. Secondary analyses

Costs of SU to ODB

·Time to event analysis (censoring on death, receipt of non-study OHA, discontinuation of study OHA)

·Physician associated factors with prescription for glyburide from 2008-2011 (time since grad, origin of training, practice location

·Characteristics of hypoglycemia episodes (time of day, number of ER's/hospitals, number of prescribers)

·Adjustment for year of cohort entry

·Percentage with hypoglycemia by year

·Baseline demographic characteristics of those with and without laboratory values (ie HbA1c and creatinine) available in the 1 year previous

Appendices

Appendix A: Drug List


OHA drug list.xls


OHA drug list extra BC.xls

Appendix B: Sample Tables


OHA and hypoglycemia tables.:

Appendix C: Cerner FSA Info


CERNER Pharmacy FSA.xls


CERNER hospitals.xls

Appendix D: Baseline Characteristics


OHA and hypoglycemia baselin


OHA new baselines.txt

Characteristic	Datasets Used	Other Details
Age	RPDB	Mean, median, SD 66-70 71-75 76-80 81-85 86-90 >90
Sex	RPDB	
Income quintile	PSTLYEAR (using %getdemo)	
Rural location	PSTLYEAR (using %getdemo)	
Year of cohort entry (index date)		
LTC utilization	ODB	
Charlson score		Measure of general comorbidity based on relative effects of a combination of diseases or risk factors on outcomes for a given individual to show expected mortality reported as 0, 1, 2, or ≥ 3; if there are no hospitalizations, code as 0 and not as 'missing'
Nephrologist visit in 1 year prior	OHIP	**First,** identify physicians who are Nephrologists: a physician who, during the study accrual period, had <u>both</u>: 1) billed ≥ 25 OHIP fee codes for "Nephrologist consult" (can be same patient, but have to be codes billed on separate days; i.e. no more than one OHIP A135 code per day)  nephro codes.txt <u>AND</u> 2) billed ≥ 50 OHIP "dialysis" codes, with no more than 1 code on a given day (i.e. evidence of at least 50 separate days of codes.

		Note: some forms of acute dialysis were excluded from this dialysis list as this can be billed by a physician other than nephrologist i.e. intensive care physicians or during continuous veno-venous hemodialysis)  ohip dialysis codes for nephro consult .t› **Second**, look for evidence of **any** of the "Nephrologist consult" OHIP Feecodes billed by a nephrologist in the past **1 year prior to index date**
Cardiologist visit	IPDB	Number of patients who have seen a cardiologist at least once in 1 year prior. Defined by mainspecialty = "CARDIOLOGY"
Ophthalmologist visit	IPDB	Number of patients who have seen a cardiologist at least once in 1 year prior. Defined by mainspecialty = "OPHTHALMOLOGY"
Endocrinologist visit	IPDB	Number of patients who have seen a cardiologist at least once in 1 year prior. Defined by mainspecialty = "ENDOCRINOLOGY"
Internist visit	IPDB	Number of patients who have seen a cardiologist at least once in 1 year prior. Defined by mainspecialty = "INTERNAL MEDICINE"
Prescribing physician main specialty	IPDB	NEPHROLOGY CARDIOLOGY OPHTHALMOLOGY ENDOCRINOLOGY INTERNAL MEDICINE GP/FP Missing Other
Alcoholism	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	
Chronic kidney disease	CIHI-DAD	

	Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Chronic liver disease	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? No OHIP Claim Type NONLAB	
Carotid ultrasound	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Coronary angiogram	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Coronary revascularization	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Echocardiography	CIHI-DAD Source	

	☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Holter monitoring	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Stress test	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Glycosylated hemoglobin	OHIP Claim Type ☒ ALL	
Diabetic retinopathy	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	
Diabetes management	OHIP Claim Type ☒ NONLAB	Look in 1 year prior (FYI – this is for GP)
Diabetes incentive	OHIP Claim Type ☒ NONLAB	Look in 1 year prior
Diabetes management by a specialist	OHIP Claim Type ☒ NONLAB	Look in 1 year prior (FYI – specialists can include internists, endocrinologists, or pediatricians)
Diabetes management by a specialist team	OHIP Claim Type	Look in 1 year prior (FYI – specialists in this case

	☒ NONLAB	can mean internists or endocrinologists) Also show diabetes management by a specialist OR team in 1 year prior
PVD	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Heart failure	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
CABG	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Sepsis	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Pituitary issues	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable	

	diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Adrenal issues	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Thyroid issues	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No OHIP Claim Type ☒ NONLAB	
Pancreatitis	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	
Cystic fibrosis	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	
Pancreatectomy	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No	
Pancreatic Cancer	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or	

	'AT') <u>Include suspected/questionable diagnoses?</u> ☒ No	
Lab values if available		
Fasting serum glucose	Gamma Dynacare ☒ Glucose serum fasting – test number 111G	Please provide mean, SD, median, IQR
Serum glucose (random)	Gamma Dynacare ☒ Glucose serum random – test number 111H	Please provide mean, SD, median, IQR
HbA1C	Gamma Dynacare ☒ Hemoglobin A1C – test number 093D	Range of acceptable values for HbA1C include 1 to 25%. Values <1% and >25% will be excluded. Values that do not lie in the specified range are likely errors. Please provide mean, SD, median, IQR
Serum creatinine	**Gamma Dynacare** <u>Type of test</u> ☒ Serum Creatinine '/home/sdixon/data/GD/fullSCr' **CERNER** <u>Type of test</u> ☒ Serum creatinine in µmol/L (Test_Done = "A") <u>Hospital Stay</u> ☒ Inpatient (Disposition = "Inpatient") ☒ Emergency Room (Disposition = "Emergency Room") ☒ Outpatient (Disposition = "Outpatient")	Range of acceptable values for serum creatinine include 10-2500 µmol/L. Values <10 µmol/L and >2500 µmol/L will be excluded. Values that do not lie in the specified range are likely errors. Please provide mean, SD, median, IQR
GFR	**Gamma Dynacare** <u>Type of test</u> ☒ Serum Creatinine - variable: "ckd_epi_egfr" Serum creatinine (main_gd_dec10tojan11_sent_mar11, [main_gd_jan02tonov10_sent_dec10) **CERNER** <u>Type of test</u> ☒ Serum creatinine in µmol/L (Test_Done = "A") <u>Hospital Stay</u> ☒ Inpatient (Disposition = "Inpatient") ☒ Emergency Room (Disposition = "Emergency Room") ☒ Outpatient (Disposition = "Outpatient")	○ For CERNER, use CKD-EPI equation $=141 \times \min([\text{serum creatinine in umol/L} / 88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine in umol/L} / 88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if Female] x 1.159 [if African American] *κ=0.7 for females and 0.9 for males,* *α= -0.329 for females and -0.411 for males,* *min=the minimum of Scr/κ or 1,* *max=the maximum of Scr/κ or 1.* Please provide mean, SD, median, IQR Also put into the following

		categories: eGFR >60 45-59 30-44 15-29 <15 mL/min/1.73m^2
Medication	**DCLASS**	
Acetohexamide	BC_ACT	
ACE inhibitors	BC_ACE	
ARBs	BC_ARB	
Aliskiren	BC_ALI	
Beta blockers	BC_BBL	
Ezetimibe	BC_EZE	
Fibrates	BC_FIB	
Glucose test strips	BC_STR	
Loop diuretics	BC_LOP	
Potassium sparing diuretics	BC_KSD	
Statins	BC_STA	
Thiazide diuretics	BC_TZD	
Gatifloxacin/Levofloxacin	BC_GAT	
Pentamidine	BC_PEN	
Quinine	BC_QUI	
Indomethacin	BC_IND	
Tacrolimus/sirolimus	BC_LIM	
Clonidine	BC_CLO	
Chloramphenicol	BC_CHL	
H2 receptor antagonists	BC_HRA	
Clarithromycin	BC_CLA	
Cyclosporine	BC_CYC	
Fluconazole/voriconazole/miconazole	BC_FLV	
Pegvisomant	BC_PEG	
Probenecid	BC_PBD	
Rifampin	BC_RIF	
Amiodarone	BC_AMI	
Valproic acid	BC_VAL	
Aprepitant	BC_APR	
Bosentan	BC_BOS	
Carbamazepine	BC_CAR	
Antidepressants	BC_DEP	
Protease inhibitors	BC_PRO	
Atypical antipsychotics	BC_APS	
Corticosteroids	BC_CCS	
Sulfonamides	BC_SUL	
MAOI Inhibitors	BC_MAO	
Barbiturates	BC_BAR	
Tetracycline	BC_TET	
Danazol	BC_DAN	
Thyroid hormone	BC_THY	
Androgens	BC_TES	
Disopyramine	BC_DIS	
Guanethidine	BC_GUA	
Ifosfamide	BC_IFO	

