A Retrospective Evaluation of Prescribing Practices Related to
Intensity of Glycemic Control among Older Adults with Type-2
Diabetes across Canada

by

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ABSTRACT

Background: Diabetes is highly prevalent among the elderly population. Optimal glucose management in this cohort remains ill-defined with high-quality evidence lacking and hypoglycemia risk a significant concern. The extent of overtreatment in Canada is not clearly established.

Methods: This retrospective observational cohort study was conducted using primary care data between 2010-2017 from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) to assess proportions of over-treatment among patients with type-2 diabetes across Canada (phase-I). A further detailed analysis was performed using administrative population-based data of the Manitoba Centre for Health Policy (MCHP) to assess over-treatment in Manitoba (phase-II). Number of overall medications and annual HbA1c testing frequency were also assessed as a measure of burden. SAS® statistical software was used for the analyses.

Results: Using CPCSSN data, overall rates of over-treatment were 7.0% in 2012 and 6.9% in 2016, while rates were significantly higher (20.4% (2012), 21.5% (2016)) using MCHP data. A considerable proportion with poorly-controlled diabetes ((41.9% (2012), 35.8% (2016) in phase-I) and (19% in 2012 & 10.5% in 2016 in phase-II)) were prescribed no medications, indicating under-treatment. The mean number of overall medications prescribed per patient was 4.4 (SD ± 4.5) in 2012 and 5.1 (SD ± 4.9) in 2016, and 39% and 41% were prescribed ≥5 medications in 2012 and 2016, respectively. Approximately 19% of patients were potentially over-tested, while just over 2% were potentially under-tested. Rates of over-treatment and over-testing were higher in those with advanced age and those with dementia.
**Conclusions:** Potential over-treatment rates in this Canadian primary care population appeared lower compared to US studies. However, rates were found to be significantly higher in Manitoba using dispensation data compared to provincial & national primary care prescription data, with no evidence of rates decreasing over time. In contrast, there was a considerable proportion of poorly controlled patients who were potentially undertreated. Patients with advanced age and dementia appear to be over-treated and tested. These findings indicate a need for individually tailored personalized diabetes management in Canada.
This thesis has been written in a grouped manuscript style, sometimes referred to as a sandwich thesis. It composed of three manuscripts (to be submitted for publication), supplemented with additional writings, that have been organized and expounded upon to create a cohesive, comprehensive document. The first chapter deals with the introduction and literature review, followed by the methods chapter. While, chapters 3, 4 and 5 represent the original research project as it was conceived, proposed and conducted from the beginning of my graduate studies. The final chapter summarizes the findings of the thesis and discusses their implications. This thesis follows the AMA (American Medical Association) citation style.

Overall, it is the hope that this thesis has accomplished two things. First, this research work herein is an important contribution to the fields of pharmacoepidemiology and pharmacy practice as they relate to the diabetes and its management. Second, that the original research conducted in the Canadian & Manitoban population may be of certain use (directly or indirectly) to academics, health professionals and policy-makers in Canada to improve upon the management strategies and decisions.
I got the unique opportunity to have two advisors during the course of my research, and I offer my sincerest gratitude to my advisor Dr. Jamie Falk and co-advisor Dr. Shawn Bugden, for being patient & supportive, and for providing valuable expert insights at various stages of the thesis. I would also like to express special thanks to my advisory committee members i.e., Dr. Christine Leong and Dr. Alexander Singer, for their support and guidance during my research journey at the College of Pharmacy, University of Manitoba.

I also would like to acknowledge CPCSSN and MCHP databases for providing me with the necessary data and letting me conduct this research work.

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Lastly, I thank my parents (Siva Rama Koteswara Rao & Jaya Lakshmi), sister (Sai Chaitanya), brother-in-law (Kiran), nephew (Sai Aayansh) and of course my dear lovely wife (Komal Krishna) for their love, support, and encouragement that continues to carry me forward in life. I couldn’t do this without you people.
This thesis is dedicated to my Dad.

“G.S.R Koteswara Rao”

My super-hero forever...!
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List of Abbreviations

ACCORD – Action to Control Cardiovascular Risk in Diabetes trial
ACP – American College of Physicians
ADA – American Diabetes Association
ADL – Activities of Daily Living
ADVANCE – Action in Diabetes and Vascular Disease: preterAx and diamicron mr Controlled Evaluation trial
ATC – Anatomical therapeutic chemical classification system
BG – Blood Glucose
CDA – Canadian Diabetes Association
CHF – Congestive Heart Failure
CI – Confidence interval
CIHI – Canadian Institute for Health Information
COPD – Chronic Obstructive Pulmonary Disease
CPCSSN – Canadian Primary Care Sentinel Surveillance Network
CVD – Cardio-Vascular Disease
DPP-4 – Di Peptidyl Peptidase-4
EMR – Electronic Medical Record
FBG – Fasting Blood Glucose
FPG – Fasting Plasma Glucose
GI – Gastro Intestinal
GLP-1 – Glucagon-Like Peptide-1
GPs – General Practitioners
HbA1c – Glycosylated Hemoglobin
HIPC – Health Information Privacy Committee
HR meds – High-Risk medications
HR – Hazard Ratio
HRQoL – Health-Related Quality of Life
ICD – International classification of diseases
IDF – International Diabetes Federation
JAMA – Journal of the American Medical Association
LDL-C – Low Density Lipoprotein Cholesterol
MaPCReN – Manitoba Primary Care Research Network
MCHP – Manitoba Centre for Health Policy
MEN 2 – Multiple Endocrine Neoplasia type-2
Mmol/L – Milli mole/litre
NHANES – Health and Nutrition Examination Survey
NOS – Nitric Oxide Synthase
NPH – Neutral Protamine Hagedorn
OGTT – Oral Glucose Tolerance Test
OHAs – Oral Hypoglycemic Agents
OR – Odds Ratio
OT – Over-Treatment
QALYs – Quality Adjusted Life Years
RCTs – Randomized Controlled Trials
RECAP-DM – Real-Life Effectiveness and Care Patterns of Diabetes Management
SAS – Statistical Analysis Software
SD – Standard Deviation
SGLT-2 – Sodium Glucose co-transporter-2
TZD – Thiazolidinedione
US – United States
UTI – Urinary Tract Infection.
VA – Veterans Affairs
VADT – Veterans Affairs Diabetes Trial
WHO – World Health Organization
Chapter 1 – Introduction

1.1 A Review of Diabetes

1.1.1 Definition

The Canadian Diabetes Association (CDA) defines diabetes as a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both [1]. Similarly, the World Health Organization (WHO) defines it as a chronic, metabolic disease characterized by elevated levels of blood glucose leading over time to serious damage to the heart, blood vessels, eyes, kidneys, and nerves [2].

1.1.2 Classification

According to the American Diabetes Association (ADA), diabetes can be classified as the following types: [3]

<table>
<thead>
<tr>
<th>TYPE</th>
<th>DIAGNOSIS OF DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type-1 diabetes</td>
<td>Primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.</td>
</tr>
<tr>
<td>Type-2 diabetes</td>
<td>It may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>Refers to glucose intolerance with onset or first recognition during pregnancy.</td>
</tr>
</tbody>
</table>
Includes a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use.

Adapted from: American Diabetes Association Diagnosis and classification of diabetes mellitus

Diabetes Care 35 suppl 1 2012 S64 S71.

1.1.3 Epidemiology

The prevalence of type-2 diabetes is increasing worldwide and is a leading cause of morbidity and mortality. The proportion of individuals living with diabetes globally has risen from 108 million in 1980 to 422 million in 2014. In 2015, the estimated prevalence of diabetes in Canada was 9.3% (3.4 million), and is predicted to rise to 12.1% (5 million) by 2025, representing a 44% increase [4]. In 2008, 1 in 10 deaths among Canadian adults was attributed to diabetes. The economic burden of diabetes in Canada was estimated at $11.7 billion in 2010 and is expected to reach $16 billion by 2020 [1]. It can also import considerable economic loss to people with diabetes & their associated families, and to the healthcare systems through direct medical costs and loss of work and wages [2].

According to the CDA, 57% of Canadians with diabetes reported that they could not adhere to prescribed treatment due to the high cost of needed medications, devices, and supplies. People with diabetes are 12 times more likely to be hospitalized with end-stage renal disease, have a 3-fold risk of hospitalization with cardiovascular diseases, and are over 20 times more likely to be hospitalized for a non-traumatic lower limb amputation when compared to the general population [5]. Among the geriatric population, diabetes contributes to 40% of heart attacks, 50% of kidney failure, 30% of strokes, and 70% of non-traumatic lower limb amputations [6].
1.1.4 Risk Factors

As type-2 diabetes is, in large part, a lifestyle-related disease, its incidence is dramatically increasing in populations who undergo westernization of their lifestyle [7]. Several studies suggest that there exists a strong positive correlation between higher levels of physical activity and a reduced incidence of type-2 diabetes [8]. This association was independent of obesity, alcohol consumption, lipoprotein concentrations, and other factors that predicted the increase of risk of type-2 diabetes. Type-2 diabetes and dyslipidemia are two components of the insulin-resistance syndrome of obesity, hypertension, glucose intolerance, and hyperinsulinemia [9]. Being overweight or obese is also an important risk factor for diabetes, and most of the Canadians in this category could increase the prevalence of diabetes [10]. Other risk factors may include family history, cigarette smoking, and stress [11, 12].

1.1.5 Diagnosis

Diabetes can be diagnosed by any of the following criteria: [1]

<table>
<thead>
<tr>
<th>TEST</th>
<th>DIAGNOSIS OF DIABETES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Plasma Glucose (FPG)</td>
<td>≥7.0 mmol/L</td>
</tr>
<tr>
<td>Glycosylated Hemoglobin (HbA1c)</td>
<td>≥6.5% (in adults)</td>
</tr>
<tr>
<td>Oral Glucose Tolerance Test (OGTT)</td>
<td>≥11.1 mmol/L (2hPG)</td>
</tr>
<tr>
<td>Random Plasma Glucose</td>
<td>≥11.1 mmol/L</td>
</tr>
</tbody>
</table>

1.1.6 Complications

If left untreated or improperly managed, increased plasma glucose can cause a variety of potentially life-threatening complications, which can be categorized into macrovascular and microvascular complications.

Macrovascular Complications

i. **Cardiovascular Diseases:** People with diabetes are at higher risk of developing heart diseases, including hypertension, atherosclerosis, and coronary artery disease compared to those without diabetes.

ii. **Cerebrovascular Diseases:** People with diabetes are at 2 to 4 fold increased risk of developing cerebrovascular events, including transient ischemic attack and cerebrovascular accidents compared to those without diabetes.

Microvascular Complications

i. **Retinopathy:** Elevated plasma glucose levels lead to endothelial/vascular dysfunction that impairs anti-thrombin-III, eventually blocking small blood vessels of the retina. The blood supply is cut off which can lead to the formation of scar tissue or possible retinal detachment (retinal angiogenesis) and can result in blindness if not addressed.

ii. **Nephropathy:** Long-term elevation of plasma glucose can lead to damage to the nephrons which could potentially interrupt the filtering system of the kidneys. Almost one in every three people who have diabetes for more than 15 years are at higher risk of developing kidney disease, and around 40% of those with diabetic nephropathy develops end-stage renal disease requiring dialysis [13].
iii. **Neuropathy**: Hyperglycemia damages the nerve cells in the peripheral nervous system, which may result in pain, numbness, and infections. Neuropathy is considered the leading cause of non-traumatic lower extremity amputations [14].

Approximately 10% of acute care hospital admissions in Canada are related to diabetes and its secondary complications. However, optimal diabetes care and management can prevent or delay the onset of these complications [1].

**1.1.7 Management of Type-2 Diabetes**

For those with HbA1c <1.5% above their individualized target, the Canadian Diabetes Association suggests initiating anti-hyperglycemic pharmacotherapy if within 3 months of initiating healthy behaviour and lifestyle interventions their target has not been achieved. In patients with type-2 diabetes with HbA1c ≥1.5% above target, anti-hyperglycemic medications should be initiated along with lifestyle modifications and should consider initiating the combination therapy with two agents, one of which may be insulin in order to attain target glycated hemoglobin within 3 to 6 months. However, there is limited evidence to support this degree of treatment urgency and intensification considering the foundational importance of durable lifestyle change and the significant delay in onset of diabetes complications for the vast majority of patients [15]. Metformin should be considered as the initial choice unless contraindicated, with the choice of second-line anti-hyperglycemic agents selected based on clinically relevant issues, such as glucose-lowering effectiveness, ability to reduce long-term complications, contraindications to a drug, risk of hypoglycemia and effect on body weight. In people receiving an anti-hyperglycemic regimen containing insulin, in whom glycemic targets are not achieved, it is recommended that the addition of a GLP-1 receptor agonist, DPP-4 inhibitor or SGLT2 inhibitor may be considered
before adding or intensifying prandial insulin therapy to improve glycemic control with less weight gain and comparable or lower hypoglycemia risk. Figure 1 depicts the flow of management strategies of type-2 diabetes in detail [1].
<table>
<thead>
<tr>
<th>Class*</th>
<th>Effect on CVD outcomes</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Relative A1C lowering when added to metformin</th>
<th>Other therapeutic considerations</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 receptor agonists</td>
<td>Ira: Superiority in people with type 2 diabetes with clinical CVD exenatide LAR &amp; lixisenatide Neutral</td>
<td>Rare</td>
<td>↓ ‡</td>
<td>↓ ‡ ‡ to ↓ ‡ ‡</td>
<td>GI side-effects, Gallstone disease</td>
<td>$$$$</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>Cana &amp; empagliflozin: Superiority in people with type 2 diabetes with clinical CVD</td>
<td>Rare</td>
<td>↓ ‡</td>
<td>↓ ‡ ‡ to ↓ ‡ ‡</td>
<td>Genital infections, UTI, hypotension, dose-related changes in LDL-C. Caution with renal dysfunction, loop diuretics, in the elderly. Dapagliflozin not to be used if bladder cancer. Rare diabetic ketoacidosis may occur with no hyperglycemia, increased risk of fractures and amputations with canagliflozin. Reduced progression of nephropathy and CHF hospitalizations with empagliflozin and canagliflozin in persons with clinical CVD.</td>
<td>$$$</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
<td>Neutral (alo, saxagliptin, sitagliptin)</td>
<td>Rare</td>
<td>Neutral</td>
<td>↓ ‡</td>
<td>Caution with saxagliptin in heart failure Rare joint pain</td>
<td>$$$</td>
</tr>
<tr>
<td>Insulin</td>
<td>Glarg: Neutral degludec: noninferior to glarg</td>
<td>Yes</td>
<td>↑ ‡</td>
<td>↓ ‡ ‡ to ↓ ‡ ‡</td>
<td>No dose ceiling, flexible regimens Requires subcutaneous injection</td>
<td>$- $$ $$ $$ $$</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Neutral</td>
<td>Rare</td>
<td>↑ ‡</td>
<td>↓ ‡</td>
<td>CHF, edema, fractures, rare bladder cancer (pioglitazone), cardiovascular controversy (rosiglitazone), 6-12 weeks required for maximal effect</td>
<td>$$</td>
</tr>
<tr>
<td>Alpha-glucosidase inhibitors (acarbose)</td>
<td>Neutral</td>
<td>Rare</td>
<td>Neutral</td>
<td>↓</td>
<td>GI side-effects common Requires 3 times daily dosing</td>
<td>$</td>
</tr>
<tr>
<td>Insulin secretagogue: Meglitinide</td>
<td>Yes</td>
<td>↑</td>
<td>↓ ‡</td>
<td>↓ ‡</td>
<td>More rapid BG-lowering response Reduced postprandial glycemia with meglitinides but usually requires 3 to 4 times daily dosing Gliclazide and glimepiride associated with less hypoglycemia than glyburide Poor durability</td>
<td>$$</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>Yes</td>
<td>↑</td>
<td>↓ ‡</td>
<td>↓ ‡</td>
<td>GI side effects Requires 3 times daily dosing</td>
<td>$</td>
</tr>
<tr>
<td>Weight loss agent (orlistat)</td>
<td>None</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>$$$</td>
</tr>
</tbody>
</table>

* Listed by CV outcome data

If not at glycemic targets

Add another antihyperglycemic agent from a different class and/or add/intensify insulin regimen

**Make timely adjustments to attain target A1C within 3-6 months**
1.2 Literature Review: Diabetes Care in Older Adults

1.2.1 Diabetes and Older Adults

Older adults represent the most vital demographic change affecting diabetes prevalence across the world [2]. Even if incidence rates were to remain stable, because of the growing number of seniors, the overall prevalence of diabetes would increase [1]. The higher prevalence of diabetes among the elderly is observed in both genders across various racial and ethnic groups. Among older populations, the incidence of type-2 diabetes is reaching epidemic proportions. In the near future, older adults might form the majority of patients with type-2 diabetes among most developed countries. There are many proposed reasons for the increase in diabetes prevalence with the aging process. These include sedentary lifestyle, cultural factors [16], age-related changes in insulin action and secretion [17], inflammatory and hormonal dysregulation [18, 19], genetic factors [20], changes in sleep pattern [21, 22], increased oxidative stress [23] and increased use of medications that increase hyperglycemic propensity. Various organ systems are affected during the aging
process with significant consequences on diabetes risk [24]. As is the case with younger populations, diabetes in the elderly is commonly associated with complications such as micro- and macro-vascular diseases [25]. Elderly patients with diabetes are at higher risk of morbidity and mortality than non-diabetic populations. However, older people with diabetes pose unique challenges as they are also at high risk for functional decline, polypharmacy, cognitive impairment, depression, limited life-expectancy, and increased risk of falls [26].

In 2012 in Canada, nearly two-thirds (65.9%) of seniors had claims for 5 or more drug classes, and more than one-quarter (27.2%) of seniors had claims for 10 or more drug classes [5]. Furthermore, the number of drugs used by the senior population increases with age. The Canadian Deprescribing Network has set the lofty goal of reducing unnecessary and inappropriate medication use in seniors by 50 percent by 2020 [27]. It also focused its efforts on major classes of medications among older adults that are the most overused, misused, and potentially harmful such as benzodiazepines, proton pump inhibitors, anti-diabetics, antipsychotics, and statins.

Unfortunately, optimal diabetes management among the elderly is hampered by a lack of high-quality evidence. Therefore, it is essential to develop evidence-based strategies in the management of diabetes among the geriatric population in order to enhance their quality of life.