Phenylbutazone	BC_PHE
Diazoxide	BC_DIA
Isoniazid	BC_ISO
Colesevelam	BC_COL
Reserpine	BC_RES

Appendix D

Supplementary Materials for “Trends in Antihyperglycemic Medication Prescriptions in Older Adults: 2002-2013”

Table 1. Checklist of recommendations for reporting of observational studies using the STROBE guidelines

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods and Appendix D Table 2 and 3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods and Appendix D Table 2 and 3
Bias	9	Describe any efforts to address potential sources of bias	Methods
Study size	10	Explain how the study size was arrived at	Not applicable
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine	Methods

		subgroups and interactions	
		(c) Explain how missing data were addressed	Not applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not applicable
		(e) Describe any sensitivity analyses	Not applicable
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Results
		(b) Give reasons for non-participation at each stage	Results
		(c) Consider use of a flow diagram	
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Results, Table 7, and Appendix D Table 4
		(b) Indicate number of participants with missing data for each variable of interest	Not applicable
		(c) Summarize follow-up time (e.g. average and total amount)	Not applicable
Outcome data	15	Report numbers of outcome events or summary measures over time	Results
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results
		(b) Report category boundaries when continuous variables were categorized	Results
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Not applicable
Discussion			
Key results	18	Summarize key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalizability	21	Discuss the generalizability (external validity) of the study results	Discussion

Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Financial Disclosures

Table 2. Coding definitions for demographic and comorbid conditions

Characteristics/ Condition	Database	Codes
Age	RPDB	
Sex	RPDB	
Income quintile	Statistics Canada	
Rural location	Statistics Canada	
Chronic kidney disease	CIHI-DAD OHIP	ICD 9: "4030", "4031", "4039", "4040", "4041", "4049", "585", "586", "5888", "5889", "2504" ICD 10: "E102", "E112", "E132", "E142", "I12", "I13", "N08", "N18", "N19" OHIP DX: "403", "585"
Chronic liver disease	CIHI-DAD OHIP	ICD 9: "4561", "4562", "070", "5722", "5723", "5724", "5728", "573", "7824", "V026", "2750", "2751", "7891", "7895", "571" ICD 10: "B16", "B17", "B18", "B19", "I85", "R17", "R18", "R160", "R162", "B942", "Z225", "E831", "E830", "K70", "K713", "K714", "K715", "K717", "K721", "K729", "K73", "K74", "K753", "K754", "K758", "K759", "K76", "K77" OHIP DX: "571", "573", "070" OHIP FEE: "Z551", "Z554"
Any cancer	CIHI OHIP	ICD 9: "V10", "140", "141", "142", "143", "144", "145", "146", "147", "148", "149", "150", "151", "152", "153", "154", "155", "156", "157", "158", "159", "160", "161", "162", "163", "164", "165", "170", "171", "172", "173", "174", "175", "176", "179", "180", "181", "182", "183", "184", "185", "186", "187", "188", "189", "190", "191", "192", "193", "194", "1950", "1951", "1952", "1953", "1954", "1955", "1958", "196", "197", "198", "1990", "1991", "2000", "2001", "2002", "2008", "2010", "2011", "2012", "2014", "2015", "2016", "2017", "2019", "2020", "2026", "2028", "2029", "203", "204", "205", "206", "207", "208", "230", "231", "232", "233", "234" ICD 10: "80003", "80006", "80013", "80023", "80033", "80043", "80102", "80103", "80106", "80113", "80123",

		"80203", "80213", "83123", "87202", "87203", "959", "965", "966", "967", "968", "969", "970", "971", "980", "982", "984", "985", "986", "987", "988", "989", "990", "991", "993", "C00", "C01", "C02", "C03", "C04", "C05", "C06", "C07", "C08", "C09", "C10", "C11", "C12", "C13", "C14", "C15", "C16", "C17 C18", "C19", "C20", "C21", "C22", "C23", "C24", "C25", "C26", "C30", "C31", "C32", "C33", "C34", "C37", "C38", "C39", "C40", "C41", "C43", "C44", "C45", "C46", "C47", "C48", "C49", "C50", "C51", "C52", "C53", "C54", "C55", "C56", "C57", "C58", "C60", "C61", "C62", "C63", "C64", "C65", "C66", "C67", "C68", "C69", "C70", "C71", "C72", "C73", "C74", "C75" ,"C76", "C77", "C78", "C79", "C80", "C81", "C82", "C83", "C84", "C85", "C90", "C91", "C92", "C93", "C94", "C95", "C96", "C97", "D00", "D01", "D02", "D03", "D04", "D05", "D06", "D07", "D09" OHIP DX: "140", "141", "142", "143", "144", "145", "146", "147", "148", "149", "150", "151", "152", "153", "154", "155", "156", "157", "158", "159", "160", "161", "162", "163 164"," 165", "170", "171", "172", "173", "174", "175", "179", "180", "181", "182", "183", "184", "185", "186", "187", "188", "189 190", "191", "192", "193", "194", "195", "196", "197", "198", "199", "200", "201", "202", "203", "204", "205", "206", "207", "208"
Coronary artery disease (excluding angina)	CIHI-DAD OHIP	ICD 9: "412", "410" ICD 10: "I21", "I22", "Z955", "T822" CCI: "1IJ50", "1IJ76" CCP: "4801", "4802", "4803", "4804", "4805", "481", "482", "483" OHIP FEE: "R741", "R742", "R743", "G298", "E646", "E651", "E652", "E654", "E655", "Z434", "Z448" OHIP DX: "410", "412"
Congestive heart failure	CIHI-DAD OHIP	ICD 9: "425", "5184", "514", "428" ICD 10: "I500", "I501", "I509", "I255", "J81" CCP: "4961", "4962", "4963", "4964" CCI: "1HP53", "1HP55", "1HZ53GRFR",

		"1HZ53LAFR", "1HZ53SYFR" OHIP FEE: "R701", "R702", "Z429" OHIP DX: "428"
Peripheral vascular disease	CIHI-DAD OHIP	ICD 9: "4402", "4408", "4409", "5571", "4439", "444" ICD 10: "I700", "I702", "I708", "I709", "I731", "I738", "I739", "K551" CCP: "5125", "5129", "5014", "5016", "5018", "5028", "5038" CCI: "1KA76", "1KA50", "1KE76", "1KG26", "1KG50", "1KG57", "1KG76MI", "1KG87" OHIP FEE: "R787", "R780", "R797", "R804", "R809", "R875", "R815", "R936", "R783", "R784","R785", "E626", "R814", "R786", "R937", "R860", "R861", "R855", "R856", "R933", "R934", "R791", "E672", "R794", "R813", "R867", "E649"
Dementia	CIHI-DAD OHIP	ICD 9: "2900", "2901", "2903", "2904", "2908", "2909", "2948", "2949", "3310", "3311", "3312", "2941", "797" ICD 10: "F065", "F066", "F068", "F069", "F09", "F00", "F01", "F02", "F03", "F051", "G30", "G31", "R54" OHIP DX: "290","331", "797"
Stroke/ Transient ischemic attack	CIHI-DAD	ICD 9: "430", "431", "434", "435", "436" ICD 10: "I630", "I631", "I632", "I633", "I634", "I635", "I638", "I639", "I64", "H341", "I600", "I601", "I602", "I603", "I604", "I605", "I606", "I607", "I609", "I61", "G450", "G451", "G452", "G453", "G458", "G459"
Neuropathy	CIHI-DAD	ICD 9: "3572" ICD 10: “E1040”,”E10400”, “E10401”,”E10402”,“E10403”, “E10404”, “E10409”, “E1041”, “E10410”, “E10411”, “E10412”, “E10413”, “E10414”, “E10419”, “E1042”, “E10420”, “E10421”, “E10422”, “E10423”,“E10424”,“E10429”,“E10480”,“E10481”,“E10482”, “E10483”,“E10484”, “E10489”, “E10490”, “E10491”, “E10492”, “E10493”, “E10494”, “E10499”, “E1140”, “E11400”, “E11401”, “E11402”, “E11403”,