1.2.2 Glycemic Targets among Older Adults

Several landmark studies specifically addressed the question of optimal glycemic targets in the general type-2 diabetes population. However, the findings of these major RCTs on the benefits of intensive treatment is controversial. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, out of 10,251 study participants, patients with median HbA1c of 8.1% were assigned to receive intensive therapy (i.e., targeting an HbA1c below 6.0%) or standard therapy
(i.e., targeting an HbA1c from 7.0 to 7.9%) [28]. The primary outcome of this trial was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. However, the finding of higher mortality (hazard ratio 1.22, 95% CI 1.01 to 1.46, P=0.04) in the intensive-therapy group led to the discontinuation of intensive therapy after a mean of 3.5 years of follow-up. Their study findings concluded that the use of intensive therapy to target normal HbA1c for 3.5 years increased mortality and did not significantly reduce major cardiovascular events [28]. In other major trials, the rates of hypoglycemia and weight gain were significantly higher in the groups receiving intensive therapy [28-30]. When conventional treatment (i.e., targeting FPG <15 mmol/l) was compared with intensive treatment (i.e., targeting fasting plasma glucose < 6 mmol/l), a statistically significant reduction (25%) of overall microvascular complication rate was observed with intensive glycaemic control in the United Kingdom Prospective Diabetes Study [31]. However, within this composite microvascular outcome, no hard outcomes, including impaired vision, amputation, or end-stage renal disease were significantly reduced [31].

In the Action in Diabetes and Vascular Disease: preterAx and diamicron MR Controlled Evaluation (ADVANCE) trial, out of 11,140 participants with a follow-up of 5 years, the mean HbA1c was lower in the intensive-control group (use of gliclazide plus other drugs as required to achieve a glycated hemoglobin value of 6.5% or less) with 6.5% compared to the standard-control group with 7.3% [29]. Intensive control reduced the incidence of combined major macrovascular and microvascular events (18.1% vs. 20.0%; hazard ratio, 0.90; 95% CI, 0.82 to 0.98) and (9.4% vs. 10.9%; hazard ratio, 0.86; 95% CI, 0.77 to 0.97) respectively, but none of the individual hard outcomes were statistically significantly reduced. A reduction in the incidence of nephropathy was observed (4.1% vs. 5.2%; hazard ratio, 0.79; 95% CI, 0.66 to 0.93; P = 0.006), but was driven primarily by a reduction in macro-albuminuria, and no significant effect on retinopathy was
observed (P = 0.50). However, significantly more severe hypoglycemia events were observed in the intensive-control group (2.7%, vs. 1.5% in the standard-control group; hazard ratio, 1.86; 95% CI, 1.42 to 2.40; P<0.001) [29].

In the Veterans Affairs Diabetes Trial (VADT), 1,791 participants were followed for a median of 5.6 years with a primary outcome of first occurrence of a major cardiovascular event, a composite of myocardial infarction, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene [30]. Their findings showed that the median HbA1c was 8.4% in the standard-therapy group (half of the maximal doses of metformin plus rosiglitazone; or glimepiride plus rosiglitazone) and 6.9% in the intensive-therapy group (maximal doses of metformin plus rosiglitazone; or glimepiride plus rosiglitazone). There was no significant difference observed between the two groups in any component of the primary outcome and microvascular complications (hazard ratio, 1.07; 95% CI, 0.81 to 1.42; P = 0.62). However, they noticed severe hypoglycemia events in 17.6% of the standard-therapy group and in 24.1% of the intensive-therapy group [30].

Several meta-analyses evaluated the effect of intensive glucose lowering in people with diabetes. Their findings suggested that there exists a lack of benefit of intensive glucose lowering treatment on all-cause mortality and deaths from cardiovascular causes [33]. A small reduction in non-fatal myocardial infarction (7 events saved per 1000) was found as was a small reduction in amputations (4 events saved per 1000) [33]. However, targeting intensive glycaemic control significantly increased the risk of severe hypoglycemia (35 events more per 1000) (RR 2.18, 95% CI 1.53 to 3.11; 28,794 participants, 12 trials) [33]. As a result, the risk-benefit ratio of intensive glucose lowering treatment in the prevention of diabetic complications remained uncertain [32, 33].
However, the majority of patients in these RCTs and the subsequent meta-analyses were younger patients with diabetes. Specifically, the United Kingdom Prospective Diabetes Study excluded patients > 65 years old and the ACCORD, VADT and ADVANCE trials excluded those > 80 years old, with a resultant mean age in the Cochrane review of 62 years [33]. Thus, their results may not necessarily apply to older patients. Glycemic control may also be an essential factor of diabetes duration in assessing all-cause mortality, as one study showed that elderly-onset diabetes was only associated with higher mortality if the initial glycated hemoglobin (HbA1c) was ≥ 7.5% [34]. A recent review by Lipska KJ et.al., has shed light upon the approach to individualize the glycemic targets in elderly populations through a framework of shared decisions. It infers that the estimation of life-expectancy can help to determine the potential long-term benefits of intensive glycemic control [36]. Importantly, it highlights that even in the broader diabetes population as a whole, it is estimated that it takes eight to ten years of treatment duration to prevent diabetes complications with intensive control. Therefore, it states that patients with estimated life expectancy <8 years are unlikely to benefit from intensive glycemic treatments and only in patients with an estimated life expectancy >15 years is there a possibility of benefit from the reduced microvascular complications through intensive glycemic control. It also suggests that several important patient-level factors such as the need for insulin, duration of diabetes, and cognitive impairment will determine the likelihood of harms associated with the intensive treatment. Considering the goals of treatment of type 2 diabetes to improve symptoms, reduce the risk of acute and chronic diabetes complications, and minimize harms and burdens of therapy [35], patient preferences should play a major role in determining the appropriate glycemic target [36].

Older patients who have complex medical conditions may attain fewer benefits from intensive strategies and are more susceptible to adverse events and recent studies suggest that in elderly
patients with multiple comorbidities, the harms of intensive glycemic control likely exceed the benefits [37]. Elderly patients with type-2 diabetes who have various comorbidities may receive decreased cardiovascular benefit from intensive blood glucose control. A study by Greenfield S et al., 2009 found that patients with high levels of comorbidity in type 2 diabetes did not receive cardiovascular benefit from intensive blood glucose control with a hazard ratio of 0.92 (0.68 – 1.25) at p = 0.61 [38]. In determining glycemic targets in older patients, it is important to devise strategies that not only limit hyperglycemia, but also limit hypoglycemia and overall treatment burden, including pill burden, cost, and follow-up testing.

1.2.3 Hypoglycemia- A Major Concern

Regarding the harms induced by treatment intensification, hypoglycemia is a highly prominent concern that poses a serious health threat among the elderly population. Falls remain the leading cause of injury-related hospital admissions among Canadian seniors and there exists a strong positive correlation between hypoglycemia & fall risk. According to the Institute for Safe Medication Practices (ISMP), hypoglycemic agents rank 4th (13.6%) among the top medication classes associated with increased risk of falls [39]. It also states that glucose lowering agents have accounted for one-fourth of emergency department visits and hospitalizations for adverse drug events associated with them, particularly among older adults [40].

A recent article in JAMA infers that the rates of hospital admissions for hypoglycemia have risen by 11.7% among US Medicare beneficiaries from 1999 to 2011 [41]. When compared, there were 40% more admissions for hypoglycemia than for hyperglycemia. In addition, hypoglycemia is a predominant complication of diabetes in older adults with a longer duration of the disease, occurring as early as a few days to weeks depending on the treatment intensity. Severe
hypoglycemic episodes are estimated to occur at a rate of over 2,400 per 100,000 person-years [33]. Recent guidelines emphasize the avoidance of hypoglycemic episodes in older adults, even in the absence of symptoms [1]. In a study conducted by Laiteerapong, et al. hypoglycemia was associated with lower health-related quality of life (HRQoL) to a comparable degree as diabetes complications [42].

Furthermore, although recent evidence suggests that hypoglycemia is common among patients with type 2 diabetes across all levels of glycemic control, not surprisingly, there exists a higher prevalence of hypoglycemia with lower HbA1c levels [32, 33]. Real-Life Effectiveness and Care Patterns of Diabetes Management (RECAP-DM), a multi-center, observational study, recruited patients ≥30 years old using any oral anti-hyperglycemic agent from seven European and five Asian countries between 2006 and 2007. Hypoglycemia events were collected through patient-reported questionnaires and HbA1c data was collected through chart review. Out of 4,399 patients with a mean age of 60 years, 75% were on sulfonylureas. They found that hypoglycemia prevalence was significantly higher for HbA1c <7.0% (odds ratio [O.R.] = 1.66 [95% C.I. 1.21, 2.28]; p = 0.002) vs. HbA1c ≥10.0% [43].

Lastly, in a retrospective study determining whether patient self-report of severe hypoglycemia is associated with increased mortality, it was reported that out of 1,013 patients, 625 (61.7%) and 76 (7.5%) patients had reported any hypoglycemia and severe hypoglycemia respectively. Their findings concluded that after five years, patients who reported severe hypoglycemia had 3.4-fold higher mortality compared with those who reported mild/no hypoglycemia [44].
1.2.4 Clinical Practice Guidelines

Most of the available practice guidelines are now trending, albeit slowly, in the direction of establishing glycemic control targets based upon an individual's overall health and projected life expectancy [45, 46].

The CDA has recommended HbA1c targets of ≤8.5% among the frail elderly, and fasting and pre-prandial plasma glucose of 5.0 to 12.0 mm/L [1]. The American Diabetes Association and American Geriatric Society advocate for glycemic control goals among patients with complex and poor health status ranging from an HbA1c of 7.5% to 8.5% and 7% to 9%, respectively [3, 47].

Table 1.3 Consensus framework for considering treatment goals for glycemia in older adults with diabetes

<table>
<thead>
<tr>
<th>Health Status</th>
<th>Rationale</th>
<th>HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>Longer remaining life expectancy</td>
<td>&lt; 7.5 %</td>
</tr>
<tr>
<td>(few coexisting chronic illnesses, intact cognitive and functional status)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex/intermediate</td>
<td>Intermediate remaining life expectancy, high treatment burden, hypoglycemia vulnerability, fall risk</td>
<td>&lt; 8.0 %</td>
</tr>
<tr>
<td>(multiple coexisting chronic illnesses or 2+ instrumental ADL impairments or mild-to-moderate cognitive impairment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very complex/poor health</td>
<td>Limited remaining life expectancy makes benefit uncertain</td>
<td>&lt; 8.5 %</td>
</tr>
<tr>
<td>(end-stage chronic illnesses or moderate to severe cognitive impairment or 2+ ADL dependencies)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADL, Activities of Daily Living.


As the treatment of chronic diseases continues to advance to achieve care that is individualized to each patient, the issue of potential over-treatment among the elderly population with diabetes is a strong example of the importance of the need to aim for improved rather than the minimized quality of life. Decisions need to be made collaboratively with patients, incorporating the likelihood of benefits and harms and patient preferences about treatment and treatment burden. A recent Canadian study found that intensity of glycemic control in practice in the context of age and comorbidities appears to be discordant with guideline recommendations and suggested that research is needed to understand these discrepancies and develop methods to assist providers in personalizing glycemic targets [48].

The lack of available evidence-based guidelines for large segments of the elderly population with diabetes is a major impediment to providing optimal clinical care. Although large, randomized trials specifically in older adults are necessary to refine an individual's glycemic control targets better and to tailor treatment accordingly, these are unlikely to be performed. Thus, high-quality evidence regarding optimal glycemic control among elderly patients is lacking. There exists significant uncertainty regarding optimal glucose management in the elderly population with type-2 diabetes because of their unique characteristics, including cognitive impairment, functional intact, comorbid conditions, and frailty issues. Therefore, more attention needs to be paid to therapeutic strategies and focus tailored to suit this population. Observational studies may provide some additional insights.
1.2.5 Observational Studies of Treatment Intensity & Implications

A US-based cross-sectional survey examined glycemic control among older adults with diabetes by health status and to estimate the prevalence of potential overtreatment of diabetes. Using Health and Nutrition Examination Survey (NHANES) data of 1288 older adults age ≥65 years found that of older adults with an HbA1c level of less than 7%, 54.9% (95% CI, 50.4%–59.3%) were treated with either insulin or sulfonylureas which may lead to severe hypoglycemia [49].

The results of a 2009 cross-sectional study identifying high-risk patients for severe hypoglycemia through intensive treatment (i.e. HbA1c <7%) of patients in the Veterans Health Administration receiving insulin and/or sulfonylureas found that when comorbid conditions were included, 430,178 patients (65.9%) were identified as high-risk for hypoglycemia and nearly half of patients (44.3%) were intensively treated (<7%) with hypoglycemic agents [50]. Similarly, another retrospective study by Thorpe, CT et al. using national Veterans Affairs (VA) administrative-clinical data and Medicare claims from 2008-2009 including 15,880 veterans aged 65 years or more with type 2 diabetes and dementia assessed the risk factors for tight glycemic control and use of medications associated with a high risk of hypoglycemia in the subset with tight control (i.e., HbA1c <7%). They reported that more than half of the patients (52%) had tight glycemic control and overall 82% of the patients were at high-risk for hypoglycemia associated with intensive treatment [51].

A retrospective cohort study including 191,590 patients from 50 US states using the Clininformatics Data Mart database evaluated whether treated HbA1c levels in adults with newly diagnosed diabetes varied by health status [52]. The study found that despite being at a higher risk for adverse effects, nearly half of very complex patients (40.6%) were still receiving insulin/sulfonylureas...
among patients with HbA1C <7%. Use of insulin or sulfonylureas was associated with an increased risk for all-cause hospitalization [aHR 1.54, 95% CI (95% CI) 1.45–1.64] and for emergency room visits [aHR 1.44, 95% CI 1.35–1.53] [52].

A study by Vijan S et al. in 2014 assessed the effect of patients' risks and preferences on health gains with plasma glucose level lowering in type-2 diabetes. They found that treatment that lowers HbA1c by 1 percentage point provided benefits ranging from 0.77–0.91 Quality Adjusted Life years (QALYs) for patients diagnosed at age 45 which declined dramatically to 0.08–0.10 QALYs for those diagnosed at age 75. Through their findings they concluded that improving glycemic control can provide substantial benefits, especially for younger patients; however, for most patients over age 50 with an HbA1c below 9% on metformin, further glycemic treatment usually offers, at most, modest benefits [53].

Another US study by Maciejewski ML et al. assessing rates of overtreatment also looked at rates of de-intensification of therapy using Medicare claims of 78,792 older adults with diabetes age ≥65 years. Of them, around 11% (8560) of the older adults were potentially over-treated, and overtreatment was found to be most common among patients with age over 75 years. Therapy was de-intensified for 14% of over-treated patients; whereas, de-intensification was less common for those over age 75 years [54].

A recent cross-sectional study has addressed intensive glycemic control in the Canadian context to examine whether glycemic control varied by age and comorbidities in Canadian primary care by using data from the CPCSSN database [48]. Data from 30,416 patients with diabetes, aged 40 or above, with at least one HbA1c measurement between 2012 and 2013 were collected from electronic medical records of 537 primary care providers across Canada. Their study findings
suggested that younger patients (aged 40–49) were more likely to have moderate as opposed to a tight control (HbA1c <7%) than the older patients (aged 80+) (OR 1.28; 95% CI 1.11 to 1.49, p=0.001). The youngest were also more likely to have uncontrolled (HbA1c >8.5%) as opposed to moderately controlled (HbA1c 7%-8.5%) glycemia (OR 3.39; 95% CI 2.75 to 4.17, p<0.0001). However, this study was not explicitly focused on the geriatric population, study participants were not restricted to type-2 diabetes, and specific anti-diabetic medications were not assessed. The primary outcomes of this study were identifying glycemic levels and treatment intensity but did not address the consequences of intensive treatment such as overall burden, quality of life, hospital admissions & emergency room visits [48]. Considering this and the significant concerns described in this population, an evaluation of glucose management intensity in Canadian elderly patients with diabetes is necessary.
1.3 References


Chapter 2 – Thesis Outline

2.1 Need for the Study

Several observational database studies have been conducted in the last several years on the treatment intensity in elderly populations with diabetes. These studies, primarily looking at the United States population, have consistently found a significant degree of overtreatment related to levels of glycemic control achieved and the medications used to achieve them [1-5]. It is generally agreed that in elderly patients with multiple comorbidities, the harms of intensive glycemic control likely exceed the benefits.

Currently, the extent of overtreatment in the elderly population in Canada is not clearly established. Considering this and the significant concerns described in this population, evaluation of glucose management intensity in elderly patients with diabetes is necessary provincially and nationally. This study was the first Canadian evaluation of this necessary research question. We intended to inform an understanding to build a foundation for future interventions to optimize diabetes management strategies in elderly Canadians.

2.2 Study Plan

This study was conducted in two phases. Phase-I was performed using the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database [6] for assessing the major objectives. Phase-II was performed by using the Manitoba Centre for Health Policy (MCHP) database [7] which deals with further objectives using strictly a Manitoba cohort by cross-linking to the Manitoba Primary Care Research Network (MaPCReN) [8], CPCSSN’s Manitoba-specific database.
As CPCSSN lacks adequate information related to non-primary care medical service utilization, medications dispensed (as opposed to prescribed), certain aspects of socio-economic status, and hospital admissions, we cross-linked the Manitoba cohort of CPCSSN (i.e., MaPCReN) with the MCHP which is robust in certain auxiliary data elements that CPCSSN lacks.

2.3 Objectives

2.3.1 Phase- I

i. To assess the potential overtreatment related to the intensity of glycemic control among older adults with diabetes across Canada.

ii. To assess the burden related to HbA1c testing frequency and overall medication burden.

2.3.2 Phase- II

i. To assess potential overtreatment related to the intensity of glycemic control among older adults with diabetes in Manitoba using population-based administrative dispensation data by cross-linking MaPCReN with the MCHP database. This will allow application of MCHP data elements, including all dispensed medications (primary care and non-primary care) to each MaPCReN patient from the original cohort. This will also enable differentiation between general practitioner prescribers and non-general practitioner prescribers.

2.4 Methodology Overview

2.4.1 Study Design, Settings & Data Sources
This is a retrospective observational cohort study using a large sample of patients from across Canada conducted at the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba. Phase-I was conducted using primary care data extracted for public health surveillance and research purposes by the Canadian Primary Care Sentinel Surveillance Network. CPCSSN is Canada's first multi-disease electronic medical record (EMR) surveillance system with a primary care research initiative. The CPCSSN database is comprised of electronic medical chart data of more than 1.8 million patients provided by 1,262 sentinel providers using 12 different EMR products from 217 participating primary care practice sites in 8 Canadian provinces and territories. In addition to creating a platform for multi-level research, it collects and maintains national epidemiological surveillance data using EMRs to improve outcomes in primary health care which can contribute to a stronger national knowledge base in the area of primary health care and chronic disease management. [6]

Phase-II was conducted using administrative data from the Manitoba Center for Health Policy database. MCHP is a research unit within the Department of Community Health Sciences, in the Max Rady College of Medicine, Rady Faculty of Health Sciences at the University of Manitoba. It maintains the Manitoba Population Research Data Repository, a collection of administrative health care databases containing records of all interactions between Manitoba residents and the health care system. All data in the Repository are de-identified (names and addresses are removed), and each record has a unique scrambled number, which allows records to be linked through time and across datasets. It enables population-based research on health services, population and public health, and the social determinants of health.

2.4.2 Intensity of Potential Over-Treatment in Canada
Two cross-sectional slices were assessed in determining glycemic control for two 1-year time spans in the study period, i.e., 2012 and 2016. These time periods were chosen as they allow a lookback period of two years for identifying billing codes for diabetes, as stated in the study’s inclusion criteria. New CDA guidelines were also published in 2013, therefore analyzing patterns from 2016 allow for assessment of practice change occurring after revised recommendations on glycemic targets. We used the first recorded HbA1C in the year in question for each patient as the index HbA1c. Glycemic control was categorized as category-1 (≤ 7 %), category-2 (7 % - < 8 %), category-3 (8% - < 9%), and category-4 (≥ 9 %). Using ATC codes, anti-diabetic medications were identified (see Appendix-1), and those with known potential for hypoglycemia (sulfonylureas, meglitinides, and insulins) were considered as high-risk medications. Potential overtreatment was defined as a patient having an index HbA1c value of less than 7 % and having been prescribed any anti-diabetic medications other than metformin within the 9 months before or 3 months after the index HbA1c value. To remain consistent with CIHI aging categories [9], patients were categorized into 65-74, 75-84, and ≥85-year age groups in assessing the impact of age on intensity of glycemic control. The rates of over-treatment in patients with dementia and in patients with age ≥80 years and with dementia were also assessed. The age of 80 years was chosen as the cut-off for this outcome as it is considered a marker for advanced age and limited life-expectancy [10]) Also, drug-use patterns of high-risk medications (i.e., insulins, sulfonylureas, and meglitinides) were assessed by dividing them based upon their sub-classes.

### 2.4.3 Burden Related to HbA1c Testing Frequency & Overall Medication Burden

HbA1c testing frequency was measured as the mean number of tests performed per year and as the annual number of tests per patient and was categorized as ≤1 time per year, 2 times/year (minimum guideline recommendation), 3-4 times/year (frequent), and ≥5 times/year (excessive). The number
of prescribed medications (both acute and chronic) per patient based on prescription entries for the year surrounding the index HbA1c was examined in assessing the medication burden. In order to compare to CIHI medication use measures [9], patients were categorized into 0, 1-4, 5-9, and ≥10 categories based on their medication usage.

2.4.4 Intensity of Potential Over-Treatment in Manitoba

This objective was analyzed using the Manitoba cohort extracted from MaPCReN and by cross-linking with the corresponding MCHP data. The main purpose of this objective was to re-assess the primary objective i.e., to assess the rates of potential over-treatment among Manitoban older adults with type-2 diabetes using the MaPCReN cohort in MCHP, and to compare these findings with the CPCSSN cohort results, as well as to analyze the non-primary care prescriber contributions.

2.4.5 Study Approvals

Approvals for this study were obtained from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), the Manitoba Centre for Health Policy (MCHP), the University of Manitoba Health Research Ethics Board (HREB), the Manitoba Primary Care Research Network (MaPCReN) and the provincial Health Information Privacy Committee (HIPC). Copies of these approvals may be found in the Appendix section of this document. Individual patient consent forms are not required for retrospective database studies as per the regulations of these regulatory bodies and provincial law.
2.5 References


CHAPTER 3 – Intensity of Potential Over-Treatment among Older Adults with Type-II Diabetes in Canada

3.1 Introduction

The International Diabetes Federation (IDF) reports that 1 in every 11 adults aged 20–79 years (415 million adults) had diabetes globally in 2015 and this is estimated to reach up to 642 million by 2040 [1]. The risk of diabetes rises with increasing age among older adults. The global prevalence of diabetes among older adults is estimated at 18.8% [1]. In addition to macrovascular and microvascular complications, older people with diabetes are at higher risk of developing functional impairment [2], dementia [3], depression [4], skin diseases [5], hyperosmolar hyperglycemic non-ketotic syndrome [6], and fractures [7]. The specific glycosylated hemoglobin (HbA1c) targets among older adults should be based on individual characteristics [7]. Over the past few years, many concerns have been raised regarding optimal glycemic control in the elderly population with diabetes.

Intensive glycaemic control is recommended to reduce the burden of cardiovascular disease and microvascular complications in people with diabetes [8]. However, the results of major randomized clinical trials on the benefits of such treatment are controversial [9-13]. Clinical trials which have investigated the effect of intensive treatment in older adults demonstrated that targeting tight glycemic control (i.e., HbA1c < 6.5%) did not reduce end-stage microvascular and cardiovascular complications, but increased the risk of severe hypoglycemia, weight gain and mortality [9, 10]. Later extended follow-up studies have inferred that intensive glycemic control might show small cardiovascular benefits on a long-term basis for those patients with greater life-expectancy [14].
Hypoglycemia is a major concern and poses serious health threats to older adults with diabetes [15-18]. Post hoc analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) [10] and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) [11] trials concluded that severe hypoglycemia was associated with an increased risk of cardiovascular events. Furthermore, epidemiological evidence suggests that hypoglycemia is also associated with unfavorable health outcomes such as higher risk of dementia [19], falls [20], fall-related fractures [21], reduced health-related quality of life [22, 23], and increased mortality [24]. Hypoglycemia has emerged as a dominant complication of diabetes in older adults [18]. A study by Budnitz DS et al. showed that glucose lowering medications were associated with one-fourth of the emergency hospitalizations, most of them for hypoglycemia [16]. Interestingly, among Medicare beneficiaries, hospitalizations for hypoglycemia have been reported to exceed those for hyperglycemia [15, 25]. Therefore, the relationship between glucose control and risk of severe hypoglycemia is critical for making informed decisions about the type and intensity of therapy.

While the purpose of glycemic control therapy is to reduce and/or prevent the risk of diabetes complications, the harms associated with such therapy should be kept in mind while implementing it among older adults, so as to not negatively affect their health-related quality of life (HRQoL). Treatment that lowers HbA1c level by 1 percentage point provided benefits in Quality Adjusted Life years (QALYs) for patients diagnosed at age 45; while, QALYs benefits were much less for those diagnosed at age 75 [26]. Diabetes management should focus on balancing the risks of long-term harms of under-treatment with the short-term and long-term harms of over-treatment.

Importantly, even in the broader diabetes population as a whole, it is estimated that it takes five to ten years of duration to prevent diabetes complications with intensive control. The ACCORD trial
found that with an observational follow up of the surviving participants over a median of 8.8 years showed a neutral long-term effect of intensive glucose control on the composite outcome and all-cause mortality [10]. The ADVANCE trial reported that no beneficial effect of intensive glucose lowering was found on major CV events or all-cause mortality either during the trial or the subsequent median observational follow up of 5.4 years [11]. One trial, VADT, did however, find that during an observational median follow up of 9.8 years, the intensive-therapy group showed a significantly lower risk of the primary outcome (MI, stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, or CV-related death) compared to standard therapy group [14]. These findings suggest that glucose lowering may not yield the benefits until years after initiation of therapy. Older people living with diabetes are more likely to be living with multiple comorbidities and functional impairments. Evidence suggests that pursuing intensive glycemic control with comorbid illnesses and functional impairments increases the risks more than benefits [18]. Numerous recent observational studies have found that a substantial proportion of older adults were tightly controlled and/or potentially over-treated [17, 18, 23, 24, 27-33]. Study definitions of intensive/over-treatment have varied somewhat, but having an index HbA1c of less than or equal to 7% while being treated with insulins or sulfonylureas is fairly consistently utilized in observational literature to define over-treatment in older age cohorts [17, 30, 31, 34, 35]

This understanding of uncertain benefit, concern for harm, and signals of overtreatment have led major diabetes societies from North America and Europe to recommend individualized targets among older patients with diabetes who have significant comorbid conditions which put them at higher risk for developing hypoglycemia [37].

The American Diabetes Association (ADA) guidelines recommends the glycemic targets of HbA1c < 7.5%, < 8%, and < 8.5% for those who are considered as healthy, complex/intermediate,
and very complex/poor health, respectively [37]. The recent American College of Physicians (ACP) clinical guidelines advise clinician to aim for HbA1c level between 7% to 8% for most of the patients with type-2 diabetes, to consider de-intensifying therapy in those who’s HbA1c is < 6.5%, and aim for to minimize hyperglycemia symptoms, avoiding targeting HbA1c entirely in those with shorter life expectancy as a result of, for example, advanced age or chronic conditions such as dementia [38]. The Diabetes Canada guidelines suggests considering HbA1c targets of ≤ 7%, 7.1-8.0%, and 7.1-8.5% for those who are considered as functionally independent, functionally dependent, and frail and/or with dementia, respectively [39]. The interpretation of the current guideline recommendations is to personalize the therapy to obtain tighter glycemic control in younger and healthier patients, and less stringent HbA1c targets for older patients with advanced age, longer disease duration, limited life expectancy, presence of multiple comorbid conditions, recurrent hypoglycemic episodes, functional dependency, and other frailty issues [36-41]. However, the extent of implementation of these guidelines in real-world practice is unclear. The main aim of this study was to evaluate the potential overtreatment related to the intensity of glycemic control among older adults with type-2 diabetes across Canada. As part of the primary objective, this study also examined the impact of age (65-74, 75-84, ≥85 years) on the intensity of glycemic control, the rates of over-treatment in patients with dementia, and drug-use patterns of high-risk medications (i.e., insulins, sulfonylureas, and meglitinides).

3.2 Methods

3.2.1 Study Design, Setting & Data source

This is a retrospective observational cohort study using a large sample of patients from across Canada conducted at the College of Pharmacy, Rady Faculty of Health Sciences, University of
Manitoba. Phase-I was conducted using primary care data extracted for public health surveillance and research purposes by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN). CPCSSN is Canada's first multi-disease electronic medical record (EMR) surveillance system with a primary care research initiative. The CPCSSN database is comprised of electronic medical chart data of more than 1.8 million patients provided by 1,262 sentinel providers using 12 different EMR products from 217 participating primary care practice sites in 8 Canadian provinces and territories. In addition to creating a platform for multi-level research, it collects and maintains national epidemiological surveillance data using EMRs to improve outcomes in primary health care which can contribute to a stronger national knowledge base in the area of primary health care and chronic disease management. [42]

3.2.2 Study Population/Cohort Selection

A validated case definition of diabetes by CPCSSN was used in determining the study population [43]. The study cohort consisted of those age 65 years or older, with two or more billing codes for diabetes (ICD-9 code 250) in the past 2 years (or) presence of at least two FBG levels greater than 7mmol/litre in one year (or) any HbA1C ≥ 7 (or) a first claim for an oral hypoglycemic drug or insulin (with the exception of Polycystic Ovarian Syndrome, Gestational Diabetes, Secondary (chemical induced) Diabetes, Hyperglycemia NOS, and Neonatal diabetes mellitus where the medication criteria alone is insufficient), between 2010 to 2016, and in patients who had at least one HbA1c measurement [43].

3.2.3 Glycemic control

Two cross-sectional slices were assessed in determining glycemic control for two 1-year time spans in the study period (2012 and 2016). We used the first recorded HbA1C in the year in
question for each patient as the index HbA1c. Glycemic control was categorized as category-1 (<7 %), category-2 (7 % - < 8 %), category-3 (8% - < 9%), and category-4 (≥ 9 %). Patients included in the 2012 cohort were allowed to enter the 2016 cohort and thus can appear in both cohorts.

3.2.4 Anti-diabetic medication use

Using ATC codes, anti-diabetic medications were identified (see Appendix-1), and those with known potential for hypoglycemia (sulfonylureas, meglitinides, and insulins) were considered as high-risk medications.

3.2.5 Treatment intensity and Overtreatment

Potential overtreatment was defined as a patient having an index HbA1c value of less than 7% and having been prescribed any anti-diabetic medications other than metformin within the 9 months before or 3 months after the index HbA1c value. Primary care practitioners in Canada generally have the ability to prescribe medications for up to a year at once. For this reason, a 12-month timeframe was desired: a 9-month (pre-index) look-back period was considered in order to capture the maximum number of prescriptions while including a look-forward period of 3-months (post-index) as any change to medications based on A1c would have likely happened within 3-months of time from the index HbA1c.

3.2.6 Secondary Objectives

3.2.6.1 Impact of age on the intensity of glycemic control

Patients were categorized into 65-74, 75-84, and ≥85-year age categories for 2012 & 2016 in assessing the associations of age and intensity of glycemic control.

3.2.6.2 Assessing rates of over-treatment in patients with dementia
The rates of over-treatment in patients with dementia and patients with age ≥80 years and with dementia were also assessed. For those with age ≥80 years and with dementia, an HbA1c target of <8 % was considered in defining potential overtreatment, instead of < 7% [39].

3.2.6.3 Assessing drug-use patterns of high-risk anti-diabetic medications

Anti-diabetic medication use was defined as medication prescriptions for any anti-diabetic drugs within the 9 months before or 3 months after the index HbA1c value (see Appendix-1 for ATC codes). Drug-use patterns of high-risk medications (i.e., insulins, sulfonylureas, and meglitinides) were assessed by dividing them based upon their sub-classes.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses. The sample characteristics were computed using descriptive statistics and the rates of over-treatment were represented as proportions. Confidence intervals and p-values are performed using test for proportions. Approvals were granted by the University of Manitoba Health Research Ethics Board (HREB) and the Canadian Primary Care Sentinel Surveillance Network. CPCSSN data are de-identified and stored on a secured data server, and the privacy of the patients is protected by the process of de-identification which result in anonymized information. These committees do not require individual consent for research conducted using de-identified administrative data where the privacy of patients is protected and when reasonable safeguards to protect confidentiality and security of personal health information are in place.

3.3 Results

3.3.1 Patient demographics & characteristics
Of 95,054 patients diagnosed with type-2 diabetes between 2010 to 2017, 23,080 in 2012 and 33,864 in 2016 satisfied the study’s inclusion criteria. An overall cohort of 41,032 patients (51.6% males) with a mean age of 76.6 years were identified and categorized based on their index HbA1c into four categories (<7%, 7%-<8%, 8%-<9%, and ≥9%). (Table 3.1) The largest proportion of the patients belonged to the age group of 65-74 years (42%); while, around 19.8% of the study population were 85 years or older. More than half of the patients belonged to category-1 (HbA1c < 7%) (58.3%); while 7.8% were poorly-controlled patients (category-4, HbA1c ≥9%). More than two-thirds (71%) of the study population had hypertension and 9.6% had a diagnosis of dementia during the study period (Table 3.1). The majority of patients (60.8% in 2012 and 56.4% in 2016) did not have a recorded prescription for anti-diabetic medications. This meant that 69.9% and 66.7% of those with HbA1c < 7% (42.9% and 38.3% of the entire cohort) in 2012 and 2016 did not have a prescription recorded, respectively. More than one-third of the patients with HbA1c ≥ 9% were prescribed no medications which meant that 41.9% in 2012 and 35.8% in 2016, or 3.0% and 2.7% of the entire cohorts, respectively appeared to be untreated (Table 3.2, Figure 3.1 and Figure 3.2).

**Table 3.1** Demographics and characteristics of older adults with type-2 diabetes in Canada from 2012 through 2016 by HbA1c categories

<table>
<thead>
<tr>
<th>Patient Characteristics (N=41,032)</th>
<th>Overall</th>
<th>HbA1c Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (&lt; 7%)</td>
<td>II (7% to &lt; 8%)</td>
</tr>
<tr>
<td></td>
<td>n = 23922</td>
<td>n = 9930</td>
</tr>
<tr>
<td></td>
<td>(58.3%)</td>
<td>(24.2%)</td>
</tr>
<tr>
<td>Mean Age ± S.D</td>
<td>2012 Cohort</td>
<td>2016 Cohort</td>
</tr>
<tr>
<td>---------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Age, 65-74</td>
<td>76.6±7.8</td>
<td>76.9±7.9</td>
</tr>
<tr>
<td>17305 (42.2%)</td>
<td>9677 (55.9%)</td>
<td>4199 (24.2%)</td>
</tr>
<tr>
<td>75-84</td>
<td>15604 (38.0%)</td>
<td>9232 (59.1%)</td>
</tr>
<tr>
<td>8123 (19.8%)</td>
<td>5013 (61.7%)</td>
<td>1882 (23.1%)</td>
</tr>
<tr>
<td>≥85</td>
<td>21203 (51.7%)</td>
<td>11939 (50.0%)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>21203 (51.7%)</td>
<td>11939 (50.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>19829 (48.3%)</td>
<td>11983 (50.1%)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Hypertension</td>
<td>29045 (70.8%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>3949 (9.6%)</td>
<td>2319 (9.7%)</td>
</tr>
<tr>
<td>COPD</td>
<td>4233 (10.3%)</td>
<td>2652 (11.1%)</td>
</tr>
<tr>
<td>Depression</td>
<td>5898 (14.4%)</td>
<td>3585 (15.0%)</td>
</tr>
<tr>
<td>Smoking status, yes (%)</td>
<td>13249 (32.3%)</td>
<td>7814 (32.6%)</td>
</tr>
</tbody>
</table>

Table 3.2 Proportion of patients by number of medications by HbA1c categories in 2012 & 2016

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>No. of patients (n=23,080)</th>
<th>2012 Cohort</th>
<th>2016 Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age ± S.D</td>
<td>75.3±7.4</td>
<td>75.6±7.4</td>
<td>75.4±7.3</td>
</tr>
<tr>
<td>Number of Medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>14039 (60.8%)</td>
<td>9896 (69.9%)</td>
<td>2642 (49.0%)</td>
</tr>
<tr>
<td>1</td>
<td>5916 (25.6%)</td>
<td>3225 (22.8%)</td>
<td>1686 (31.2%)</td>
</tr>
<tr>
<td>2</td>
<td>2191 (9.5%)</td>
<td>795 (5.6%)</td>
<td>736 (13.6%)</td>
</tr>
<tr>
<td>≥3</td>
<td>934 (4.0%)</td>
<td>228 (1.6%)</td>
<td>328 (6.1%)</td>
</tr>
</tbody>
</table>
3.3.2 Rates of potential over-treatment

The overall rate of over-treatment was 7.0% in 2012 and 6.9% in 2016, showing no statistically significant difference between the two time points (p = 0.54 [95% CI -0.29 to 0.55]). High-risk hypoglycemic agents (insulins, sulfonylureas, and meglitinides) accounted for 84.4% and 68.0% (95% CI 15.71-17.08; p=0.0001) of over-treatment medications in 2012 and 2016, respectively. Metformin-only users made up 19.1% and 21.5% of the cohorts in 2012 and 2016. A statistically significant increase (0.9% vs 1.8%, 95% CI 0.71-1.08; p=0.0001) in the utilization of anti-diabetic medications with less hypoglycemic potential (i.e., other OHA’s class) were observed across all the HbA1c categories in 2016. Notably, 42% and 36% of patients with poor glycemic control (HbA1c ≥ 9%) were receiving no medication in 2012 and 2016, indicating under-treatment (Figure 3.1 and 3.2).
HR meds- High-Risk medications (Insulins, Sulfonylureas, and Meglitinides); Other OHAs- other Oral Hypoglycemic agents (alpha-glucosidase inhibitors, Thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists).