		“E11404”, “E11409”, “E1141”, “E11410”, “E11411”, “E11412”, “E11413”, “E11414”, “E11419”, “E1142”, “E11420”, “E11421”, “E11422”, “E11423”, “E11424”, “E11429”, “E11480”, “E1148”, “E11482”, “E11483”, “E11484”, “E11489”, “E11490”, “E11491”, “E11492”, “E11493”, “E11494”, “E11499”, “E1340”, “E13400”, “E13401”, “E13402”, “E13403”, “E13404”, “E13409”, “E1341”, “E13410”, “E13411”, “E13412”, “E13413”, “E13414”, “E13419”, “E1342”, “E13420”, “E13421”, “E13422”, “E13423”, “E13424”, “E13429”, “E13480”, “E13481”, “E13482”, “E13483”, “E13484”, “E13489”, “E13490”, “E13491”, “E13492”, “E13493”, “E13494”, “ “E13499”, “E1440”, “E14400”, “E14401”, “E14402”, “E14403”, “E14404”, “E14409”, “E1441”, “E14410”, “E14411”, “E14412”, “E14413”, “E14414”, “E14419”, “E1442”, “E14420”, “E14421”, “E14422”, “E14423”, “E14424”, “E14429”, “E14480”, “E14481”, “E14482”, “E14483”, “E14484”, “E14489”, “E14490”, “E14491”, “E14492”, “E14493”, “E14494”, “E14499”, “G590”, “G632”
Retinopathy	CIHI-DAD	ICD 9: “36201”, “36202”, “36210”, “36212”, “36229” ICD 10: “E1030”, “E10300”, “E10301”, “E10302”, “E10303”, “E10304”, “E10309”, “E1031”, “E10310”, “E10311”, “E10312”, “E10313”, “E10314”, “E10319”, “E1032”, “E10320”, “E10321”, “E10322”, “E10323”, “E10324”, “E10329”, “E1033”, “E10330”, “E10331”, “E10332”, “E10333”, “E10334”, “E10339”, “E10340”, “E10341”, “E10342”, “E10343”, “E10344”, “E10349”, “E1130”, “E11300”, “E11301”, “E11302”, “E11303”, “E11304”, “E11309”, “E1131”, “E11310”, “E11311”, “E11312”, “E11313”, “E11314”, “E11319”, “E1132”, “E11320”, “E11321”, “E11322”, “E11323”, “E11324”, “E11329”, “E1133”, “E11330”, “E11331”, “E11332”, “E11333”, “E11334”, “E11339”, “E11340”, “E11341”, “E11342”, “E11343”, “E11344”, “E11349”, “H360”
Number of cholesterol tests	OHIP	OHIP FEE: “L055”
Number of HbA1c tests	OHIP	OHIP FEE: “L093"
Number of creatinine tests	OHIP	OHIP FEE: OHIP FEE: "L065", "L067", "L068"
Number of glucose tests	OHIP	OHIP FEE: "L111"
Major eye examination	OHIP	OHIP FEE: "A112", "A233", "A234", "A235", "A236", A239", "V401", "V406", "V402"

Abbreviations: CIHI, Canadian Institute for Health Information's Discharge Abstract Database; CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures; HbA1c, hemoglobin A1c; ICD 9, International Classification of Diseases 9th Revision; ICD 10, International Classification of Diseases 10th Revision; OHIP, Ontario Health Insurance Plan; RPDB, Registered Persons Database of Ontario

Table 3. Coding definitions for hospital presentation with hypoglycemia

Condition	Database	Codes
Hypoglycemia	CIHI-DAD NACRS	ICD 10: E15, E160, E161, E162, E1063, E1163, E1363, E1463

Abbreviations: CIHI, Canadian Institute for Health Information Discharge Abstract Database; ICD 10, International Classification of Diseases 10th Revision; NACRS, National Ambulatory Care Reporting System Database

Table 4. Baseline characteristics of patients with newly treated diabetes

	April 1, 2002		April 1, 2007		April 1, 2012	
	N=3,498	%	N=5,863	%	N=4,478	%
Age (yr)						
Mean (SD)	74.22 (6.24)		74.45 (6.43)		74.31 (6.63)	
Median (IQR)	73 (69-78)		73 (69-78)		73 (69-79)	
66-69	926	26.47%	1599	27.27%	1314	29.34%
70-74	1083	30.96%	1661	28.33%	1275	28.47%
75-79	801	22.90%	1337	22.80%	911	20.34%
80-84	416	11.89%	780	13.30%	570	12.73%
85-89	200	5.72%	355	6.05%	297	6.63%
90+	72	2.06%	131	2.23%	111	2.48%
Sex - Female	1686	48.20%	2765	47.16%	2125	47.45%
Income quintile						
Missing	9	0.26%	24	0.41%	8	0.18%
1 (lowest)	797	22.78%	1238	21.12%	882	19.70%
2	834	23.84%	1261	21.51%	947	21.15%
3	679	19.41%	1110	18.93%	923	20.61%
4	625	17.87%	1118	19.07%	901	20.12%
5 (highest)	554	15.84%	1112	18.97%	817	18.24%
Rural						
Missing	≤5	---	≤5	---	≤5	---
No	2955	84.48%	5146	87.77%	3890	86.87%
Yes	542	15.49%	715	12.20%	587	13.11%
Comorbidities[a]						
Chronic kidney disease	167	4.77%	575	9.81%	396	8.84%
Chronic liver disease	130	3.72%	236	4.03%	170	3.80%
Any cancer	920	26.30%	1508	25.72%	1153	25.75%
Coronary artery disease (excluding cancer)	1136	32.48%	1,832	31.25%	1202	26.84%
Congestive heart failure	559	15.98%	800	13.64%	513	11.46%
Peripheral vascular disease	100	2.86%	129	2.20%	55	1.23%

Dementia	271	7.75%	488	8.32%	444	9.92%
Stroke/TIA	139	3.97%	185	3.16%	135	3.01%
Neuropathy	≤5	---	21	0.36%	29	0.65%
Retinopathy	13	0.37%	44	0.75%	17	0.38%
Investigations[b]						
Mean (SD) number cholesterol tests	0.96 (1.15)	---	1.19 (1.19)	---	1.11 (1.07)	---
Median (IQR) cholesterol tests	1 (0-1)	---	1 (0-2)	---	1 (0-2)	---
Mean (SD) HbA1c tests	1.25 (1.50)	---	1.49 (1.62)	---	1.45 (1.35)	---
Median (IQR) HbA1c tests	1 (0-2)	---	1 (0-2)	---	1 (0-2)	---
Mean (SD) creatinine tests	1.48 (1.91)	---	1.84 (2.14)	---	1.76 (1.91)	---
Median (IQR) creatinine tests	1 (0-2)	---	1 (1-2)	---	1 (1-2)	---
Mean (SD) glucose tests	2.03 (2.44)	---	1.92 (2.04)	---	1.62 (1.59)	---
Median (IQR) glucose tests	1 (0-3)	---	2 (1-3)	---	1 (0-2)	---
At least 1 eye exam	1,113	31.82%	1,887	32.18%	1,127	25.17%
Laboratory Data[c]						
At least 1 HbA1c outpatient lab value	---	---	1,235	21.06%	994	22.20%
Mean (SD) HbA1c (%)	---	---	6.8% (1.1%)	---	7.2% (1.2%)	---
Mean (SD) HbA1c (mmol/mol)			51 (12)		55 (13.1)	
Median (IQR) HbA1c	---	---	6.6% (6.1%-7.2%)	---	6.9% (6.5%-7.5%)	---
Median (IQR) HbA1c (mmol/mol)			49 (43-55)		52 (48-58)	

Abbreviations: TIA transient ischemic attack, SD standard deviation, IQR interquartile range, HbA1c glycosylated hemoglobin
For reasons of privacy, cell sizes less than 6 are not presented.
[a]Comorbidities were examined in the 5 years prior.
[b]Investigations were examined in the 1 year prior.
[c]Lab values were available in the 1 year prior.

Table 5. Timeline of safety events during the study period– thiazolidinediones

October 2006	Pioglitazone added to the province's general benefit drug formulary
January 2007	Rosiglitazone added to the province's general benefit drug formulary
February 2007	Safety signals emerge re: fracture risk with rosiglitazone [1]
May 2007	Regulatory warnings re: cardiac safety of rosiglitazone [2,3]
June 2007	Meta-analysis on cardiac safety of rosiglitazone published in the New England Journal of Medicine [4]
Nov 2007	Black box warning issued for rosiglitazone in the United States [5]
June 2009	Funding status for thiazolidinediones changed from General Benefit to the Exceptional Access Program in Ontario [6]
Sept 2010	Prescribing restrictions on thiazolidinediones placed in the United States [7]
June 2011	Regulatory attention to risk of bladder cancer with pioglitazone therapy [8]

1. Health Canada. Important safety information on rosiglitazone-containing products: AVANDIA®, AVANDAMET® and AVANDARYL™ [Internet]. 2007. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2007/13994a-eng.php, Accessed Jan 30, 2015.
2. Health Canada. Cardiac Safety of Avandia (rosiglitazone maleate) - For Health Professionals [Internet]. 2007. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2007/14440a-eng.php, Accessed Jan 30, 2015
3.US Food and Drug Administration. Information for Healthcare Professionals Rosiglitazone maleate (marketed as Avandia, Avandamet, and Avandaryl) [Internet]. http://www.fda.gov/Drugs/DrugSafety/ PostmarketDrugSafetyInformationfor PatientsandProviders/ucm143460.htm, Accessed Jan 30, 2015
4. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007; 356: 2457-71.
5.US Food and Drug Administration. FDA Adds Boxed Warning for Heart-related Risks to Anti-diabetes Drug Avandia [Internet]. 2007. http://www.fda.gov/NewsEvents/ Newsroom/ PressAnnouncements/2007/ucm109026.htm, Accessed Jan 30, 2015.
6.Ontario Ministry of Health and Long-term Care. Change in Funding Status Rosiglitazone and Pioglitazone [Internet]. 2009. http://www.health.gov.on.ca/en/pro/ programs/drugs/opdp_eo/notices/notices_docs/tzd_faq.pdf, Accessed Jan 30, 2015.
7.US Food and drug Administration. FDA significantly restricts access to the diabetes drug Avandia [Internet]. 2010. http://www.fda.gov/ Drugs/DrugSafety/Postmarket DrugSafetyInformationforPatientsandProviders/ucm226956.htm, Accessed Jan 30, 2015.

8. Health Canada. Health Canada reviewing diabetes drug pioglitazone (Actos) and potential risk of bladder cancer [Internet]. http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2011/13617a-eng.php, Accessed 30 Jan 2015.