**Figure 3.1** Proportions of treatment by HbA1c category in 2012
**HR meds**- High-Risk medications (Insulins, Sulfonylureas, and Meglitinides); **Other OHAs**- other Oral Hypoglycemic agents (alpha-glucosidase inhibitors, Thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists).

**Figure 3.2** Proportions of treatment by HbA1c category in 2016

### 3.3.3 Impact of age on intensity of glycemic control

A modest rise in potential over-treatment rates was observed between the youngest and the older cohorts in 2012, with an apparent drop as age increased in 2016 (Figure 3.3). Among older adults with diabetes age ≥ 80 years the rate of over-treatment (considering a threshold HbA1c < 8%) was 14.5% in 2012 and 13.0% in 2016.
3.3.4 Rates of potential over-treatment in patients with dementia

Among older adults with dementia, the rate of potential over-treatment was 8.4% in 2012 and 8.1% in 2016 (Figure 3.4). In patients age ≥ 80 years with dementia, using a conservative threshold of HbA1c < 8%, rates of overtreatment increased to 14.5% (2012) and 12.2% (2016) (Figure 3.5).
Figure 3.4 Proportions of treatment by medication category among older adults with dementia and type-2 diabetes with an HbA1c level < 7%
Figure 3.5 Proportions of treatment by medication category among older adults with dementia, type-2 diabetes and age ≥ 80 years with an HbA1c level < 8%

3.3.5 Drug-use patterns of high-risk anti-diabetic medications

Among the high-risk medication classes, sulfonylureas made up 55.2% [95% CI 53.8% – 56.6%] in 2012 and 53.9% [95% CI 52.7% – 55.1%] in 2016; while, gliclazide was the most utilized drug (35.4% in 2012; 45.6% in 2016). Glyburide, with arguably a higher likelihood of hypoglycemia, was less commonly prescribed (19.1% [95% CI 18.1% – 20.3%]) in 2012 and declining even further to 7.9% in 2016). Among the insulins, long-acting insulins were the most prescribed type of insulins in both the cohorts (14.9% and 23.6%), followed by rapid-acting insulins (8.7% and
9.8%). Intermediate-acting insulins (NPH) were less commonly prescribed (5.0% and 2.3%) during the study period (Table 3.3).

Table 3.3 Proportions of high-risk medication use by HbA1c categories in 2012 & 2016

<table>
<thead>
<tr>
<th>High-risk Medications (sub-class)</th>
<th>2012 Cohort</th>
<th>2016 Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (≤ 7%)</td>
<td>II (7% to &lt; 8%)</td>
</tr>
<tr>
<td>Insulins (n = 1946)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting</td>
<td>109 (7.0%)</td>
<td>127 (7.8%)</td>
</tr>
<tr>
<td>Short-acting</td>
<td>38 (2.4%)</td>
<td>44 (2.7%)</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>53 (3.4%)</td>
<td>67 (4.1%)</td>
</tr>
<tr>
<td>Long-acting</td>
<td>154 (9.9%)</td>
<td>237 (14.6%)</td>
</tr>
<tr>
<td>Combinations</td>
<td>87 (5.6%)</td>
<td>116 (7.1%)</td>
</tr>
<tr>
<td>Sulfonylureas (n = 2768)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>324 (20.8%)</td>
<td>332 (20.5%)</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>690 (44.3%)</td>
<td>583 (36.0%)</td>
</tr>
<tr>
<td>Others</td>
<td>12 (0.8%)</td>
<td>16 (1.0%)</td>
</tr>
<tr>
<td>Meglitinides (n = 298)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>89 (5.7%)</td>
<td>96 (5.9%)</td>
</tr>
</tbody>
</table>

| Insulins (n = 2864)              |             |             |               |             |             |             |             |               |             |             |
| Rapid-acting                     | 143 (7.8%)  | 212 (9.6%)  | 162 (11.5%)   | 140 (10.9%) | 657 (9.8%)  | 155 (8.5%)  | 172 (7.8%)  | 121 (8.6%)  | 82 (6.4%)   | 530 (7.9%)  |
| Short-acting                     | 33 (1.8%)   | 43 (1.9%)   | 33 (2.3%)     | 39 (3.0%)   | 148 (2.2%)  | 947 (52.0%) | 1090 (49.4%)| 550 (39.2%) | 473 (37.0%) | 3060 (45.6%)|
| Intermediate-acting              | 34 (1.8%)   | 50 (2.2%)   | 36 (2.5%)     | 36 (2.8%)   | 156 (2.3%)  | 12 (0.6%)   | 11 (0.5%)   | 2 (0.1%)    | 1 (0.1%)    | 26 (0.4%)   |
| Long-acting                      | 339 (18.6%) | 468 (21.2%) | 383 (27.3%)   | 391 (30.6%) | 1581 (23.6%)| 62 (3.4%)   | 76 (3.4%)   | 39 (2.8%)   | 49 (3.8%)   | 226 (3.4%)  |
| Combinations                     | 95 (5.2%)   | 84 (3.8%)   | 77 (5.5%)     | 66 (5.1%)   | 322 (4.8%)  | 947 (52.0%) | 1090 (49.4%)| 550 (39.2%) | 473 (37.0%) | 3060 (45.6%)|
| Sulfonylureas (n = 3616)         |             |             |               |             |             |             |             |               |             |             |
| Glyburide                        | 155 (8.5%)  | 172 (7.8%)  | 121 (8.6%)    | 82 (6.4%)   | 530 (7.9%)  | 155 (8.5%)  | 172 (7.8%)  | 121 (8.6%)  | 82 (6.4%)   | 530 (7.9%)  |
| Gliclazide                       | 947 (52.0%) | 1090 (49.4%)| 550 (39.2%)   | 473 (37.0%) | 3060 (45.6%)| 947 (52.0%) | 1090 (49.4%)| 550 (39.2%) | 473 (37.0%) | 3060 (45.6%)|
| Others                           | 12 (0.6%)   | 11 (0.5%)   | 2 (0.1%)      | 1 (0.1%)    | 26 (0.4%)   | 12 (0.6%)   | 11 (0.5%)   | 2 (0.1%)    | 1 (0.1%)    | 26 (0.4%)   |
| Meglitinides (n = 226)           |             |             |               |             |             |             |             |               |             |             |
| Repaglinide                      | 62 (3.4%)   | 76 (3.4%)   | 39 (2.8%)     | 49 (3.8%)   | 226 (3.4%)  | 62 (3.4%)   | 76 (3.4%)   | 39 (2.8%)   | 49 (3.8%)   | 226 (3.4%)  |
3.4 Discussion

Using a national-level database of older adults with type-2 diabetes from 2010 through 2017 across Canada, more than half of the older adults had HbA1c levels < 7%. Overall, 7% were potentially over-treated, with no indication of change over time. Among tightly controlled patients, 12% of the patients were treated with anti-diabetic agents in addition to metformin, and 8% were on high-risk hypoglycemic agents (insulins, sulfonylureas, or meglitinides). High-risk hypoglycemic agents accounted for the vast majority of over-treatment medications in 2012 and more than two-thirds of over-treatment medications in 2016. Conversely, despite high HbA1c levels (≥ 9%) in some, more than one-third of these patients were receiving no medications. In general, this study suggests an imbalance with relative under-treatment among poorly controlled patients coupled with potential over-treatment among some tightly controlled patients.

Most of the studies addressing potential over-treatment have been conducted in the United States, with rates all significantly higher than what was found in this study. A cross-sectional study using an NHANES database from 2001-10 with 1,288 older adults (mean age of 73.2 years) found that a substantial proportion of older adults (55%) with diabetes were potentially over-treated with insulins and sulfonylureas [17]. A retrospective study using a Clinformatics Data Mart database from 2004-09 evaluated 191,590 adults (mean age of 54 years) reporting that despite being at a higher risk for adverse events, 40.6% of the very complex patients with HbA1c <7% were still receiving insulins and sulfonylureas and exhibited higher risk of all-cause hospitalizations or emergency visits subsequently [34]. Another study using a Veterans Health Administration database with 652,375 older adults (mean age of 66.5 years) concluded that more than two-thirds of the patients were at high risk of developing hypoglycemia [28]. A study using Veteran Affairs Health Care Systems data with 15,880 older adults with dementia suggested that overall, 82% of
the patients used a regimen associated with increased hypoglycemia risk [30]. A recent study using Medicare Claims data with 78,792 older adults (mean age of 75.6 years) reported that patients are more frequently over-treated than undertreated for diabetes [35]. In contrast to these studies, we found relatively lower rates of potential over-treatment among older adults with diabetes in Canada. It should be noted, however, that the majority of the US studies reported over-treatment rates representing within-category estimates (e.g. by HbA1c category or health status group) rather than reporting rates for the overall diabetes study population which might have led to higher rate estimates. Several studies reported over-treatment rates based on their overall cohort or allowed for rates to be calculated (using HbA1c <6.5-7% and use of sulphonylureas and/or insulin as criteria), showing rates of 11%, 34%, and 39% [35, 17, 30]. The reasons for this difference are not known for certain, but may include a variety of factors. Overtreatment in Canada may in fact be significantly less common than in the US. However, knowing that such a large difference is unlikely, other factors may explain the difference. A large proportion of patients were on no medications, despite using a highly utilized case definition. It is possible that there are people without diabetes (e.g. nearing a diabetes diagnosis threshold or being simply being tested for diabetes) being billed or diagnosed as having diabetes in our cohort. In addition, by using only primary care data in assessing over-treatment we may be missing prescription data from specialists or there is some evidence that providers contributing to the repository are more likely to be high-performers which may alter the treatment picture [45].

A cross-sectional study conducted among frail elderly patients with diabetes residing in nursing homes of British Columbia, Canada found that over-treatment was prevalent among frail elderly patients who were living in nursing homes and polypharmacy was associated with the more intensive treatment [46]. Recent studies investigating the prevalence, harms, and burden related to
intensive treatment [17, 28, 30, 34, 35], support an individualized approach in setting glycemic targets, keeping certain factors in mind such as age, life expectancy, risk of hypoglycemia, comorbid conditions, and polypharmacy. In our study, initially there appeared to be a rise in the rate of over-treatment with increasing age in the 2012 cohort. A recent Canadian study using the CPCSSN database between 2012 and 2013 reported that younger patients were more likely to have poorly controlled glycemic levels; while, older patients (80+ years) were more likely to have tight control [44]. Analysis of our more recent cohort showed a decreasing trend in the rate as age increased in 2016 cohort, suggesting that treatment approaches with increasing age may have become more appropriate over time.

The American Geriatric Society discusses the role of dementia in setting glycemic targets among older adults, stating that dementia could be considered as a quality indicator in defining over-treatment [47, 48]. Recent Diabetes Canada clinical practice guidelines recommend to target an HbA1c of 7.1% - 8.5% if a person is frail and/or with dementia [39]. In addition, the American College of Physicians suggests that clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA1c level in patients with a life expectancy less than 10 years due to advanced age (80 years or older), or chronic conditions such as dementia [38]. In a study, Tseng and colleagues reported a high prevalence of intensive treatment as a risk-factor causing hypoglycemia, including dementia [28]. Thus, the present study attempted to focus on the intensity of over-treatment among patients with comorbid dementia. Despite the unlikely chance of receiving any clinical benefit, older adults with diabetes and with the combination of dementia & advanced age (≥ 80 years) appeared to be slightly more likely to be potentially over-treated in comparison to those without dementia and advanced age. Using the appropriately higher HbA1c cut-off of 8% for this subgroup increased the rate of potential
overtreatment substantially. There are several reasons for such practices which may include the issue that de-intensifying a therapy requires a transition from a conventional generalized approach to individually tailored care of balancing risks and benefits, involving a more nuanced, patient-level approach and discussion [30]. These approaches to care can sometimes be more challenging initially to adopt, suggest, and accept. Also, since guidelines mostly focus on preventing under-treatment rather than over-treatment, and indisposition to risk under-treatment [29] might contribute to the practice of intensive treatment. Therefore, until clinical practice guidelines invest specific focus on de-intensification or avoidance of over-treatment, these practice patterns will likely continue to go unchanged [49].

Although recent American Geriatric society guidelines emphasize avoidance of tight glycemic targets and, where possible, minimizing usage of glucose-lowering medications other than metformin among older adults [50], in this study, a proportion of older adults were on multiple antidiabetic medications. Without knowing the decision-making that preceded the initiation of additional agents, one can only make inferences about the relative risk that additional medications pose. Among high-risk hypoglycemic medications, the use of long-acting insulins and gliclazide gradually increased. This is somewhat encouraging considering that basal insulins (NPH or long-acting analogues), are associated with the least fluctuation in day-time blood glucose, and it is believed that gliclazide is the safer of the sulfonylureas regarding the potential for hypoglycemia. In conjunction with this, the use of short-acting, combination insulins, and glyburide decreased from 2012 to 2016. Arguably, these are associated with a higher degree of unpredictability in blood glucose readings, and their decline is, again, encouraging. Surprisingly, intermediate-acting insulins (e.g., NPH), which have been a standard of care for basal insulin initiation and are approximately half the cost of long-acting analogs, also declined in use as long-acting agents
increased. Although the proportion of older adults on hypoglycemic medications remained marginal over-time, there were no extreme differences in treatment patterns and choice of antidiabetic therapies from 2012 to 2016. The use of insulins, arguably the highest-risk medications and resulting in an increased inconvenience to patients, steadily increased among tightly controlled patients (HbA1c < 7%) from 2012 to 2016. From these findings, it appears that clinical practice guideline recommendations for looser glycemic targets may be overlooked or overshadowed by recommendations intended for other age groups in addition to a lack of clarity on what constitutes the need to loosen targets. Medications with less hypoglycemic potential (SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors) were prescribed slightly more in 2016, and these differences in prescribing patterns over time is likely a reflection of many of these new drugs being marketed in 2016 that were not in 2012. A population-based cross-sectional study conducted using linked healthcare databases in Ontario, Canada reported that the trend in use of insulin among elderly patients with diabetes in Ontario between 2002 to 2013 remained stable. However, antidiabetic medications with potentially safer profiles were increasingly prescribed among older adults with newly diagnosed diabetes [51].

This study has several important strengths which addressed the gap in the literature regarding diabetes care of older adults treated in primary care settings in the Canadian context. The present study is the first of its kind to report the rates of potential over-treatment in the broad Canadian elderly population. This study extends the scope of past research by focussing on the impact of demographic characteristics such as age on the intensity of glycemic control and rates of potential over-treatment among those with dementia, as well as the specific drug-use pattern of high-risk anti-diabetic medications among older adults with type-2 diabetes in Canada. Thus far, most studies either considered before or after index HbA1c time frames in defining potential over-
treatment. Considering a pre-index medication window of index HbA1c only does not reflect if a patient was de-intensified after the HbA1c test; similarly, considering only a post-index medication window would not capture over-treatment in the months before the HbA1c test. Thus, an additional strength of this study is the use of both pre- and post-index medication windows around the index HbA1c in defining over-treatment. However, there exist certain limitations that should be addressed. Firstly, the definition of over-treatment is based on interpretation of best evidence and previous models, but it should be recognized that in the context of individual patient scenarios, one could argue this definition to be too restrictive or too lenient, thus the use of the term “potential overtreatment”. Secondly, this study looked at the rates of potential over-treatment in those with HbA1c < 7% on hypoglycemic agents which could lead to severe hypoglycemia; however, the actual hypoglycemic events were not able to be assessed. Next, prescriptions that were captured by EMRs might under-estimate the treatment intensity for patients who had visited multiple physicians including specialists (e.g., endocrinologists) or walk-in visits which are not captured by the primary care EMR, and who had visited clinics that were not part of CPCSSN.

This study used prescription data in assessing the rates of potential over-treatment rather than dispensation data. Use of prescription data doesn’t indicate whether the patients filled the prescription. However, the prescribers intention and practice patterns could be observed using prescription data which cannot be identified through dispensation data if patients make their own decision not to follow through with filling the prescription. Of particular interest, more than half of the older adults during the study period were on no medications which, as mentioned previously, might be one of the reasons for low rates of potential over-treatment. Similar results were observed in a recent Canadian study which used the CPCSSN database in assessing the glycemic control of individuals with diabetes. They reported that 63.6% of their population were receiving no
medications [44]. Thus, our research using MCHP data will look beyond primary care prescriptions and aim to investigate the possible reasons for most of the older adults with diabetes in this Canadian primary care population being on no medications or, in the case of those poorly controlled, being under-treated. Moreover, due to difficulty tracking changes to doses in this extensive primary care database, changes in the dose of prescription medications of the patients were not taken into consideration while defining over-treatment. Although both pre and post index medication windows were considered in assessing potential over-treatment rates, medication/dose de-escalation (de-prescribing) was not determined. Also, we considered only a surrogate marker (HbA1c) and medications in defining over-treatment, not including other factors such as functional status, frailty issues, episodes of hypoglycemia, disease duration and life-expectancy as EMRs do not capture these variables consistently or at all. However, we looked at those with age >80 years and with dementia as ways of forming an understanding as we do not have usable frailty or life-expectancy measures.

3.5 Conclusion

Although potential over-treatment exists in this broad Canadian primary care population, the rate was low compared with US cohorts with no evidence that it was increasing over time. However, with over one-third of patients with poorly controlled diabetes receiving no medications, there appears to be an imbalance with under-treatment among poorly controlled patients coupled with potential over-treatment among tightly controlled patients. Using more rational glycemic targets, those with advanced age and presence of dementia had higher rates of overtreatment. Although there was a variation in drug-use pattern of high-risk medications over time, the trend has to be continually shifted towards de-intensification and de-prescribing, particularly in those at highest risk of harm and lowest likelihood of benefit. Despite changes to the clinical practice guideline
recommendations, a minimal change in the potential over-treatment rates were observed over time. Thus, there is a need for individually tailored personalized diabetes management among older adults in Canada.
3.6 References


37. American Diabetes Association. Older Adults: *Standards of Medical Care in Diabetes.* *Diabetes Care.* 42 (Supplement-1) S139-S147. 


CHAPTER 4 – Assessment of burden related to medications & HbA1c testing frequency among older adults with type-II diabetes in Canada

4.1 Introduction

Over 2.3 million (7.3%) Canadian aged 12 years and older are living with diabetes as of 2017 [1]. The prevalence of diabetes increases with age and older adults represent almost 48% of the total number of people living with the disease [2]. Diabetes is a condition associated with a medical and financial burden to both individuals and society. Diabetes represents a significant cost to the Canadian healthcare system, with a projected estimated direct healthcare cost of around 15 billion dollars by 2022 [3]. A study conducted in the United States reported that a person living with diabetes would spend around $85,000 in a lifetime as a medical cost to treat the disease and its related complications [4]. In Canada, older adults were prescribed an average of 6.9 different drug classes in 2016 with nearly every 1 in 4 (1.6 million) prescribed 10 or more drug classes [5], which is similar to the approximately 20% of elderly Americans receiving 10 or more medications [6]. Older adults with diabetes have higher chances of receiving polypharmacy than those without diabetes [7]. In addition to management of hyperglycemia, prevention of macro and microvascular complications and associated clinical conditions such as geriatric syndromes (dementia, falls, malnutrition, urinary incontinence, and visual disturbances) might act as contributing factors for multiple drug-use among those with diabetes [8]. Within the last decade there has been a surge of new classes of antidiabetic drugs, focusing on their potential to deliver more convenient administration and to exhibit a lower risk of hypoglycemia over conventional alternatives. However, adopting newer more costly therapies can be of concern in older adults, some of whom may have limited income. In addition, older adults have a higher risk of experiencing adverse drug
events than younger counterparts and there is a general lack of study of these agents specifically in older adults. However, multiple-drug use is not always inappropriate, especially among complex older adults with multiple comorbidities. It is challenging for clinicians to determine what is appropriate prescribing for the individual patient. The risks and benefits of pharmacological interventions should be weighed and discussed with the patients to facilitate shared decision making, thereby ensuring care that provides the most benefit and the least burden.

Use of multiple medications is highly prevalent among older adults with diabetes and is attributable to factors such as advanced age, multiple comorbidities, and complications of diabetes. More than one-third (36%) of Canadian adults have two or more health conditions such as hypertension, heart disease, chronic obstructive pulmonary disease, and arthritis, in addition to diabetes [9]. Concerns regarding the possible harms of polypharmacy have been supported by observational studies showing an association between polypharmacy and adverse events such as hospitalizations and falls [7]. This is in addition to the everyday challenges of medication management including pill burden and timing of administration, cost, and the added testing associated with added medications. Thus, assessing the burden among older adults with diabetes is essential and should inform current clinical practices.

Although non-pharmacological approaches for managing diabetes are appropriately recommended as the initial and continual approach to care, the treatment of diabetes often advances to the use of multiple antidiabetic agents, including insulins and medications for other comorbidities. Elderly patients with diabetes pose a particular challenge to clinicians for managing medications. The ultimate goal of diabetes management is to prevent and control hyperglycemia, macrovascular, and microvascular complications, thereby reducing the clinical and economic burden. However, before the initiation of pharmacological interventions, providers should consider the magnitude of
risk and benefit associated with each medication, particularly in the context of potential to achieve long-term complication reduction considering shortened life expectancy [10].

A study using National Health and Nutrition Examination Survey data found that initiating a second or third medication for glycemic control achieves a smaller reduction in HbA1c when compared with the first medication as monotherapy [11]. In addition, a meta-analysis examining the efficacy of oral glucose-lowering agents concluded that lower reduction in average HbA1c levels would be observed in patients having tight glycemic controls [12]. These findings suggest that there are diminished benefits of putting patients on multiple medications in order to achieve treatment targets. As well, in addition to multiple drug-therapy posing a risk for adverse drug reactions [13], drug-drug interactions [14], and economic burden [15], recent evidence suggests that the greater the number of medications the patient is on, the less likely they are of being adherent to the regimen in the first place [16]. Furthermore, the burden imposed by diabetes treatments such as insulins can also eventually have a negative effect on their quality of life [17]. At times, multiple drug-use is associated with the prescribing cascades where ADRs are misinterpreted as new medical conditions, which might result in adding-up new medications to treat the condition [18].

Although many studies have assessed the drug-use pattern of antidiabetic medications among diabetes patients [19-22], very few have looked at the burden. Most of the studies that evaluated the burden among diabetes patients relied on self-reported data [19, 22-26]; thus, there is minimal information on burden and its transition over time among older adults with diabetes.

Laboratory tests are essential in clinical practice as test results could serve as decision-making nodes in diagnosis, treatment, and assist in monitoring response to therapy. Generally, haemoglobin A1c (HbA1c) testing is considered as a gold-standard which infers the patient’s
disease status and performance with regards to blood glucose levels over the past 3-4 months [27]. However, measures, such as HbA1c, although important, need to be utilized with the appropriate frequency. With the continuous rise in the prevalence of diabetes, it is estimated that there is an average annual increase of 8-10% in the workload of medical laboratories [28]. In Ontario there was an increase in HbA1c tests performed of 55% from 2006/07 to 2011/12 with an associated cost of $30 million [29], emphasizing the need to determine an optimal frequency for HbA1c testing in order to manage both patient burden and healthcare productivity.

More frequent monitoring of HbA1c is appropriate for patients with fluctuating glycemic control levels, those receiving intensified treatment, or those who require close monitoring such as pregnant women, but not for patients who maintain balanced glycemic control. Over-testing among patients with stable and controlled glycemic levels not only is unhelpful, but would contribute to their treatment burden. As a result, there is a consensus in several current guidelines that HbA1c should be tested less frequently (i.e. once or twice annually among well-controlled patients) [30-35]. The Canadian Diabetes Association (CDA) guidelines recommend measurement of HbA1c at least once in every 3 months when glycemic targets are not being met, and therapy is being adjusted often [36]. Otherwise, it is suggested to test twice a year in stable patients where glycemic targets have been consistently achieved [37].

Concerns have been raised regarding the over-testing of HbA1c among elderly patients with diabetes. Studies conducted in the United States and Europe reported a high-prevalence of HbA1c over-testing [28, 38-39]. There is a lack of studies addressing the burden related to overall prescribed medications and HbA1c testing frequencies. Therefore, we sought to examine burden in terms of the number of medications prescribed and the frequency of HbA1c testing overall and across various glycemic control cut-offs among the elderly population with type-2 diabetes across
Canada. This exploration may suggest a relationship between treatment intensity and the burden among older adults, which could serve as an adjunct to current approaches that identify potential over-treatment issues in this population.

4.2 Methods

4.2.1 Study Design, Setting & Data source

This is a retrospective observational cohort study using primary care data extracted for public health surveillance and research purposes by the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) [40]. The CPCSSN database is comprised of electronic medical chart data of more than 1.8 million patients provided by 1,262 sentinel providers using 12 different EMR products from 217 participating primary care practice sites in 8 Canadian provinces and territories.

4.2.2 Study Population/Cohort Selection

A validated case definition of diabetes by CPCSSN was used in determining the study population [41]. The study cohort consisted of those age 65 years or older, with two or more billing codes for diabetes (ICD-9 code 250) in the past 2 years (or) presence of at least two FBG levels greater than 7mmol/litre in one year (or) any HbA1C ≥ 7 (or) a first claim for an oral hypoglycemic drug or insulin (with the exception of Polycystic Ovarian Syndrome, Gestational Diabetes, Secondary (chemical induced) Diabetes, Hyperglycemia NOS, and Neonatal diabetes mellitus where the medication criteria alone is insufficient), between 2010 to 2016, and in patients who had at least one HbA1c measurement. This definition infers that for those who are 65 years of age, a period of as much as the two years before them turning 65 was used to define them as having diabetes.

4.2.3 Glycemic control
Two cross-sectional slices were assessed in determining glycemic control for two 1-year time spans in the study period (2012 and 2016). We used the first recorded HbA1c in the year in question for each patient as the index HbA1c. Glycemic control was categorized as category-1 (<7 %), category-2 (7 % - < 8 %), category-3 (8% - < 9%), and category-4 (≥ 9 %).

4.2.4 Treatment intensity and Overtreatment

Potential overtreatment was defined as a patient having an index HbA1c value of less than 7% and having been prescribed any anti-diabetic medications other than metformin within the 9 months before or 3 months after the index HbA1c value. Since primary care practitioners in Canada generally prescribe medications for up to a year at a time, a 12-month timeframe was desired: a 9-month (pre-index) look-back period was considered in order to capture the maximum number of prescriptions while including a look-forward period of 3-months (post-index) as any change to medications based on HbA1c could likely have happened within 3-months of the index HbA1c. Those with known potential for hypoglycemia (sulfonylureas, meglitinides, and insulins) were considered as high-risk medications.

4.2.5 Medication burden

Using ATC codes, medications prescribed within the 9 months before or 3 months after the index HbA1c value were identified to assess the number of medications per patient. Patients were categorized based on the usage of number of medications as 0, 1-4, 5-9, and ≥10, and medication burden is defined as the patients who were on ≥10 medications.

4.2.6 HbA1c testing frequency

Total number of HbA1c tests performed in the respective cross-sectional years (2012 and 2016) for each patient were assessed and represented as means with standard deviation and frequencies.
Testing three or more times a year in patients with well-controlled glycemic levels (HbA1c <7%) was considered over-testing. Testing once a year in patients with poorly-controlled glycemic levels (HbA1c ≥9%) was considered under-testing.

4.2.7 Secondary Objectives

4.2.7.1 Impact of age on medication burden

Patients were categorized into 65-74, 75-84, and ≥85-year age categories for 2012 & 2016 in assessing the associations of age with medication & test burden. Then patients were categorized based on the usage of number of medications as 0, 1-4, 5-9, and ≥10 medication, and represented as proportions in assessing medication burden.

4.2.7.2 Assessing medication burden among potentially over-treated patients

The extent of medication burden among potentially over-treated patients, and those who were potentially over-treated with age ≥80 years were also assessed. For those age ≥80 years, an HbA1c target of <8 % was considered in defining potential over-treatment, instead of < 7%.

4.2.7.3 Assessing HbA1c testing frequency based on medication-use

The frequency of HbA1c tests were assessed based on usage of number of medications across various glycemic control levels and represented as means and standard deviations for the 2012 and 2016 cohorts.

4.2.7.4 Assessing HbA1c testing frequency in patients with dementia

Frequency of HbA1c tests performed in patients with dementia and advanced age (≥ 80 years) was assessed for both the 2012 & 2016 cohorts based on their glycemic control levels as category-1 (<7 %), category-2 (7 % - < 8 %), category-3 (8% - < 9%), and category-4 (≥ 9 %). Among those
with dementia, age ≥ 80 years, and HbA1c < 8% testing three or more times a year was considered over-testing.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses. The sample characteristics were computed using descriptive statistics and the degree of medication burden and HbA1c tests were represented as proportions. Approvals were granted by the University of Manitoba Health Research Ethics Board (HREB) and the Canadian Primary Care Sentinel Surveillance Network.

4.3 Results

4.3.1 Patient demographics & characteristics

Of 95,054 patients diagnosed with type-2 diabetes between 2010 to 2016 23,080 in 2012 and 33,864 in 2016 satisfied the study’s inclusion criteria. An overall cohort of 41,032 patients (51.6% males) with a mean age of 76.6 years were identified and categorized based on their index HbA1c into four categories (<7%, 7%-<8%, 8%-<9%, and ≥9%). (Table 4.1) The largest proportion of the patients belonged to the age group of 65-74 years (42%); while, 19.8% of the study population were 85 years or older. More than half of the patients belong to category-1 (HbA1c < 7%) (58.3%); while 7.8% were poorly-controlled patients (category-4, HbA1c ≥9%). 9.6% had a diagnosis of dementia during the study period (Table 4.1).

Table 4.1 Demographics and characteristics by HbA1c categories
### Patient Characteristics (N=41,032)

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N=41,032)</td>
</tr>
<tr>
<td>Mean Age ± S.D</td>
<td>76.6±7.8</td>
</tr>
<tr>
<td>Age, 65-74</td>
<td>76.9±7.9</td>
</tr>
<tr>
<td></td>
<td>76.4±7.7</td>
</tr>
<tr>
<td></td>
<td>76.0±7.6</td>
</tr>
<tr>
<td></td>
<td>75.3±7.8</td>
</tr>
<tr>
<td>Age, 75-84</td>
<td>9677 (55.9%)</td>
</tr>
<tr>
<td></td>
<td>4199 (24.2%)</td>
</tr>
<tr>
<td></td>
<td>1790 (10.3%)</td>
</tr>
<tr>
<td></td>
<td>1639 (9.5%)</td>
</tr>
<tr>
<td>Age, ≥85</td>
<td>5013 (61.7%)</td>
</tr>
<tr>
<td></td>
<td>1882 (23.1%)</td>
</tr>
<tr>
<td></td>
<td>687 (8.4%)</td>
</tr>
<tr>
<td></td>
<td>541 (6.6%)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>11939 (50.0%)</td>
</tr>
<tr>
<td></td>
<td>5336 (53.7%)</td>
</tr>
<tr>
<td></td>
<td>2200 (55.6%)</td>
</tr>
<tr>
<td></td>
<td>1728 (53.5%)</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>11983 (50.1%)</td>
</tr>
<tr>
<td></td>
<td>4594 (46.2%)</td>
</tr>
<tr>
<td></td>
<td>1753 (44.3%)</td>
</tr>
<tr>
<td></td>
<td>1499 (46.4%)</td>
</tr>
</tbody>
</table>

### HbA1c Categories

<table>
<thead>
<tr>
<th>HbA1c Categories</th>
<th>I (&lt; 7%)</th>
<th>II (7% to &lt; 8%)</th>
<th>III (8% to &lt; 9%)</th>
<th>IV (≥ 9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 23922 (58.3%)</td>
<td>n = 9930 (24.2%)</td>
<td>n = 3953 (9.63%)</td>
<td>n = 3227 (7.86%)</td>
</tr>
<tr>
<td>Mean Age ± S.D</td>
<td>76.6±7.8</td>
<td>76.9±7.9</td>
<td>76.4±7.7</td>
<td>76.0±7.6</td>
</tr>
<tr>
<td>Age, 65-74</td>
<td>9677 (55.9%)</td>
<td>4199 (24.2%)</td>
<td>1790 (10.3%)</td>
<td>1639 (9.5%)</td>
</tr>
<tr>
<td>Age, 75-84</td>
<td>9232 (59.1%)</td>
<td>3849 (24.6%)</td>
<td>1476 (9.4%)</td>
<td>1047 (6.7%)</td>
</tr>
<tr>
<td>Age, ≥85</td>
<td>5013 (61.7%)</td>
<td>1882 (23.1%)</td>
<td>687 (8.4%)</td>
<td>541 (6.6%)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>11939 (50.0%)</td>
<td>5336 (53.7%)</td>
<td>2200 (55.6%)</td>
<td>1728 (53.5%)</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>11983 (50.1%)</td>
<td>4594 (46.2%)</td>
<td>1753 (44.3%)</td>
<td>1499 (46.4%)</td>
</tr>
</tbody>
</table>

### Comorbidities

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Overall</th>
<th>II (7% to &lt; 8%)</th>
<th>III (8% to &lt; 9%)</th>
<th>IV (≥ 9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>29045 (70.8%)</td>
<td>17258 (72.1%)</td>
<td>6932 (69.8%)</td>
<td>2698 (68.2%)</td>
</tr>
<tr>
<td>Dementia</td>
<td>3949 (9.6%)</td>
<td>2319 (9.7%)</td>
<td>912 (9.2%)</td>
<td>380 (9.6%)</td>
</tr>
<tr>
<td>COPD</td>
<td>4233 (10.3%)</td>
<td>2652 (11.1%)</td>
<td>901 (9.1%)</td>
<td>370 (9.3%)</td>
</tr>
<tr>
<td>Depression</td>
<td>5898 (14.4%)</td>
<td>3585 (15.0%)</td>
<td>1213 (12.2%)</td>
<td>577 (14.6%)</td>
</tr>
<tr>
<td>Smoking status, yes (%)</td>
<td>13249 (32.3%)</td>
<td>7814 (32.6%)</td>
<td>3129 (31.5%)</td>
<td>1208 (30.5%)</td>
</tr>
</tbody>
</table>

#### 4.3.2 Assessing medication burden

Overall, the mean number of medications prescribed per patient was 4.4 (SD ± 4.5) in 2012 and 5.1 (SD ± 4.9) in 2016. There was a decline in the proportion of patients who were on no medication from 2012 (22%) to 2016 (17%). There were only minor differences observed between patients who were on 1 - 4 and 5 - 9 medications over time, no difference in the proportion of
patients who were receiving 10 or more medications, and 39% and 41% were prescribed 5 or more medications in the 2012 and 2016 cohorts, respectively (Figure 4.1).

![Pie charts showing medication use categories in 2012 and 2016](image)

**Figure 4.1** Proportions of medication use categories based on number of medications in 2012 & 2016

4.3.3 Impact of age on medication burden

An apparent drop was observed among no medication users as age increased in 2012; in contrast, there was a modest rise as age increased in 2016 (Figures 4.2 & 4.3). The proportion of patients on 5 or more medications rose by 9.5% in 2012 and 3.5% in 2016, indicating a rise in medications used as patient’s age; however, the rise was smaller in the 2016 cohort. The proportion of patients on 10 or more medications increased as age increased in both 2012 and 2016 cohorts.
Figure 4.2 Proportions of medication use by age categories 2012

Figure 4.3 Proportions of medication use by age categories 2016
3.3.4 Assessing medication burden among potentially over-treated patients

There was a significant rise in 10 or more medication users among those who were potentially over-treated, and age ≥ 80 years compared to the overall patients in both cohorts (Figures 4.4 and Figures 4.5). More than one-third of the intensively treated patients (36.3% in 2012 and 33.7% in 2016) and those with age ≥ 80 years (40.5% in 2012 and 37.5% in 2016) were receiving 10 or more drugs in both the cohorts. There was a modest decline in 10 or more medication users from 2012 to 2016.