Figure 1. Mono and combination therapy 2002-2013

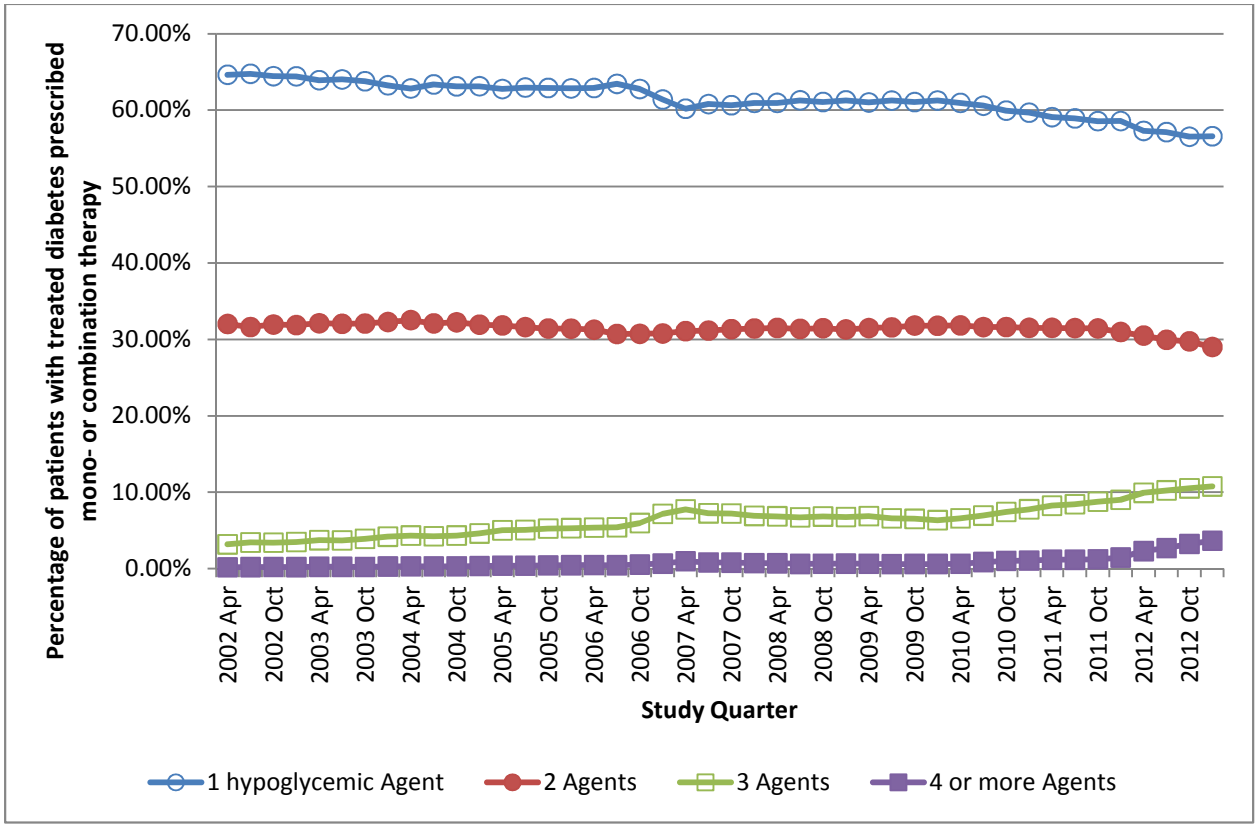


Figure 2. Insulin mono and combination therapy 2002-2013

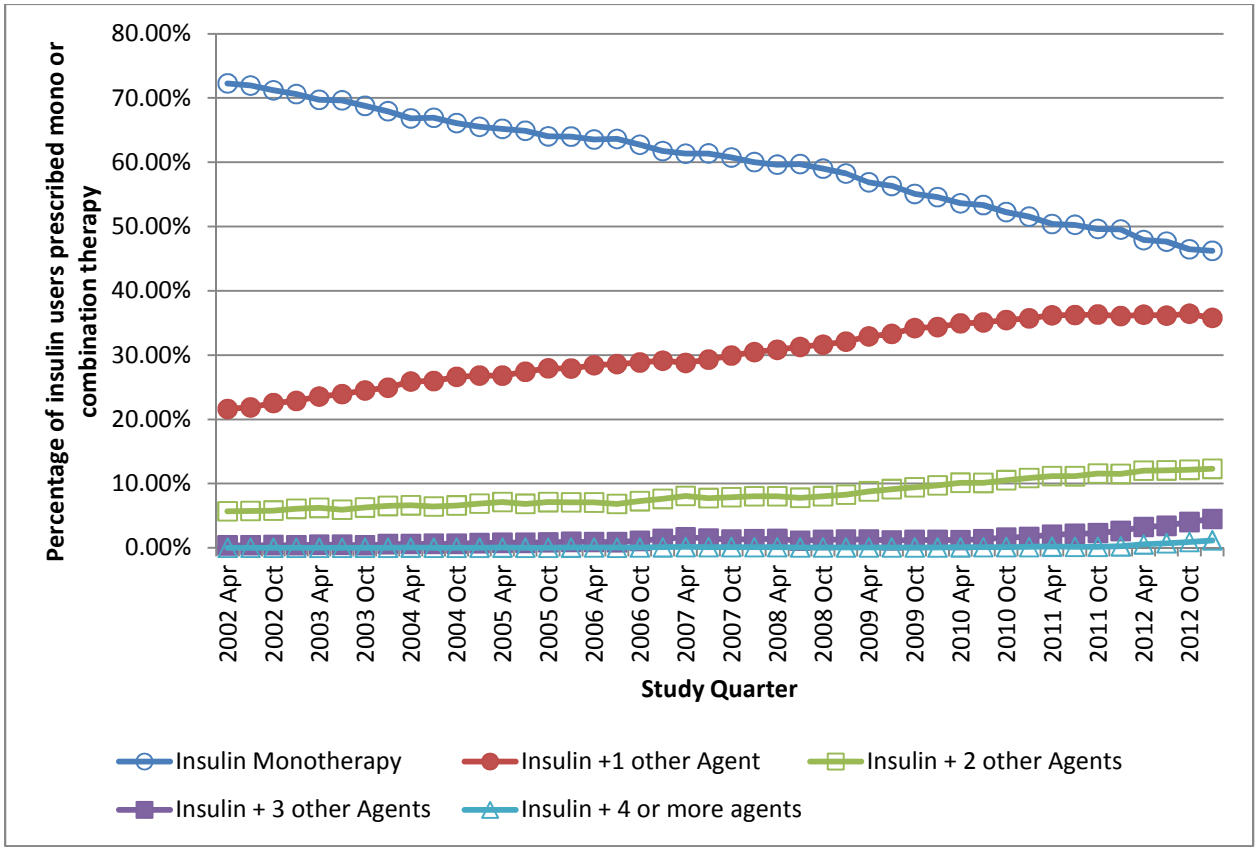
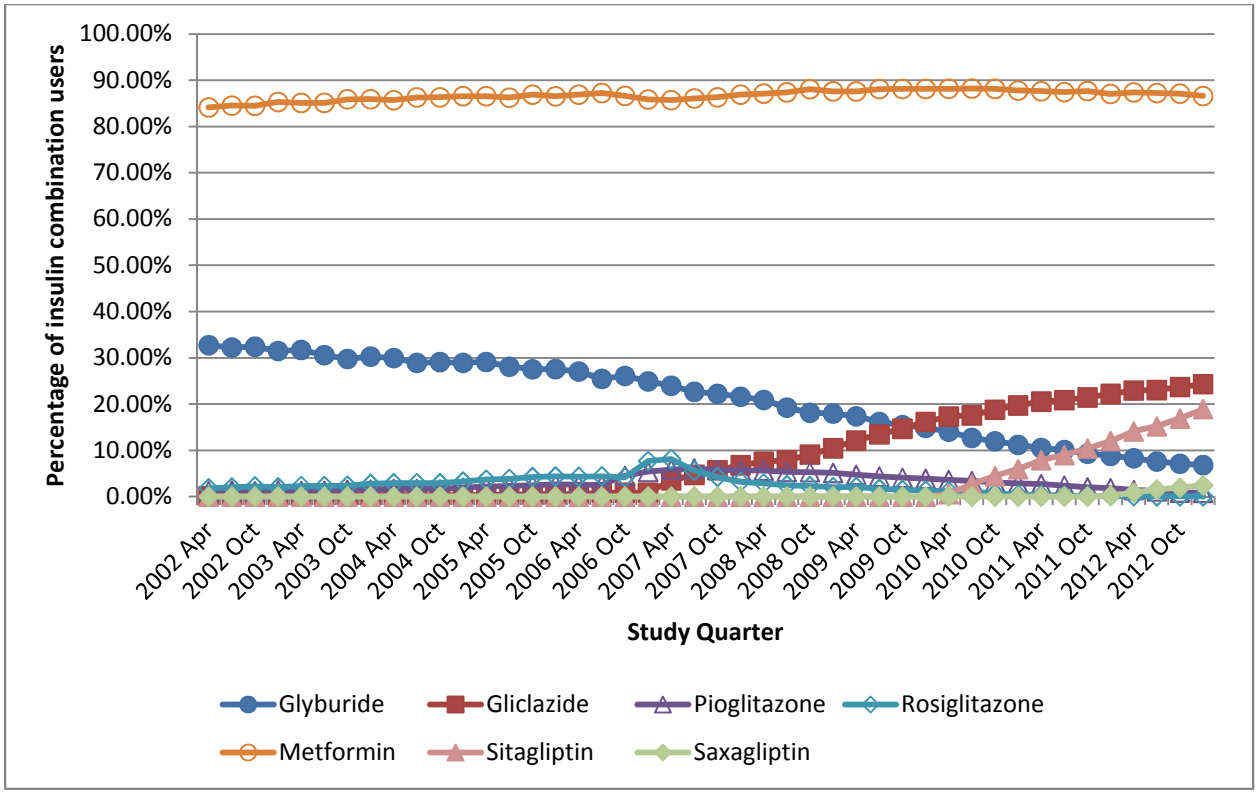
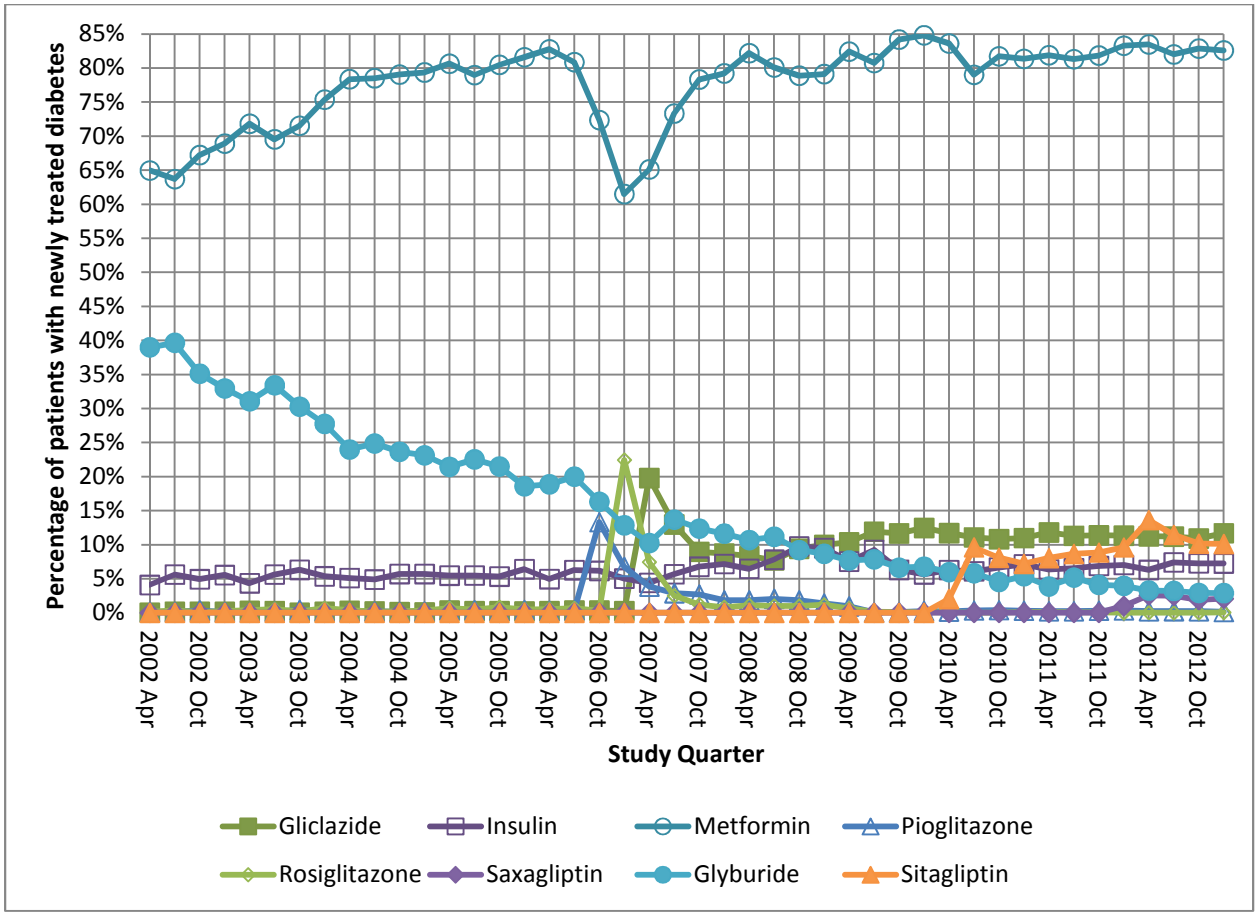


Figure 3. Oral antihyperglycemic medication prescriptions in insulin combination therapy users 2002-2013



*Drugs prescribed to less than 5% not illustrated (acarbose, acetohexamide, chlorpropamide, glimepiride, nateglinide, repaglinide, tolbutamide)

Figure 4. Antihyperglycemic medication prescriptions in patients with newly treated diabetes 2002-2013



*Drugs prescribed to less than 5% not illustrated (acarbose, acetohexamide, chlorpropamide, glimepiride, nateglinide, repaglinide, tolbutamide)

Figure 5. Mono and combination therapy in patients with newly treated diabetes 2002-2013

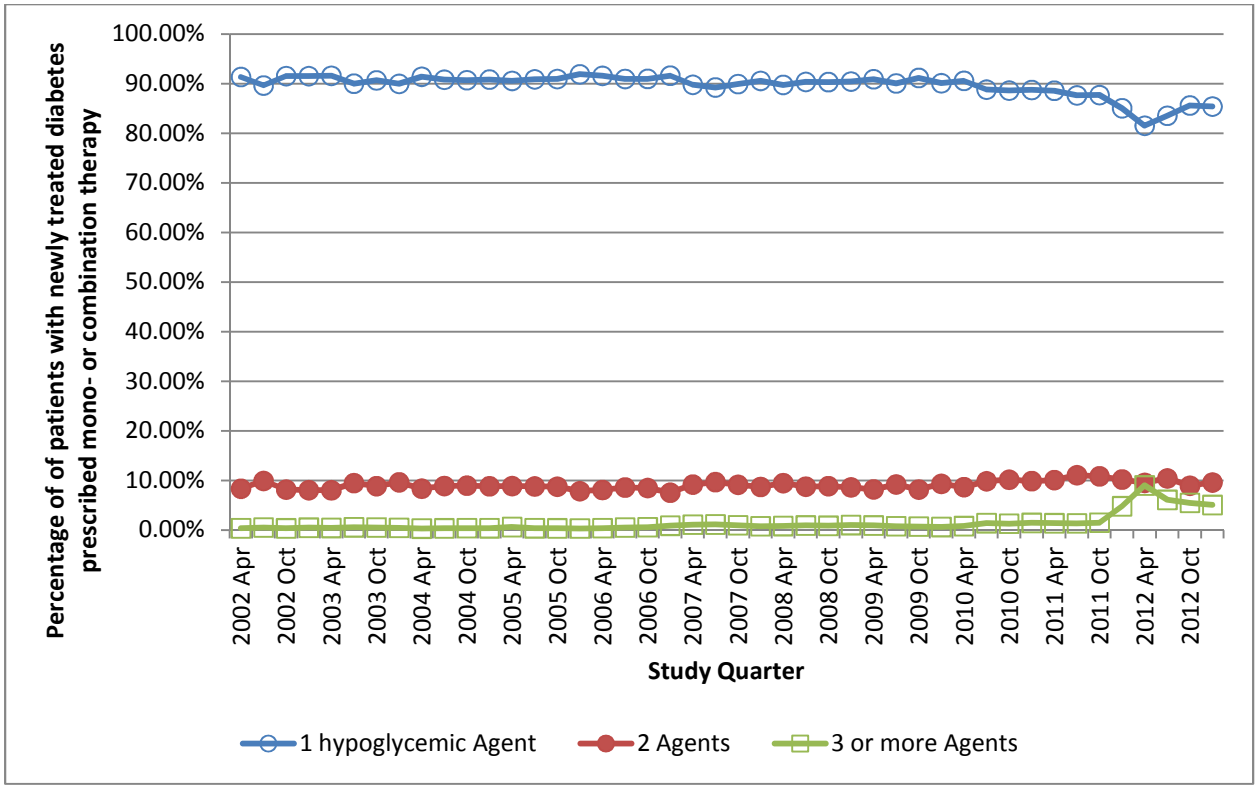
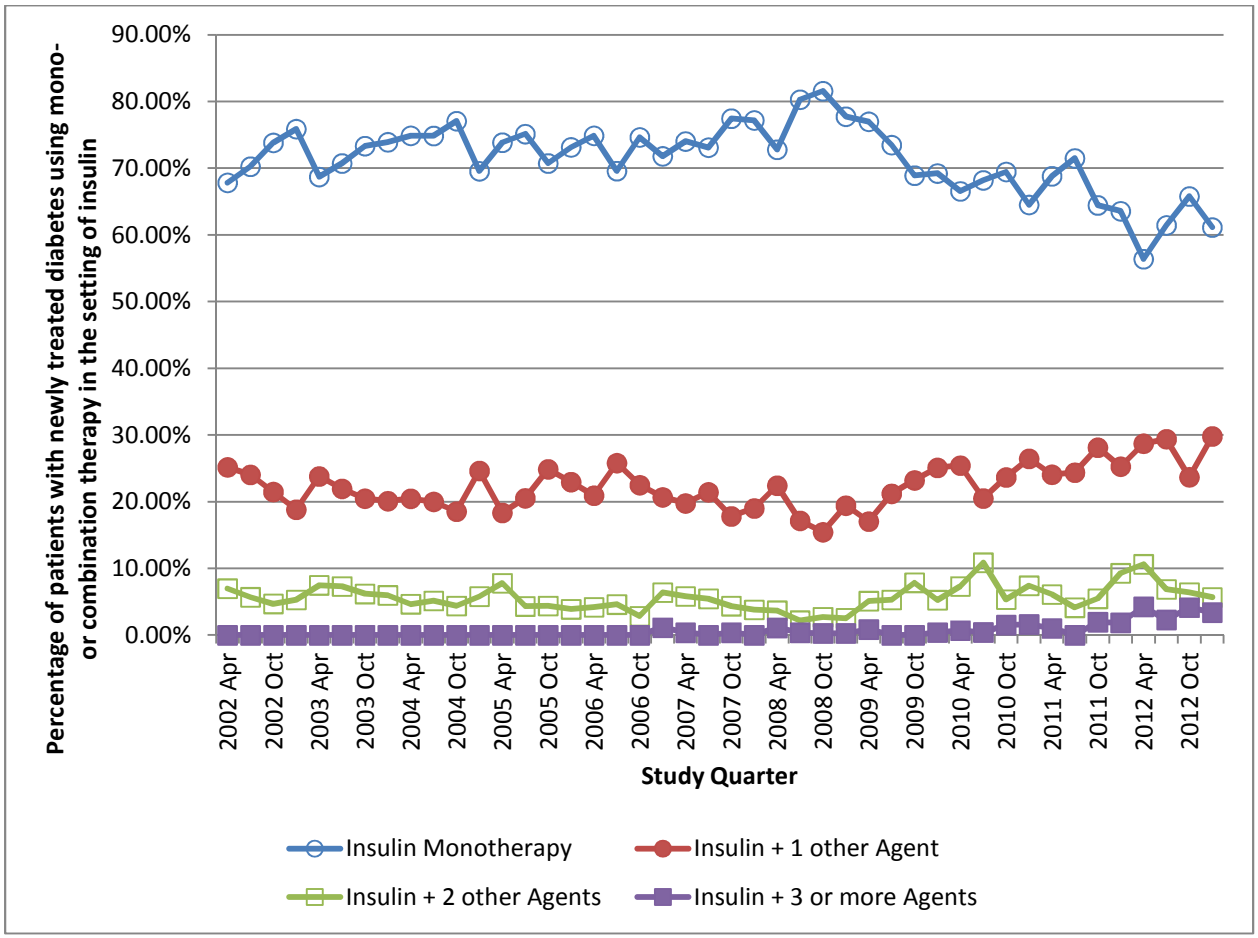