![Figure 4.4](image)  
**Figure 4.4** Comparison of proportions of medication-use in 2012 cohort
3.3.5 Assessing HbA1c testing frequency

The mean number of tests per patient in 2012 and 2016 cohorts were 2.6 (±1.9) and 2.7 (±1.6). Overall, 19.2% (2012) and 19.0% (2016) of patients had both tight control and 3 or more HbA1c tests per year (i.e. potentially over-tested), while 2.4% (2012) and 2.3% (2016) of patients had inadequate control and had 1 or less HbA1c tests per year (i.e. potentially under-tested). As a reflection of all patients with inadequate control, this translates to 33.9% and 29.8% of patients being potentially under-tested. Regardless of glycemic control, 6.3% in 2012 and 5.8% in 2016 were tested 5 or more times in a year (Table 4.2).
### Table 4.2 Proportions of HbA1c testing frequency by HbA1c categories in 2012 & 2016

<table>
<thead>
<tr>
<th>HbA1c Testing Frequency</th>
<th>2012 cohort</th>
<th>2016 cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (&lt; 7%) (n=14144)</td>
<td>II (7% - &lt; 8%) (n=5392)</td>
</tr>
<tr>
<td>1</td>
<td>5744 (40.61%)</td>
<td>1442 (26.74%)</td>
</tr>
<tr>
<td>2</td>
<td>3978 (28.12%)</td>
<td>1475 (27.35%)</td>
</tr>
<tr>
<td>3</td>
<td>2271 (16.05%)</td>
<td>1204 (22.32%)</td>
</tr>
<tr>
<td>4</td>
<td>1399 (9.89%)</td>
<td>836 (15.50%)</td>
</tr>
<tr>
<td>≥5</td>
<td>752 (5.31%)</td>
<td>435 (8.06%)</td>
</tr>
<tr>
<td></td>
<td>I (&lt; 7%) (n=19454)</td>
<td>II (7% - &lt; 8%) (n=8471)</td>
</tr>
<tr>
<td>1</td>
<td>7515 (38.62%)</td>
<td>2004 (23.65%)</td>
</tr>
<tr>
<td>2</td>
<td>5515 (28.34%)</td>
<td>2246 (26.51%)</td>
</tr>
<tr>
<td>3</td>
<td>3568 (18.34%)</td>
<td>2194 (25.90%)</td>
</tr>
<tr>
<td>4</td>
<td>1967 (10.11%)</td>
<td>1414 (16.69%)</td>
</tr>
<tr>
<td>≥5</td>
<td>889 (4.56%)</td>
<td>613 (7.23%)</td>
</tr>
</tbody>
</table>

* Yellow indicates the proportions contributing to the over-testing rates. Green indicates the proportions contributing to the under-testing rates.

3.3.6 Assessing HbA1c testing frequency in patients with dementia

In patients age ≥ 80 years with dementia, using a conservative cut-off of HbA1c < 8% to define overtreatment, overall 29.2% in 2012 and 25.0% in 2016 over-testing rates were observed. Regardless of the glycemic control, 35.6% (2012) and 33.0% (2016) of the older adults with dementia were tested 3 or more times in a year (Table 4.3).
Table 4.3 Proportions of HbA1c testing frequency in patients with dementia and age ≥ 80 years by HbA1c categories in 2012 & 2016

<table>
<thead>
<tr>
<th>HbA1c Frequency</th>
<th>2012 cohort</th>
<th>2016 cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (n=884)</td>
<td>II (n=329)</td>
</tr>
<tr>
<td></td>
<td>(&lt; 7%)</td>
<td>(7% to &lt; 8%)</td>
</tr>
<tr>
<td>1</td>
<td>355 (40.15%)</td>
<td>101 (30.69%)</td>
</tr>
<tr>
<td>2</td>
<td>255 (28.84%)</td>
<td>90 (27.35%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>274 (30.99%)</td>
<td>138 (41.94%)</td>
</tr>
<tr>
<td></td>
<td>I (n=1115)</td>
<td>II (n=432)</td>
</tr>
<tr>
<td></td>
<td>(&lt; 7%)</td>
<td>(7% to &lt; 8%)</td>
</tr>
<tr>
<td>1</td>
<td>521 (46.72%)</td>
<td>157 (36.34%)</td>
</tr>
<tr>
<td>2</td>
<td>296 (26.54%)</td>
<td>105 (24.30%)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>298 (26.72%)</td>
<td>170 (39.35%)</td>
</tr>
</tbody>
</table>

* Yellow indicates the proportions contributing to the over-testing rates.

3.3.7 Assessing HbA1c testing frequency based on medication-use

Among intensely-controlled patients (HbA1c < 7%), the mean number of tests per year for those on no medications were 2.1 (2012) and 2.0 (2016), with a small increase to 2.4 tests for those on 3 or more medications in 2012 and a larger increase to 3.5 tests in 2016 (Table 4.4). Overall, frequency of testing did not differ dramatically between patients who were well-controlled (< 7%) and those who were poorly-controlled (≥ 9%).
Table 4.4 HbA1c testing frequency by medication use in 2012 & 2016

<table>
<thead>
<tr>
<th>No. of Meds</th>
<th>2012 cohort</th>
<th>2016 cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I (&lt; 7%) Mean tests (SD)</td>
<td>II (7% - &lt; 8%) Mean tests (SD)</td>
</tr>
<tr>
<td>0</td>
<td>2.1 (1.4)</td>
<td>2.5 (1.6)</td>
</tr>
<tr>
<td>1</td>
<td>2.5 (2.0)</td>
<td>2.9 (2.4)</td>
</tr>
<tr>
<td>2</td>
<td>2.5 (1.9)</td>
<td>2.8 (1.9)</td>
</tr>
<tr>
<td>≥ 3</td>
<td>2.4 (1.3)</td>
<td>3.6 (2.5)</td>
</tr>
</tbody>
</table>

4.4 Discussion

Using EMR data from a national-level database from 2010 through 2016, we examined the overall use of prescription drugs and frequency of HbA1c testing in a large elderly cohort of patients with type-2 diabetes across Canada. The mean number of medications prescribed per elderly patients was 4.4 in 2012 and increased to 5.1 in 2016. Comparing this to the average number of medications prescribed to Canadian seniors of 6.9 in 2016 according to the Canadian Institute for Health Information (CIHI), it should be noted that patient reporting for CIHI includes all prescriptions whereas our data was exclusively from primary care [5]. The proportion of patients who were receiving no medications in 2012 was notably decreased in 2016 indicating an increase in overall medication use in this population over time. The proportions of patients with multiple drug use were high, as nearly 39% and 41% were prescribed with five or more medications in 2012 and
2016, respectively. Similar findings among patients with diabetes have been observed in other populations [42-44]. Furthermore, in the current study the rate of medication burden (≥ 10 medications) was significantly higher among those who were potentially over-treated, and this situation is exaggerated further among those with advanced age (≥ 80 years). There was no difference in the proportion of patients who were on ten or more medications (13%) from 2012 to 2016 in our cohorts of patients with diabetes. While CIHI also reported similar proportions in 2016 to their previous report in 2011, they reported more than one-quarter (26.5%) of overall seniors were prescribed ten or more different drug classes [5]. Again, it should be noted that this accounted for any reported prescriptions, which would include sources beyond primary care. CIHI also stated that in 2016 approximately 13%, 51% and 29.8% were on 0, 1-4, 5-9 chronic medications respectively, which closely lined-up with our study findings (17%- 0, 42%- 1 to 4, 28%- 5 to 9) [5].

Many studies have examined the rates of polypharmacy among older adults with diabetes around the globe, suggesting a high prevalence ranging from 40% to as high as 80% [45-48]. However, there is limited information in the literature regarding medication burden among potentially over-treated patients and variations within the different age groups. In this study, we noticed an increase in the proportion of patients who were on 10 or more medications as age increased. These findings are in accordance with the 2016 CIHI report on Drug Use Among Seniors in Canada, where there was an increase among users of 10-14 and 15 or more medications as age increased [5]. More than one-third of the intensively treated patients as well as those age ≥ 80 years were receiving 10 or more drugs in both cohorts.

The presence of comorbidities associated with diabetes and advanced age is a strong factor favoring the addition of multiple agents to an individual's medication regimen. A similar study
which assessed the drug burden among elderly patients with diabetes found that the mean number of drug classes used by newly-diagnosed diabetes patients was high before diagnosis (5.0) and increases significantly after diabetes diagnosis (6.6) [49]. A Canadian study examining the prevalence of polypharmacy among older adults living in nursing homes of British Columbia reported that patients who were potentially over-treated are prescribed more non-diabetic medications than those with a higher HbA1c level [50]. Clinicians caring for older adults with diabetes face a therapeutic challenge in balancing the needs of the patients and attempting to achieve optimum control of medical problems while trying to keep the medication profile as simple as possible. Naturally, use of multiple medications increases the likelihood of unintended therapeutic outcomes because of underlying physical disability [51]. At times, prescribing multiple medications might increase the chances of prescribing and dispensing errors, highlighting the need for healthcare providers to routinely monitor vulnerable individuals for potentially inappropriate medications, adverse drug events, and drug-drug interactions.

The current study is novel in its look at the associations between overall drug burden and treatment intensification in the context of HbA1c testing frequency among those with advanced age and dementia in a broad cross-section of older adults with diabetes in Canada. Evidence suggests that clinical outcomes for well-controlled patients tested twice a year or quarterly a year were similar [52-53]. Our study found that about one-fifth of patients were potentially over-tested and that regardless of glycemic control, approximately 6% were tested 5 or more times in a year. On the other hand, approximately a third of patients with inadequate glycemic control (HbA1c ≥9%) were tested once a year, suggesting under-testing.

High testing frequency may be due in part to practice guidelines only providing recommendations on the minimum testing required but providing little mention of appropriate maximum limits [37],
particularly regarding patient context and circumstances to guide the clinician in a patient-centred approach. As HbA1c testing is relatively inexpensive, over-use might be easily ignored by clinicians and accepted by patients if implied that it is important. However, unnecessary testing can have adverse effects on both patients and the healthcare system, as over-testing can cause patient discomfort, inconvenience, and changes in treatment [54]. In addition to the healthcare cost and the burden posed on individuals with diabetes, over-testing naturally also contributes to increased provider workload through test ordering, follow-up, and the aforementioned potential for subsequent treatment changes. [55-56]. Although, as noted above, our study found a significant portion of patients to be potentially over-tested, the rates and severity of over-testing appear to be lower than rates found in several other studies internationally. A retrospective study using national administrative claims data in the US reported that excessive HbA1c testing (at least five tests per year) was observed in more than half of their study population and found that excessive testing was associated with treatment intensification [57]. In contrast, we observed much lower rates of 6.3% in 2012 and 5.8% in 2016 for testing 5 or more times in a year. A retrospective study assessing the over-use of HbA1c testing among older adults in the US reported that 8.4% of patients received at least one repeat HbA1c within 30 days of their initial test and 30.8% within 90 days [58]. A study conducted in Alberta, Canada found that the most common testing interval among diabetes patients in Alberta was around 3 months [59].

This study also assessed the HbA1c testing frequency among patients with advanced age (≥80 years) and those with dementia, finding that despite advanced age and dementia, almost one-third of patients were tested three or more times in a year in both cohorts with a minimal drop in these rates over time. Considering the burden of disease for those with dementia, special attention to minimally disruptive approaches to care becomes of significant importance in this population. Of
note, our study found that the rates of potential HbA1c over-testing were significantly higher among patients with dementia (29.2% in 2012 & 25.0% in 2016) compared to the overall over-testing rates (19.2% in 2012 & 19.0% in 2016).

This study has provided important insights into the burden related to medications and testing frequency of HbA1c among elderly patients with diabetes across Canada. The overall findings of this study suggest that the rates of multiple drug-use are higher as age increases, including, and in particular, among those who were potentially over-treated with advanced age. In addition, our findings reveal a higher frequency of testing in those with dementia and advanced age. This information may be useful to policy & decision-makers seeking to understand care patterns and drug regimens for diabetes patients over time. However, it must be noticed that multiple drug-use and over-testing are not harmful all the time, as various underlying clinical conditions compel such use at times. Thus, future studies to assess inappropriate medication-use and testing in this population are warranted. In order to provide older adults with appropriate diabetes care, multidisciplinary strategies must be employed with a comprehensive approach by keeping the patient's goals of care in mind. In order to minimize inappropriate drug-use, providers should actively involve patients in clinical decision-making. Since older adults with more medications have increased risk of adverse health outcomes, reducing polypharmacy and preventing inappropriate drug-use should be a major goal of care in this population.

There are certain limitations in the current study. Firstly, due to difficulty in extracting specifics about the type of medications, we could not differentiate between acute and chronic medications. Thus, the proportions that are reported are likely an over-estimate of chronic medication use. Secondly, we did not consider the number of comorbid conditions in assessing multiple drug-use, which in and of itself can pose significant burden. In addition, as eluded to previously, definitions
of over- and under-use are consensus definitions based on the best available evidence in the literature, but might not be universally agreed upon. Furthermore, including patients with at least one HbA1c value according to one of the study’s inclusion criteria might under-estimate the under-testing rates. Lastly, only prescription and test order data that were captured by primary care EMRs, which do not typically consist of orders by specialists, were considered in defining over & under-use, which likely under-estimates patient burden. Lastly, in order to encompass a more comprehensive measure of burden, future directions for this research include aspects of care burden that were not addressed in this study, namely medication costs and provider visits for follow-up.

4.5 Conclusion

A significant burden with non-diabetic medications was observed among older adults with diabetes, appearing to be in line with the recent Canadian statistics. Those with potential over-treatment with anti-diabetic medications were also prescribed more non-diabetic medications. Older adults with advanced age and dementia did not appear to have been targets for minimizing burden, instead they appear to be posed with greater burden of both over-testing and treatment. Although some of the outcomes measured including use of 10 or more medication, 5 or more annual HbA1c tests, and under-testing, appear to show improving trends over time, the potential improvements are very modest, suggesting that testing and treatment practices need to consider the individual patient, their individual context, and the potential net benefit of management decisions.
4.6 References


CHAPTER 5 – Relationship Between Prescribed vs. Dispensed Anti-Diabetic Medications in assessing the intensity of potential over-treatment among Older Adults with Type-II Diabetes in Manitoba

5.1 Introduction

The prevalence of type-2 diabetes is increasing worldwide and is a leading cause of morbidity and mortality. In 2015, the estimated prevalence of diabetes in Canada was 9.3% (3.4 million), and is predicted to rise to 12.1% (5 million) by 2025, representing a 44% increase [1]. Similarly, the prevalence of diabetes in Manitoba is estimated to increase by 37%, reaching 11.3% by 2026 [2]. People with diabetes incur health care costs two to three times greater than people without diabetes. The annual out-of-pocket cost for Manitobans with type 2 diabetes is approximately $1930, which accounts for 2-5% of their annual income [3].

Diabetes is highly prevalent among older adults in Canada; however, there remains significant uncertainty regarding the interpretation of the available evidence regarding optimal glycemic management. The specific glycosylated hemoglobin (HbA1c) targets among older adults should be based on individual characteristics. Over the past decade, many concerns have been raised regarding optimal glycemic control in the elderly with diabetes. Intensive glycaemic control is recommended to reduce the burden of cardiovascular disease and microvascular complications in people with diabetes [4]. However, the results of major randomized clinical trials and systematic reviews on the net benefits of such treatment bring into question the robustness and applicability of these recommendations [5-9]. Furthermore, clinical trials investigating the effect of intensive treatment in older adults have demonstrated that targeting tight glycemic control (i.e., HbA1c < 6.5%) did not reduce end-stage microvascular and cardiovascular complications, but increased the
risk of severe hypoglycemia, weight gain and mortality [5-6]. Long-term follow-up studies have only shown associations with intensive glycemic control and small cardiovascular benefits for those patients with greater life-expectancy [10].

Hypoglycemia is a major concern and poses serious health threats to older adults with diabetes [11-14]. Epidemiological evidence suggests that hypoglycemia is also associated with unfavorable health outcomes such as higher risk of dementia [15], falls [16], fall-related fractures [17], reduced health-related quality of life [18-19], and increased mortality [20]. Therefore, addressing the relationship between glucose control and risk of severe hypoglycemia is critical for making informed decisions about the type and intensity of therapy. Diabetes management should focus on balancing the long-term harms of under-treatment with the short-term and long-term harms of over-treatment. [21-23].

Numerous recent observational studies have shown that a substantial proportion of older adults are tightly controlled and/or potentially over-treated [13-14, 19-20, 24-30]. Study definitions of intensive/over-treatment have varied somewhat, but having an index HbA1c of less than or equal to 7% while being treated with insulins or sulfonylureas is fairly consistently utilized in observational literature to define over-treatment in older age cohorts [13, 27, 28, 31, 32]. This understanding of uncertain benefit, concern for harm, and signals of overtreatment have led major diabetes societies from North America and Europe to recommend individualized targets among older patients with diabetes who have significant comorbid conditions which put them at higher risk for developing hypoglycemia [33]. As the treatment of chronic diseases such as diabetes continues to advance to achieve care that is individualized to each patient, the issue of potential over-treatment among the elderly population is a strong example of the importance of the need to aim for improved rather than minimized quality of life.
The American Diabetes Association (ADA) guidelines recommend glycemic targets of HbA1c < 7.5%, < 8%, and < 8.5% for those who are considered as healthy, complex/intermediate, and very complex/poor health, respectively [34]. The recent American College of Physicians (ACP) clinical guidelines advise clinicians to aim for HbA1c level between 7% to 8% for most of the patients with type-2 diabetes, to consider de-intensifying therapy in those who’s HbA1c is < 6.5%, and aim to minimize hyperglycemia symptoms, avoiding targeting HbA1c entirely in those with shorter life expectancy as a result of, for example, advanced age or chronic conditions such as dementia [35]. The Diabetes Canada guidelines suggest considering HbA1c targets of ≤ 7%, 7.1-8.0%, and 7.1-8.5% for those who are considered as functionally independent, functionally dependent, and frail and/or with dementia, respectively [36]. Despite differences in actual targets the Canadian guidelines along with other major guideline groups, do agree on a consistent message to personalize therapy to obtain tighter glycemic control in younger and healthier patients, and less stringent HbA1c targets for older patients with advanced age, longer disease duration, limited life expectancy, presence of multiple comorbid conditions, recurrent hypoglycemic episodes, functional dependency, and other frailty issues [33-38]. However, the extent of implementation of these guidelines in real-world practice is unclear.

Currently, the extent of overtreatment in the elderly population in Manitoba has not been addressed. Considering this and the significant concerns described in this population, an evaluation of glucose management intensity in elderly patients with diabetes is necessary province-wide and nationally. In phase-I using CPCSSN database, we have looked at potential over-treatment at the national level based on prescription data, finding lower rates of potential overtreatment among older adults with diabetes in Canada compared to US observational studies. Importantly, prescriptions that were captured by primary care EMRs might underestimate treatment intensity.
for patients who had visited multiple physicians including specialists (e.g., endocrinologists) or other non-primary care centres. In addition, using prescription-only data doesn’t infer whether the patients filled the prescription. Thus, the main aim of this study was to evaluate the potential overtreatment related to the intensity of glycemic control among older adults with type-2 diabetes across in Manitoba using dispensation data.

5.2 Methods

The current study was conducted in two phases. Phase-I was conducted using primary care data extracted from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) [39]. However, since CPCSSN lacks certain information regarding non-primary care medical service utilization, medications dispensed (as opposed to prescribed), and hospital admissions, we aim to utilize the Manitoba Centre for Health Policy (MCHP) database [40] by extrapolating the Manitoba cohort of CPCSSN (Manitoba Primary Care Research Network (MaPCReN)) [41] through a linkage with MCHP.

5.2.1 Study Design, Setting & Data source

This is a retrospective observational cohort study using a large sample of patients from across Manitoba conducted at the College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba. The study used a cohort extracted from MaPCReN and was linked with corresponding MCHP data in assessing the further objectives of the current study.