Figure 6. Insulin mono/combination therapy in patients with newly treated diabetes 2002-2013



Appendix E

Dataset Creation Plan for "Trends in Antihyperglycemic Medication Prescriptions and Hypoglycemia in Older Adults: 2002-2013"

TRIM Number of Study	
Research Program	KDT
Study Team (including contact information)	Kristin Clemens Amit Garg Salimah Shariff Kuan Liu Eric McArthur
Who will be responsible for DCP updates?	KC
PIA Approved?	Yes
DCP update history	Version 1 KC (July 21, 2014) Version 2 KC (July 29th, 2014 after meeting with S.S.) Version 3 KC (September 14th, 2014 after meeting with IH, SS and KL) Version 4 KC (October 16 2014 after feedback from faculty scholars session and meeting with AG, SS, KL) Trends DCP Updates.docx
Short Description of Research Question	Hypoglycemia is one of the most common acute complications of diabetes management. If severe it may result in hospital presentation, cardiovascular compromise, neurological dysfunction and even death. In the current project we will aim to examine trends in hypoglycemic agent drug use, demographics, comorbidities and hospital encounters for hypoglycemia in a cohort of adult diabetic patients from 2002 until 2013. To our knowledge such a detailed examination has not been carried out in our region previously. We anticipate that this project will help to provide insight into the changing diabetes population and their disease complications and help to improve the care of patients with this disease.
Study Design	Time series analysis
List of Datasets Used	**RPDB** (April 2002 to March 2013) **ODB** (April 2001 to March 2013) Population ☒ Age 65+

Is druglist with DIN & DCLASS provided in Appendix?
☒ Yes

CIHI-DAD (April 1997 to March 2013)
Source
☒ All
Institution types
☒ Acute care (insttype = 'AP' or 'AT')

Diagnosis Type (dxtype)
☒ All (alldx)

OHIP (April 1997 to March 2013)

Claim Type
☒ Nonlab
☒ Lab

Codes
☒ Fee codes
☒ Diagnostic codes

NACRS (April 1997 to March 2013)
Source
☒ Emergency Department visits
Include planned visits
☒No
Include suspected/questionable diagnoses?
☒ No

Gamma-Dynacare (April 2001-March 2013)

Dataset

☒ Southwestern Ontario
☒ All of Ontario

Type of test

☒ Serum creatinine '/home/sdixon/data/GD/fullSCr'
☒ Hemoglobin A1C – test number 093D

CERNER (April 2001-March 2012)
File name: /ices/CDP/cerner/cerner_apr99_dec10.sas7bdat
Type of test

☒ Serum creatinine (Test_Done="A")
☒ Hemoglobin A1C (Test Done="B")

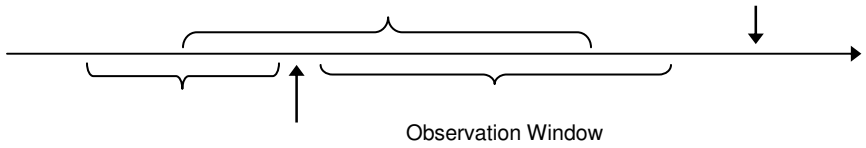
Hospital Stay
☒ Inpatient
☒ Emergency Room
☒ Outpatient

ODD (April 2002-March 2013)

Defining the Cohort

Cohort Inclusion/ Denominator (for each study interval)	For each 3 month interval, identify patients with diabetes as defined by the Ontario Diabetes Database) See Appendix C and D for variable definitions
Exclusions (to be applied during each study interval)	1. Missing or invalid IKN 2. Missing age or sex 3. Invalid ages (negative ages or age >105) 4. Death on or before the beginning of the study interval 5. Non Ontario residents (individuals without the RPDB variable "prdcddablk" beginning with "35") 6. Age □66 years at the beginning of the study interval

Time Frame Definitions



Accrual Start/End Dates	April 1, 2002-March 31, 2013
Study intervals	The 11 year (fiscal year) study will be divided into 44 intervals (each interval will be 3 months in duration) Thus, each fiscal year will be divided into 4 quarters, defined by calendar months Quarter 1: April, May, June Quarter 2: July, August, September Quarter 3: October November December Quarter 4: January February March
Look back Window(s)	1 year for baseline medications 5 years for comorbidities 1 year for laboratory data 1 year for investigations

Variable Definitions

Main Exposure/ Numerator	Users of at least one of the following study hypoglycemic agents during the study interval -Insulin -Acetohexamide -Chlorpropamide -Tolbutamide

	-Glyburide -Gliclazide -Glimepiride -Repaglinide -Nateglinide -Pioglitazone -Rosiglitazone -Metformin -Acarbose -Sitagliptin -Saxagliptin -Sitagliptin-Metformin *See Appendix B and C for drug list and DCLASS definitions
Baseline Characteristics (determine at the beginning of 3 study quarters – April 1, 2002, April 1, 2007, April 1, 2012)	We will determine the baseline characteristics of to examine if they remain similar over time. 1. Age 2. Sex 3. Income quintile 4. Rural location In the previous 5 years, evidence of the following: 1. Chronic kidney disease 2. Chronic liver disease 3. Cancer 4. Retinopathy 5. Neuropathy 6. Dementia 7. Stroke/TIA 8. Cardiovascular disease (excluding angina) 9. Congestive heart failure 10. Peripheral vascular disease For those with evidence of an HbA1c test in the 1 year previous (Gamma Dynacare OR CERNER): 1. Mean, SD, Median, IQR HbA1c *Note if multiple HbA1c tests for an individual, use the most recent value In the previous 1 year: 1. Mean, SD, median, IQR number of HbA1c tests 2. Mean, SD, median, IQR number cholesterol tests 3. Mean, SD, median, IQR number of creatinine tests 4. N (%) with at least one major eye exam/ophthalmology assessment

*See Appendix A for sample tables, B for drug lists and C and D for variable definitions

Outline of Analysis Plan

1. Cohort creation

- Apply inclusion and exclusion criteria during each interval to determine denominator for each interval (Sample Table 1)

2. Prescriptions

-Determine drug use for each interval (ie numerator). Examine this by individual DCLASS (Sample Table 2), number of hypoglycemic agent drugs prescribed (Sample Table 3), number of NEW drug users (Sample Table 4) where NEW hypoglycemic agent users are those with no evidence of ANY study hypoglycemic agent prescription in the previous 1 year

-For NEW hypoglycemic agent users, examine also the number of hypoglycemic agent drugs prescribed during the interval (Sample Table 13)