5.2.2 Study Population/Cohort Selection

A validated case definition of diabetes by CPCSSN was used in determining the study population [42]. The CPCSSNN study cohort consisted of those age 65 years or older, with two/more billing
codes for diabetes (ICD-9 code 250) in the past 2 years (or) presence of at least two FBG levels greater than 7mmol/litre in one year (or) any HbA1c ≥ 7% (or) a first claim for an oral hypoglycemic drug or insulin with the exception of Polycystic Ovarian Syndrome, Gestational Diabetes, Secondary (chemical induced) Diabetes, Hyperglycemia NOS, and Neonatal diabetes mellitus where the medication criteria alone is insufficient, between 2010 to 2016, and in patients who had at least one HbA1c measurement. This definition infers that for those who are 65 years of age, as much as the two years before them turning 65 was used to define them as having diabetes. The MaPCReN cohort (those patients seen in CPCSSN primary care centres in Manitoba) was then extracted from this.

5.2.3 Glycemic control

Two cross-sectional slices were assessed in determining glycemic control for two 1-year time spans in the study period (2012 and 2016). We used the first recorded HbA1c in the year in question for each patient as the index HbA1c. As the CPCSSN database captures actual HbA1c values, glycemic control was determined and was categorized as category-1 (<7 %), category-2 (7 % - < 8 %), category-3 (8% - < 9%), and category-4 (≥ 9 %). This allowed for the categorization of patients by intensity of glycemic control to be carried forward into the MCHP linkage.

5.2.4 Anti-diabetic medication use

Using ATC codes, anti-diabetic medications were identified (see Appendix-1), and those with known potential for hypoglycemia (sulfonylureas, meglitinides, and insulins) were considered as high-risk medications.

5.2.5 Primary Objective: Treatment intensity and Overtreatment
Potential overtreatment was defined as a patient having an index HbA1c value of less than 7% (based on CPCSSN HbA1c data) and having been dispensed any anti-diabetic medications other than metformin (using MCHP data) within the 3 months before or 3 months after the index HbA1c value. Since patients in Manitoba are able to fill up to 3 months of medication at once, a look-back period of 3 months (pre-index) was considered in order to capture the maximum number of prescriptions while including a look-forward period of 3-months (post-index) as any change to medications based on HbA1c could have happened within 3-months of time from the index HbA1c.

5.2.6 Secondary Objectives

5.2.6.1 Assessing the impact of age on the intensity of diabetes management:
Patients were categorized into 65-74, 75-84, and ≥85-year age categories for 2012 & 2016 in assessing the associations of age and intensity of glycemic control. In addition, rates of potential over-treatment among patients age ≥ 80 years with a more conservative cut-off of HbA1c < 8% in defining over-treatment was also assessed.

5.2.6.2 Assessing the impact of prescriber type on the intensity of diabetes management:
The purpose of this objective is to evaluate the contribution of general practitioners (GPs) and non-general practitioners (non-GPs) towards potential over-treatment and the prescribing of high-risk medications among older adults with diabetes in Manitoba. Patients determined to be potentially over-treated were categorized based upon the prescriber type.

5.2.6.3 Comparison of intensity of potential over-treatment using CPCSSN, MCHP and MaPCReN:
Using the unique patient identification numbers of the CPCSSN, MCHP and MaPCReN cohorts, patients were extracted in order to assess differences between potential over-treatment rates between these data sources among older adults with diabetes in Manitoba.

SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for all data analyses. The sample characteristics were computed using descriptive statistics and the rates of potential over-treatment were represented as proportions. Confidence intervals and p-values are performed using test for proportions. MCHP is the custodian of the Manitoba Population Health Research Data Repository of longitudinal, continuously collected population-based data. The repository is composed of anonymized administrative data of Manitobans that permits linkage of records from different databases. Approvals and access were granted by the University of Manitoba Health Research Ethics Board (HREB), the Health Information and Privacy Committee (HIPC) of Manitoba Health, Seniors and Active Living, and MaPCReN. These committees do not require individual consent for research conducted using de-identified administrative data where the privacy of patients is protected and when reasonable safeguards to protect confidentiality and security of personal health information are in place.

5.3 Results

5.3.1 Patient demographics & characteristics

Of 7505 patients diagnosed with type-2 diabetes between 2010 to 2017, 1808 in 2012 and 2815 in 2016 satisfied the study’s inclusion criteria. An overall cohort of 3376 patients (51.8% females) with a mean age of 76.6 years were identified and categorized based on their index HbA1c into four categories (<7%, 7%-%<8%, 8%-%<9%, and ≥9%). (Table 5.1) The largest proportion of the patients belonged to the age group of 65-74 years (46.9%), while 17.1% of the study population
were 85 years or older. Approximately two-thirds (66.1%) of the patients belong to category-1 (HbA1c < 7%), while 5.7% were poorly-controlled patients (category-4, HbA1c ≥9%).

Table 5.1 Demographics and characteristics (2012-2016) by HbA1c categories

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Overall (N=3376)</th>
<th>HbA1c Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (≤7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2231 (66.08%)</td>
</tr>
<tr>
<td>Mean Age ± S.D</td>
<td>76.64±7.67</td>
<td>77.0±7.53</td>
</tr>
<tr>
<td>Age, 65-74</td>
<td>1583 (46.89%)</td>
<td>1000 (63.2%)</td>
</tr>
<tr>
<td>75-84</td>
<td>1215 (35.99%)</td>
<td>840 (69.1%)</td>
</tr>
<tr>
<td>≥85</td>
<td>578 (17.12%)</td>
<td>391 (67.6%)</td>
</tr>
<tr>
<td>Gender, Male</td>
<td>1628 (48.22%)</td>
<td>1044 (46.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>1748 (51.78%)</td>
<td>1187 (53.8%)</td>
</tr>
</tbody>
</table>

5.3.2 Rates of potential over-treatment

The overall rates of potential over-treatment were 20.4% in 2012 and 21.5% in 2016, showing no statistically significant difference between the two years (p = 0.37 [95% CI -1.32 to 3.47]). High-risk hypoglycemic agents (insulins, sulfonylureas, and meglitinides) accounted for 97.0% and 96.7% of over-treatment medications in 2012 and 2016, respectively. Metformin-only users made up 22.4% and 23.3% of the cohorts in 2012 and 2016. Notably, 19.0% and 10.5% of patients with
poor glycemic control (HbA1c ≥ 9%) were receiving no medication in 2012 and 2016 cohorts, indicating under-treatment (Figure 5.1 and 5.2).

<table>
<thead>
<tr>
<th>Proportion of overall 2012 cohort (%)</th>
<th>A1C &lt;7%</th>
<th>A1C 7% -&lt;8%</th>
<th>A1C 8% -&lt;9%</th>
<th>A1C ≥9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Meds</td>
<td>30.2</td>
<td>16.7</td>
<td>8.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Only Metformin</td>
<td>0.1</td>
<td>4.4</td>
<td>7.6</td>
<td>0.8</td>
</tr>
<tr>
<td>HR Meds</td>
<td>0.5</td>
<td>0.06</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Other OHAs</td>
<td>0.06</td>
<td>0.3</td>
<td>0.06</td>
<td>0.5</td>
</tr>
<tr>
<td>Combinations</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Potential overtreatment rate = 20.4%

**HR meds**- High-Risk medications (Insulins, Sulfonylureas, and Meglitinides); Other OHAs- other Oral Hypoglycemic agents (alpha-glucosidase inhibitors, Thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists).

**Figure 5.1** Proportions of treatment by HbA1c category in 2012
HR meds - High-Risk medications (Insulins, Sulfonylureas, and Meglitinides); Other OHAs - other Oral Hypoglycemic agents (alpha-glucosidase inhibitors, Thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 agonists).

**Figure 5.2** Proportions of treatment by HbA1c category in 2016

### 5.3.3 Impact of age on the intensity of diabetes management

A minimal rise in potential over-treatment rates was observed between the youngest and the older cohorts in 2012 with a similar trend in 2016 as well. However, the rates were observed to decrease for the oldest cohort compared to the other age groups. (Figure 5.3). Among older adults with diabetes age ≥ 80 years, the rate of potential over-treatment (using HbA1c < 8% instead of <7%)
was 29.5% in 2012 and 26.1% in 2016 showing no statistically significant difference between the two years (p = 0.18 [95% CI -1.56 to 8.42]).

![Figure 5.3 Proportions of potential over-treatment by age categories among older adults with type-2 diabetes](image)

5.3.4 Impact of prescriber type on the intensity of diabetes management

Among potentially over-treated patients (category-1 (HbA1c < 7%)), 80.2% (2012) and 78.5% (2016) of the over-treatment medications were prescribed by general practitioners (Figure 5.4).
5.3.5 Comparison of intensity of potential over-treatment using CPCSSN, MCHP and MaPCReN

A significant variation in the potential over-treatment rates were observed among older adults with diabetes in Manitoba using the different data sources. Using the MCHP data, as reported above, the rates of potential over-treatment were observed to be higher compared to the MaPCReN and CPCSSN analyses (Figure 5.5). Comparing analyses using MaPCReN and CPCSSN indicated that potential overtreatment rates were higher in Manitoba compared to the rest of the country using primary care EMR data.
Figure 5.5 Comparison of proportions of potential over-treatment between different data sources in 2012 & 2016 cohorts.

5.4 Discussion

Linking provincial primary care prescription data from a national-level database with the population-based administrative dispensation data of Manitoba, we examined rates of potential over-treatment and the variations in these rates using prescription data and dispensation data separately among elderly patients with type-2 diabetes in Manitoba. Two-thirds of older adults were tightly controlled (HbA1c levels < 7%), and 20.4% in 2012 and 21.5% in 2016 were potentially over-treated. High-risk hypoglycemic agents accounted for the vast majority (97%) of over-treatment medications in both 2012 and 2016 cohorts. Encouragingly, potential over-treatment rates declined among the oldest patients in both the cohorts. Among those intensively
treated, about 20% of over-treated medications were prescribed by the non-general practitioners. A considerable differences in the rates of potential over-treatment was noticed using different databases. Overall, the rates were found to be considerably higher among older adults with diabetes in Manitoba using MCHP data compared to MaPCReN and for MaPCReN compared to CPCSSN databases. Conversely, under-treatment rates were significantly lower using provincial MCHP data compared to national CPCSSN data from the original phase-1 study.

Most of the studies addressing potential over-treatment have been conducted in the United States, with rates all significantly higher than what was found in this study. Studies using different databases in assessing potential intensive treatment among older adults with diabetes reported a range of rates varying between 11% to 75% [13, 25, 27, 31, 32]. In contrast to the majority of these studies, we noticed lower rates of potential over-treatment among older adults with diabetes in Canada (phase-I) and as well as in Manitoba (phase-II). The reasons for such differences are not known for certain, but may include a variety of factors. Overtreatment in Canada may in fact be significantly less common than in the US. However, knowing that such a large difference is unlikely, other factors may contribute to this difference. Most obvious is the fact that due to a wide variety in methods of over-treatment capture including definition of over-treatment, age ranges included, and data sources, direct comparisons cannot be made. In addition, with more than one-third of patients being on no medications in our cohort, the use of the highly utilized CPCSSN diabetes case definition may have included patients without “active” diabetes into the study, or issues related to quality of data capture within the databases may have been a factor as well. In this study, we observed significant variations in rates of potential over-treatment with the use of different data sources. Using MCHP’s dispensation data, rates were found to be much higher compared to the primary care data of MaPCReN. As MCHP data also provides information on
non-primary care physicians such as endocrinologists this will be one of the potential reasons for the variations in these provincial rates of potential over-treatment where non-general practitioners accounted for approximately 20% of overtreatment medications. This rationale could also be applied to the previous discrepancies to US databases. In addition, lag time in updating data and including data from all the clinics into MaPCReN due to data sharing agreement issues might be the possible reasons for observing such differences in the potential over-treatment rates between these databases. Of interest, the rates of potential overtreatment in Manitoba were found to be higher than the entire country’s rate (which includes Manitoba) using CPCSSN-sourced data (10.7% vs. 7.0% in 2012 and 11.1% vs. 6.9% in 2016). Although one cannot make definite conclusions on rates for the entire province, it does suggest that for this large EMR database cohort, Manitoba has significantly higher rates than the country as a whole. These 3 different analyses highlight valuable insights into the combined and separate use of broad population dispensation databases and specific primary care EMR databases which require further exploration.

Recent studies investigating the prevalence, harms, and burden related to intensive treatment [13, 25, 27, 31, 32], support an individualized approach in setting glycemic targets, keeping certain factors in mind such as age, life expectancy, risk of hypoglycemia, comorbid conditions, and polypharmacy. In this study rates of potential over-treatment with increasing age over the first two age categories was similar in both 2012 and 2016 cohorts. However, an encouraging decreasing trend was noticed in the rate among patients with age ≥85 years. A recent Canadian study using the CPCSSN database between 2012 and 2013 reported that younger patients were more likely to have poorly controlled glycemic levels; while, older patients (80+ years) were more likely to have tight control [43]. A study conducted in British Columbia, Canada found that over-treatment was
prevalent among frail elderly patients with diabetes who were living in nursing homes and polypharmacy was associated with the more intensive treatment [44]. Our study findings found that, using an HbA1c of <8% as a criteria for overtreatment to account for advanced age, despite advanced age (>80 years) around 30% of the older adults with diabetes were potentially overtreated in 2012, which was only slightly decreased over time to 26% in 2016. Since guidelines mostly focus on preventing under-treatment rather than over-treatment, and indisposition to risk under-treatment [26] might contribute to the practice of intensive treatment. Thus, until clinical practice guidelines invest specific focus on de-intensification or avoidance of over-treatment, these practice patterns will likely continue to go unchanged [45].

With the availability of wide range of different anti-diabetic classes and medications, physicians may exhibit variations in the choice of medications prescribed for diabetes management. A national survey assessing factors in choosing glucose-lowering agents among academic generalists and specialists inferred that the majority of the physicians considered the overall patient’s health condition, comorbidities, HbA1c levels, and adherence behaviour but not the patient age or expert guideline recommendations [46]. It also concluded that factors reported by the physicians in choice of medications are in contrast with the current evidence-based treatment guideline. A retrospective cohort study of older adults with diabetes assessing variations in care by general internists, endocrinologist and geriatricians suggested that endocrinologists were more likely to prescribe multiple types of insulin and combinations of oral anti-diabetic medications aggressively than compared to general internists and geriatricians [47]. A study conducted using administrative data in Ontario, Canada assessing variations in care among older adults with diabetes between primary care physicians and specialists inferred that specialists prescribed more intensive therapies and were more aggressive in initiating insulin than primary care physicians [48]. The role of different
physician practice styles on the care of elderly patients with diabetes in Canada, particularly in prescribing high-risk medications is under-examined. In the current study, we examined the contributions of general practitioners and other specialists (non-GPs) in prescribing high-risk medications to the older adults with diabetes in Manitoba. Likely owing to the large proportion of general practitioners prescribing overall, a substantial proportion (80%) of high-risk medications were prescribed by general practitioners with 20% being attributed to non-general practitioners. Determining the rates of potential over-treatment by non-general practitioners as a group would be of interest and is an outcome considered for future analysis.

This study has several important strengths which addressed the gap in the literature regarding diabetes care of older adults with diabetes in the Manitoba context. The present study is the first of its kind to report the rates of potential over-treatment in a Manitoban elderly population and enhanced this picture by subsequently assessing the intensity of glycemic control and rates of potential over-treatment among those with advanced age, as well as the contributions of general and non-general practitioners towards management. The majority of studies in the current literature either considered pre- or post-index HbA1c time frames in defining potential over-treatment. Although it is uncertain which method of medication capture is ideal, considering a pre-index medication window only doesn’t reflect if a patient got de-intensified after the HbA1c test; similarly, considering only a post-index medication window would not capture over-treatment in the months before the HbA1c test. Thus, an additional strength of this study is the use of both pre- and post-index medication windows around the index HbA1c in defining potential over-treatment. This study has assessed and compared primary care prescriptions and dispensation data in assessing the potential over-treatment rates. However, there exist certain limitations that should be addressed. Firstly, the definition of potential over-treatment is based on interpretation of best
evidence and previous models, but it should be recognized that in the context of individual patient scenarios, one could argue this definition to be too restrictive or too lenient, thus the use of the term “potential overtreatment”. Secondly, this study looked at the rates of potential over-treatment in those with HbA1c < 7% on hypoglycemic agents which could lead to severe hypoglycemia; however, the actual hypoglycemic events were not able to be assessed. Moreover, due to difficulty tracking changes to doses in these databases, changes in the dose of prescription medications of the patients were not taken into consideration while defining potential over-treatment. Also, we considered only a surrogate marker (HbA1c) and medications in defining potential over-treatment, not including other factors such as functional status, frailty issues, episodes of hypoglycemia, disease duration and life-expectancy due to difficulty capturing these variables consistently or at all. However, we looked at those with age >80 years and with dementia as ways of forming a rudimentary understanding of potential over-treatment in those with higher likelihood of frailty or shorter life-expectancy.

5.5 Conclusion

The rates of potential over-treatment among older adults with type-2 diabetes were found to be significantly higher in the province of Manitoba using dispensation data compared to provincial primary care prescription data and for the latter in comparison to the rest of the country using national primary care data. There was no evidence of these rates decreasing over time. Non-general practitioners contributed to 20% of over-treatment prescriptions which will have accounted for some of the difference between overtreatment rates between MCHP and MaPCReN. A smaller, but considerable proportion of patients with poorly-controlled diabetes received no medications indicating under-treatment. Of concern was the finding that, using more reasonable conservative glycemic targets, patients with advanced age exhibited high rates of potential over-treatment.
5.6 References


34. American Diabetes Association. Older Adults: *Standards of Medical Care in Diabetes.* *Diabetes Care.* 2019, 42 (Supplement-1) S139-S147. 


CHAPTER 6: Thesis conclusions

Diabetes is highly prevalent among the elderly population. However, high-quality evidence regarding optimal glycemic control in this cohort is lacking. It is generally agreed that in elderly patients, especially those with multiple comorbidities, the harms of intensive glycemic control likely exceed the benefits. Currently, the extent of overtreatment in the elderly population with type-2 diabetes in Canada is not clearly established. Considering this and the significant concerns described in this population, evaluation of glucose management intensity in elderly patients with diabetes is necessary provincially and nationally. Through this study, we intended to inform an understanding to build a foundation for future interventions to optimize diabetes management strategies in elderly Canadians. This study is the first Canadian evaluation of this research question. Using national and provincial-level databases, we were able to capture a large, well-represented cohort of elderly patients with type-2 diabetes. The depth of information available in these databases allowed for significant evaluations related to demographics, co-morbidities, and treatment & testing patterns.

Overall, using primary care prescription data, around 7% of older adults with type-2 diabetes in Canada were potentially over-treated, with no evidence of change over time. Although potential over-treatment exists in this broad Canadian primary care population, the rate was low compared with other countries. High-risk hypoglycemic agents accounted for the majority of over-treatment medications with more than one-third of patients with poorly controlled diabetes receiving no medications, and some over-treatment among tightly controlled patients. Despite the unlikely chance of receiving any clinical benefit, older adults with diabetes and with the combination of dementia & advanced age (≥ 80 years) appeared to be more likely to be potentially over-treated in
comparison to those without dementia and advanced age. The use of insulins, arguably the highest-risk medications, steadily increased among tightly controlled patients over the time. However, medication sub-classes with less hypoglycemic potential appeared to be used slightly more in 2016 than in 2012.

The rates of potential over-treatment among older adults with type-2 diabetes were found to be significantly higher in the province of Manitoba using dispensation data compared to provincial & national primary care prescription data, with no evidence of these rates decreasing over time. The contribution of non-general practitioners to 20% of over-treatment prescriptions will have accounted for some of the difference between overtreatment rates between MCHP and MaPCReN. A smaller proportion of patients with poorly-controlled diabetes received no medications in the MCHP analysis compared to the national CPCSSN data analysis, although still at a rate of 10-20%. There are several possible reasons for the significant number of patients being on no medications. It would be conceivable that people without diabetes (e.g. nearing a diabetes diagnosis threshold or simply being worked up for diabetes) were billed or diagnosed as having diabetes in our cohort. Also, although the CPCSSN diabetes case definition has been widely utilized, as with any case definition, it may have allowed the inclusion of some patients without diabetes into the study cohort. Of note, the rates of potential over-treatment were observed to be higher using MaPCReN primary care prescription data compared to the national rates using CPCSSN data.

During the study period, a significant burden with non-diabetic medications was observed among older adults with diabetes. The mean number of medications prescribed per patient was 4.4 in 2012 and increased to 5.1 in 2016. The proportions of patients with multiple drug use were high, as nearly 39% and 41% were prescribed five or more medications in 2012 and 2016, respectively.
The proportion of patients who were on 10 or more medications increased as age increased, consistent with broad Canadian patterns reported by CIHI in 2016. Furthermore, those with potential over-treatment with anti-diabetic medications were also prescribed more non-diabetic medications. This study repeatedly suggests that older adults with advanced age and dementia do not consistently appear to be targets for minimizing burden, but instead they appear to be posed with greater burden of treatment.

Approximately one-fifth of patients were potentially over-tested and, regardless of glycemic control, approximately 6% were tested 5 or more times in a year. On the other hand, about one-third of patients with inadequate glycemic control (HbA1c ≥9%) were tested only once a year, suggesting under-testing. As with the trends in treatment burden, those with advanced age and dementia also appear to be more likely to be over-tested.

Although some of these trends have improved over time, the improvements are very modest, suggesting that consideration of the individual patient, their context, and the potential net benefit of management strategies should be a focus for prescribing change. Particularly, the trend has to be continually shifted towards de-intensification and de-prescribing, particularly in those at highest risk of harm and lowest likelihood of benefit. Decisions need to be made collaboratively with patients, incorporating the likelihood of benefits and harms and patient preferences about treatment and its related burden.

There are numerous implications of this thesis work related to practice patterns, patient care, and future research directions. Dissemination of these findings to clinicians regarding potential over-treatment and over-testing rates, especially in those with advanced age is a knowledge translation priority. These efforts would be expected to prompt further individualization of care with minimal
and acceptable burden for older adults with diabetes and chronic disease in general. Through future collaborative work, this study has the potential to inform further refining of data capture, case definitions, and linkage efficiencies of the primary care and administrative databases. The further evaluations that would be expected to flow from this study are the assessment of the relationship between prescribed and dispensed anti-diabetic medications related to adherence, rates of potential over-treatment between non-general practitioners (specifically endocrinologists) and general practitioners, hospital admissions for hypoglycemia, and over-treatment related to comorbidity indices. These explorations will add further depth to the findings of this thesis work and hopefully expand the network of researchers with an interest in advancing the appropriate care of older adults in Canada.
Appendix-1: ATC codes (Anatomical Therapeutic Chemical Classification System) of anti-diabetic medications

A10A INSULINS AND ANALOGUES:

1. A10AB Insulins and analogues for injection,

Fast-acting:

A10AB01 insulin (human)

A10AB03 insulin pork

A10AB04 insulin lispro

A10AB05 insulin aspart

A10AB06 insulin glulisine

Intermediate acting:

A10AC01 insulin human

A10AC03 insulin pork

2. A10AD Insulins and analogues for injection,

Intermediate- or long-acting combined with fast-acting:

A10AD04 insulin lispro

A10AD01 insulin human
A10AD05 insulin aspart

3. **A10AE Insulins and analogues for injection, long-acting**

A10AE04 insulin glargine

A10AE05 insulin detemir

A10AE06 insulin degludec

A10B BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS:

1. **A10BA Biguanides**

A10BA02 metformin

2. **A10BB Sulfonylureas**

A10BB01 glyburide

A10BB02 chlorpropamide

A10BB03 tolbutamide

A10BB09 gliclazide

A10BB12 glimepiride

3. **A10BD Combinations of oral blood glucose lowering drugs**

A10BD07 metformin and sitagliptin

A10BD09 pioglitazone and alogliptin
A10BD10 metformin and saxagliptin
A10BD11 metformin and linagliptin
A10BD13 metformin and alogliptin
A10BD15 metformin and dapagliflozin
A10BD16 metformin and canagliflozin
A10BD19 linagliptin and empagliflozin
A10BD20 metformin and empagliflozin
A10BD21 saxagliptin and dapagliflozin
A10BD03 metformin and rosiglitazone

4. A10BF Alpha glucosidase inhibitors

A10BF01 acarbose

5. A10BG Thiazolidinediones

A10BG02 rosiglitazone
A10BG03 pioglitazone

6. A10BH Dipeptidyl peptidase 4 (DPP-4) inhibitors

A10BH01 sitagliptin
A10BH03 saxagliptin
A10BH04 alogliptin

A10BH05 linagliptin

7. A10BJ Glucagon-like peptide-1 (GLP-1) analogues

A10BJ01 exenatide

A10BJ02 liraglutide

A10BJ03 lixisenatide

A10BJ04 albiglutide

A10BJ05 dulaglutide

8. A10BK Sodium-glucose co-transporter 2 (SGLT2) inhibitors

A10BK01 dapagliflozin

A10BK02 canagliflozin

A10BK03 empagliflozin

9. A10BX Other blood glucose lowering drugs, excl. insulins

A10BX02 repaglinide

A10BX03 nateglinide
Appendix-2: Study approvals documentation

HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

<table>
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<tr>
<th>PRINCIPAL INVESTIGATOR:</th>
<th>Siva Krishna Gudi</th>
<th>INSTITUTION/DEPARTMENT:</th>
<th>University of Manitoba_College of Pharmacy</th>
<th>ETHICS #:</th>
<th>HS21974 (R20-8:035)</th>
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<td>STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable):</td>
<td>Dr. Jamison Falk</td>
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| PROTOCOL NUMBER: | NA |

| PROJECT OR PROTOCOL TITLE: | A retrospective evaluation of prescribers’ practices related to intensity of glycemic control among elderly population with type 2 diabetes across Canada |

| SPONSORING AGENCIES AND/COORDINATING GROUPS: | University of Manitoba |

| Submission Date of Investigator Documents: | January 2, 2018 |
| HREB Receipt Date of Documents: | January 2, 2018 |

THE FOLLOWING ARE APPROVED FOR USE:

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<th>Document Name</th>
<th>Version(s)</th>
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<td>December 18, 2017</td>
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<td>Consent and Assent Form(s):</td>
<td>V. 1</td>
<td>December 19, 2017</td>
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<td>Other:</td>
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<td>V. 1</td>
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CERTIFICATION
The above named/research study/project has been reviewed in a delegated manner by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
The University of Manitoba (UM) Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

Research Ethics and Compliance is a unit of the Office of the Vice-President (Research and International)
umanitoba.ca/research

118
QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from
this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy
on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. For logistics of
   performing the study, approval must be sought from the relevant institution(s).
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to
   the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual
   Study Status Report must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be
   reported to the HREB for consideration in advance of implementation of such changes on the Bannatyne Campus
   Research Amendment Form.
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research
   Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation of study/project closures on the Bannatyne Campus Final
   Study Status Report.

Sincerely,

Removed for privacy purpose

John Arnett, Ph.D. C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary Telephone: (204) 789-3650 Fax: (204) 789-3414
April 11th, 2018

Dr. Sai Krishna Gudi
Faculty of Pharmacy
University of Manitoba
Email: gudisk@myunmanitoba.ca

Dear Dr. Gudi:

Re: CPCSSN Request for Data – Project ID: 2018RSC102
Title: A retrospective evaluation of prescribing practices related to intensity of glycemic control among elderly population with type 2 diabetes across Canada

Upon review of your letter of intent, we are pleased to inform you that your project has been approved to receive data from the CPCSSN network. In order to facilitate this process, you can please:

1. Complete the attached CPCSSN Data Access Request Form and email a signed copy to our Administrative Assistant: Marissa Beckles – marissa.beckles@lfm.queensu.ca

2. Review the Data Sharing Agreement with your Institution’s Office of Research Services. Changes applied to the agreement by your intuition, must be sent to us for approval by the Queen’s University Office of Research Services before obtaining your institutional signature. Please send the amended agreement with track changes to our Administrative Assistant: Marissa Beckles – marissa.beckles@lfm.queensu.ca

Please carefully read the agreement, as you will be required to comply with the conditions in that agreement for use of CPCSSN data. This agreement will need to be signed by both parties, and proof of REB approval provided, before any data will be released.

Queens University
20 University Avenue, Kingston, ON, K7L 3N6
http://www.queensu.ca
Dr. Gudi
April 11th, 2018
Page 2

Please be advised that, as part of the CPCSSN data access policy, the Network Directors are informed of ongoing research projects. If there are members of the Network who are interested in your project, they are encouraged to contact you. While you are not obliged to include these members as part of your research team, we hope that you will consider any request to accept these potential collaborators for your project.

Please also note the reporting requirements as part of the data agreement for use of CPCSSN Network information.

If you require any further assistance, you may contact me. We look forward to working with you in securing the data for your project.

Sincerely

Removed for privacy purpose

Walter Rosser MD, CCFP, FCFP, MRCP (UK), FCAMS, C.M.
Chair, CPCSSN Surveillance Research Standing Committee
Tel: 613-533-9300 • Extension: 73934

cc – Dr. Richard Bratwhistle (Chair, CPCSSN)
Dr. Alexander Singer (Director MaREli)
Diana Purvis (Queen’s University, Research Contracts Coordinator)

Enclosed: Data Access Request Form V2.1
Information and Data Sharing Agreement
HEALTH RESEARCH ETHICS BOARD (HREB)
CERTIFICATE OF FINAL APPROVAL FOR NEW STUDIES
Delegated Review

PRINCIPAL INVESTIGATOR: Sai Krishna Sudhi
INSTITUTION/DEPARTMENT: U of M and MCHP/College of Pharmacy
ETHICS #: HR22366 (H2018-421)

APPROVAL DATE: October 11, 2019
EXPIRY DATE: October 11, 2019
STUDENT PRINCIPAL INVESTIGATOR (if applicable): Dr. Jamie Falk

PROTOCOL NUMBER: NA
PROJECT OR PROTOCOL TITLE:
A retrospective evaluation of prescribing practices related to intensity of glycemic control among elderly population with type 2 diabetes across Canada: Phase 2 (Manitoba cohort) [linked to H321474 (B2018-030)]

SPONSORING AGENCIES AND/OR COORDINATING GROUPS: NA

Submission Date of investigator Documents: September 14, 2018
HREB Receipt Date of Documents: October 1, 2018

THE FOLLOWING ARE APPROVED FOR USE:

Document Name: Protocol
Version: V.3
Date: September 24, 2018

Document Name: Consent and Assent Form(s):
Version: V.3
Date: September 24, 2018

Other:
MCHP - Data Field/Capture Sheet
Version: V.3
Date: September 24, 2018

CERTIFICATION
The above named research study/project has been reviewed in a delegated manner by the University of Manitoba (UM) Health Research Board (HREB) and was found to be acceptable on ethical grounds for research involving human participants. The study/project and documents listed above was granted final approval by the Chair or Acting Chair, UM HREB.

HREB ATTESTATION
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QUALITY ASSURANCE
The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

CONDITIONS OF APPROVAL:
1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. For logistics of performing the study, approval must be sought from the relevant institution(s).
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. This approval is valid until the expiry date noted on this certificate of approval. A Bannatyne Campus Annual Study Status Report must be submitted to the HREB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the Bannatyne Campus Research Amendment Form.
6. Adverse events and unanticipated problems must be reported to the HREB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closures on the Bannatyne Campus Final Study Status Report.

Sincerely,

Removed for privacy purpose

John Arrell, Ph.D., C. Psych.
Chair, Health Research Ethics Board
Bannatyne Campus

Please quote the above Human Ethics Number on all correspondence.
Inquiries should be directed to the REB Secretary Telephone: (204) 789-3250 Fax: (204) 789-3414
March 26, 2019
Sai Krishna Gudi
University of Manitoba
750 McDermot Avenue, Winnipeg, R3E 0T5
zudisk@mansumanitoba.ca

HIPC No. 2018/2019 – 71
File number to be quoted on correspondence

Re: A retrospective evaluation of prescribing practices related to intensity of glycemic control among elderly population with type 2 diabetes across Canada: Phase 2 (Manitoba cohort)

Dear Dr. Gudi,

The Health Information Privacy Committee has considered and approved your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Seniors and Active Living for review. Specifically, manuscripts must be submitted at least 30 calendar days prior to the intended publication and presentation materials must be submitted at least 10 calendar days prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by MCHP. If you have any questions or concerns, please do not hesitate to contact Saisa Parveen, Committee Coordinator at (204) 786-7204.

Yours truly,

Removed for privacy purpose

Chair, Health Information Privacy Committee

cc. D. Maliszewicz
Kara Dyck

From: Alexander Singer <awinger@bgh.mb.ca>
Sent: March 18, 2019 6:36 PM
To: Kara Dyck
Cc: william.peeler@umanitoba.ca; alydia.horsfall@umanitoba.ca; leanne.kosowan@umanitoba.ca
Subject: RE: MCHP Data Access Request

Permission granted. 
Alydia, please add to our tracking form.
Alex

---
Alexander Singer MB BAO BCh, CCFP
Associate Professor
Director; Manitoba Primary Care Research Network
Quality Improvement and Informatics Stream Lead
Department of Family Medicine, University of Manitoba

From: Kara Dyck [Kara_Dyck@cw.umanitoba.ca]
Sent: Monday, March 18, 2019 3:56 PM
To: Alexander Singer
Cc: william.peeler@umanitoba.ca; alydia.horsfall@umanitoba.ca
Subject: MCHP Data Access Request

Hi Alex,

Re: project entitled, A retrospective evaluation of prescribing practices related to intensity of glycemic control in the older adults with type 2 diabetes across Canada: Phase 2 (Manitoba cohort)

PI: Sai Krishna Gudi

Please find attached letter which is seeking permission to access/use the CPSSN data for the above-named project. A copy of the protocol synopsis and data extraction form is also attached for your review. This project is an independent research project led by Sai Krishna Gudi.

As part of the approval process, we ask that you review the attached letter and protocol synopsis. If you require any changes to the letter or have any questions about the request, please reply by return email. If this request meets your approval, please reply by email indicating your approval.

If you have any questions, please don’t hesitate to contact me.

Kind regards,

Kara Dyck
Repository Access Coordinator

Manitoba Centre for Health Policy
Data | Insight | Informing Solutions
April 26, 2019

Sai Krishna Gudi
College of Pharmacy
Rady Faculty of Health Sciences
University of Manitoba
Apotex Centre, 750 McDermot Ave.
Winnipeg MB  R3E 0T5

Dear Sai:

Re: project entitled, A Retrospective Evaluation of Prescribing Practices Related to Intensity of Glycemic Control among Elderly Population with Type 2 Diabetes across Canada: Phase 2 (Manitoba cohort)
MCHP project number: 2019-019

Enclosed is a copy for your records of the fully executed Researcher Agreement, representing approval to proceed with the above-named research project at the Manitoba Centre for Health Policy (MCHP). It is important that the requirements outlined in this agreement be shared with all members of your project team, specifically Section 5 obligations respecting use and disclosure and Section 6 regarding reports, monitoring and enforcement. It is also important that all correspondence with MCHP relating to this project reference the MCHP project number.

We look forward to facilitating access to the Manitoba Population Research Data Repository for your project. To proceed, please contact Charles Burchill (Associate Director, Data Access and Use) at charles_burchill@cpe.umanitoba.ca. Prior to project commencement, we will require the University of Manitoba FOP number for billing or if your project is externally-based, please provide the contact name and mailing address to which invoices should be sent. Charges are processed on a monthly basis once work has begun on the project.

There are several ongoing project requirements that need to be met to maintain access to the data throughout the life of your project:

1. If any changes are made to the original approved study protocol, they must be submitted to the Health Information Privacy Committee (HIPC), Health Research Ethics Board (HREB) and non-Manitoba Health, Seniors and Active Living (non-MHSAL) data providers for approval. Please contact the Repository Access Unit (RAU) when an amendment is required as we will assist in this process.
2. Annual Approval Certificates from HREB must be submitted to the RAU within the month of expiry. If the annual approval is not received the project will be closed and access to the data will cease.

3. The Principal Investigator and any team members with access to line-level data must have a current MCHP Accreditation status. The initial Accreditation session must be attended in person and yearly updates are required through our online training module. An email will be sent from the Accreditation Coordinator when it is time to renew your Accreditation.

4. Publications or presentation must be submitted to HIPC and the non-MHSAL data providers 30 days prior to public release. Acknowledgement of MCHP, HIPC and non-MHSAL data providers must be included and can be found on our website: [http://umanitoba.ca/medicine/units/mchp/resources/access_acknowledgments.html](http://umanitoba.ca/medicine/units/mchp/resources/access_acknowledgments.html)

We would be glad to assist you in meeting ongoing project requirements for maintaining access to the data, as outlined at our website: [http://umanitoba.ca/medicine/units/mchp/resources/access_reporting.html](http://umanitoba.ca/medicine/units/mchp/resources/access_reporting.html). Should you have any questions, please do not hesitate to contact the Repository Access Unit at MCHP_Access@cpe.umanitoba.ca or (204) 975-7770.

Sincerely,

**Removed for privacy purpose**

Charles Burchill  
Associate Director, Data Access and Use  
Manitoba Centre for Health Policy  

cc Sophie Buternowsky, Senior Grants Accountant