-**Notes**: For those prescribed sitagliptin-metformin combination, count a script for each DCLASS separately (ie. patient prescribed sitagliptin-metformin will have evidence of a prescription for both sitagliptin and for metformin)

For calculation of general drug prescription rate, make denominator those prescribed hypoglycemic agents rather than the entire diabetic population (see Table 2 amendments)

-For insulin users, examine number of other hypoglycemic agents prescribed (Table 11)

-For those on insulin combination therapy (ie evidence of insulin and at least 1 other hypoglycemic agent during the interval) show rates of other DCLASS prescriptions (Table 12)

2. **Baseline characteristics** Show number and proportion with the characteristics listed in Appendix C at the beginning of 3 study intervals (April 1, 2002, April 1, 2007, April 1, 2012) for all diabetics (Table 6), for those prescribed at least one hypoglycemic agent (Table 9), and for NEW hypoglycemic agent users (Table 10)

3. Hypoglycemia

Examine hospital encounters for hypoglycemia for each study interval. Show the total number of hypoglycemic events during each interval (Sample Table 7)

For the calculation of hypoglycemia rate, change denominator to those prescribed any hypoglycemic drug during the interval rather than the entire diabetic population

*Note: Definitions of hypoglycemic events outlined in Appendix D

Appendix

Appendix A – Sample Tables

Trends Tables.xlsx

Appendix B – Drug Lists

Trends Druglist.xlsx

Appendix C – Variable Definitions

TrendsBaselines.txt

Appendix D – Variable Tables

Table 1. Denominator Definition

Characteristic	Dataset Used	Other details
Diabetes with at least one hypoglycemic agent prescription (ie. diabetes drug users)	ODD ODB	

Table 2: Study Medications

Medication Name	DCLASS
Insulin	S_INS
Glyburide	S_GLY
Gliclazide	S_GLI
Repaglinide	S_REP
Metformin	S_MET
Pioglitazone	S_PIO
Rosiglitazone	S_ROS
Acarbose	S_ACA
Sitagliptin -Metformin	S_SIM
Sitagliptin	S_SIT
Saxagliptin	S_SAX
Tolbutamide	S_TOL
Acetohexamide	S_ACT
Chlorpropamide	S_CHL
Glimepiride	S_GLM

Nateglinide	S_NAT

Table 3. Baseline Characteristics

Characteristic	Dataset Used	Other details
Year of index date		
Age	RPDB	Mean, SD, Median, IQR, 66-69, 70-74, 75-79, 80-84, 85-89, ≥90
Sex	RPDB	
Income quartile	PSTLYEAR %getdemo	1, 2, 3, 4, 5, missing
Residential status	PSTLYEAR %get demo	Rural, urban, missing
CKD	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	For main cohort only Report as N (%)
Retinopathy	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	

Dementia	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)
Liver Disease	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)
Coronary artery disease (excluding angina)	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No	Report as N (%)

	OHIP Claim Type ☒ NONLAB	
Stroke/TIA	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)
Peripheral Vascular Disease	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)
Cancer	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source	Report as N (%)

	☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	
Neuropathy	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)
CHF	CIHI-DAD Source ☒ All Institution types ☒ Acute care (insttype = 'AP' or 'AT') Include suspected/questionable diagnoses? ☒ No NACRS Source ☒ Emergency Department visits Include planned visits ☒ No OHIP Claim Type ☒ NONLAB	Report as N (%)

HbA1c value	**Gamma-Dynacare** Dataset ☒ Southwestern Ontario ☒ All of Ontario Type of test ☒ Hemoglobin A1C – test number 093D **CERNER** File name: /ices/CDP/cerner/cerner_apr99_dec10.sas7bdat Type of test ☒ Hemoglobin A1C (Test Done=”A”) Hospital Stay ☒ Inpatient ☒ Emergency Room ☒ Outpatient	Report as mean, SD, median, IQR
HbA1c test	**OHIP** Claim Type ☒ All Code Types ☒ Feecodes	Report as mean, SD, median, IQR
Cholesterol test	**OHIP** Claim Type ☒ All Code Types ☒ Feecodes	Report as mean, SD, median, IQR
Creatinine test	**OHIP** Claim Type ☒ All Code Types ☒ Feecodes	Report as mean, SD, median, IQR
Glucose test	**OHIP** Claim Type ☒ All Code Types ☒ Feecodes	Report as mean, SD, median, IQR
Major eye exam/optho assessment	**OHIP** Claim Type ☒ All Code Types ☒ Feecodes	Report as N(%)

Curriculum Vitae

Name: Kristin Clemens

Post-secondary Education and Degrees:

Western University
London, Ontario, Canada
2000-2004 BSc Biology

Western University
London, Ontario, Canada
2004-2008 MD

Western University
London, Ontario, Canada
2008-2011 Internal Medicine Residency

Western University
London, Ontario, Canada
2011-2013 Endocrinology and Metabolism Fellowship

Western University
London, Ontario, Canada
2014-Present Research Fellow Clinical Investigator Program/
ICES Faculty Scholars Program

Western University
London, Ontario, Canada
2014-Present MSc Candidate Epidemiology

Honours and Awards:

First Poster Prize Diabetes Research Day – London Ontario
2014

PSI Foundation Resident Research Prize
2014

Class of 55 Prize
2008

JB Campbell Scholarship in Medicine
2008

Gold Medal Biology
2004

Frederick N Lewis Prize
2002

Dean's List Biology
2000-2004

Publications:

1.Clemens KK, McArthur E, Dixon SN, Fleet JL, Hramiak I, Garg AX. The hypoglycemic risk of glyburide (glibenclamide) compared with modified release gliclazide. *Can J Diabetes*. 2015 Mar 31. pii: S1499-2671(15)00027-1. doi: 10.1016/j.jcjd.2015.01.001. [Epub ahead of print]

2. Clemens KK, McArthur E, Fleet JL, Hramiak I, Garg AX. The risk of pancreatitis with sitagliptin therapy in older adults: a population-based cohort study. *CMAJ Open* 2015; 3: E172-181.

3. Shih AW, Weir MA, Clemens KK, Yao Z, Gomes T, Mamdani MM, Juurlink DN, Hird A, Hodsman A, Parikh CR, Wald R, Cadarette SM, Garg AX. Oral bisphosphonate use in the elderly is not associated with acute kidney injury. *Kidney Int*. 2012; 82(8): 903-8.

4. Clemens K, Van Uum S. A pituitary mass as consequence of a decimal error in levothyroxine dose. *CMAJ.* 2012; 184: 210.

5. Kitchlu A, Clemens K, Gomes T, Hackam DG, Juurlink DN, Mamdani M, Manno M, Oliver MJ, Quinn RR, Suri RS, Wald R, Yan AT, Garg AX. Beta blockers and cardiovascular outcomes in dialysis patients: a cohort study in Ontario, Canada. *Nephrology Dialysis Transplantation.* 2011; 27(4): 1591-8.

6. Clemens K, Payne W, Van Uum SH. Central hypothyroidism. *Canadian Family Physician.* 2011; 57: 677-680.

7. Clemens KK, Boudville N, Dew MA, Geddes C, Gill JS, Jassal V, Klarenbach S, Knoll G, Muirhead N, Prasad GV, Storsley L, Treleaven D, Garg A; Donor Nephrectomy Outcomes Research (DONOR) Network. The long term quality of life of living kidney donors: a multicentre cohort study. *American Journal of Transplantation.* 2011; 11: 463-469.

8. Moody EM, Clemens KK, Storsley L, Waterman A, Parikh CR, Garg AX; Donor Nephrectomy Outcomes Research (Donor) Network. Improving online information for potential living kidney donors. *Kidney International.* 2007; 71: 1062-70.

9. Clemens KK, Thiesen-Philbrook H, Parikh CR, Yang RC, Karley ML, Boudville N, Ramesh Prasad GV, Garg AX; Donor Nephrectomy Outcomes Research (Donor) Network. Psychosocial health of living kidney donors: a systematic review. *American Journal of Transplantation.* 2006; 6: 2965-77.