Self-Monitoring of Blood Glucose and Hypoglycemia-Related Healthcare Utilization in Saskatchewan

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Abstract

Background

Use of blood glucose test strips has dramatically increased over the past two decades in Saskatchewan and has emerged as a major health care expenditure. Although regular self-monitoring of blood glucose using test strips is imperative in certain patient groups, there is no strong evidence for clinical benefit in the majority of patients with diabetes. As a result, public and private payers have begun to limit the quantity of test strips eligible for reimbursement under drug benefit plans. The majority of literature supporting self-monitoring of blood glucose focuses on improvements in glycemic control. Self-monitoring of blood glucose may also be used to detect hypoglycemia, but the relationship between test strip use and hypoglycemic events has not been well studied. Thus, the purpose of this study was to determine the relationship between blood glucose test strip use and hypoglycemia-related healthcare utilization.

Methods

Hypoglycemia endpoints and test strip utilization among beneficiaries of the Saskatchewan Drug Plan were described using Saskatchewan's administrative health databases from 1996 to 2014. A time-series analysis using generalized estimating equations was conducted to test the association between hypoglycemia hospitalizations and utilization of blood glucose test strips at a population level. A nested case-control study was conducted within a cohort of patients with diabetes using a conditional logistic regression model to determine if individual risk of hospitalization for hypoglycemia was lower among patients who used blood glucose test strip compared to those who do not.

Results

A total of 5,166 hospitalizations for hypoglycemia were recorded during the study period. The average crude rate of hospitalization for hypoglycemia was 26.2 admissions per 100,000. No consistent trend in hypoglycemia hospitalizations was evident. All measures of blood glucose test strip use increased over the study period. After controlling for health care utilization and changes in population size, the number of test strips dispensed was not associated with a significant change in the rate of hospitalization for hypoglycemia ($p=0.41$). Due to substantial clinical differences between cases and controls, modeling was not conducted in the overall cohort of diabetic patients. Instead, two subgroups were created to represent those at highest (i.e. patients using insulin) and lowest (i.e. patients using low risk oral hypoglycemic agents) risk of developing drug-induced hypoglycemia. After controlling for confounders, blood glucose test strip use was not associated with hospitalization for hypoglycemia in insulin users [adjusted OR 1.08; 95% CI (0.88,1.31); $p=0.48$], or in low risk oral hypoglycemic users [adjusted OR 1.04; 95% CI (0.55,1.94); $p=0.91$].

Discussion

Blood glucose test strip use was not associated with hospitalization for hypoglycemia in both population and individual level analyses. These findings were consistent among those at high risk and low risk of developing drug-induced hypoglycemia. This research adds to the existing body of literature suggesting that policies limiting blood glucose test strip reimbursement in patients not on insulin are unlikely to be detrimental to patient safety.

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List of Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetics
ADA	American Diabetes Association
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
AHFS	American Hospital Formulary System
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CADTH	Canadian Agency for Drugs and Technology in Healthcare
CCDSS	Canadian Chronic Disease Surveillance System
COMPUS	Canadian Optimal Medication Prescribing and Utilization Service
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
DACON	Daily Average Consumption of Insulin
DAD	Discharge Abstract Database
DC	Diabetes Canada
DCCT	Diabetes Control and Complications Trial
DIN	Drug Identification Number
DPP-4	Dipeptidyl peptidase-*4*
ED	Emergency Department
FPG	Fasting Plasma Glucose
GEE	Generalized Estimating Equations
GLM	General Linear Model
GLP	Glucagon-like Peptide
HbA1c	Hemoglobin A1c; Glycosylated Hemoglobin
HQC	Health Quality Council
HR	Hazard Ratio
HSN	Health Services Number
ICD	International Classification of Diseases
ICD-9	International Classification of Diseases (Ninth Revision)
ICD-10-CA	International Classification of Diseases (Tenth Revision, Canada)
NDSS	National Diabetes Surveillance System
OR	Odds ratio
QIC	Quasi-likelihood Information Criterion
RQHR	Regina Qu'Appelle Health Region
RR	Relative Risk
SDUORT	Saskatchewan Drug Utilization and Outcomes Research Team
SHR	Saskatoon Health Region
SLCDC-DM	Survey on Living with Chronic Diseases in Canada-Diabetes Component
SMBG	Self-monitoring of blood glucose
UKPDS	UK Prospective Diabetes Study
VIF	Variance Inflation Factor

Chapter 1: Introduction

Diabetes is a metabolic disorder characterized by persistently elevated blood glucose levels (hyperglycemia)[1, 2]. Approximately 7 % of Canadians have been diagnosed with diabetes and its prevalence continues to increase [3]. Individuals who suffer from diabetes are at risk of both immediate complications of hyperglycemia as well as long-term comorbidities, such as cardiovascular disease (including stroke), kidney disease, blindness, and amputation[2]. Current management of diabetes involves using pharmacologic therapies to lower blood glucose to guideline recommended targets, which are chosen to minimize complications of hyperglycemia.

Patients with diabetes can easily monitor their own blood glucose levels using testing strips, which provide an immediate estimation of blood glucose concentration to the user [4, 5]. As a result, self-monitoring of blood glucose (SMBG) has become a common strategy to engage patients in the process of achieving blood glucose targets and to minimize the risk of drug-induced hypoglycemia [1, 2]. Indeed, current evidence suggests that routine SMBG is imperative in certain diabetic patient populations such as those using high doses of insulin [2, 6]. However, SMBG does not appear to benefit all patients with diabetes. In fact, it may be unnecessary in individuals at low risk of developing hypoglycemia [7, 8].

SMBG has been associated with improved glycemic control in patients receiving non-insulin medications, but the degree of benefit is too small to be of any clinical significance and is not likely to translate into improvements in long-term outcomes or quality of life [7-9]. Moreover, no evidence can be found to support the use of SMBG for preventing drug-induced hypoglycemia in low-risk patients. However, it is theoretically possible that patients employing SMBG may be able to detect and subsequently self-treat episodes of drug-induced hypoglycemia in a timely fashion, thereby avoiding the need to present to healthcare services for treatment. In this case, higher use of blood glucose testing strips in the population would be expected to reduce hospitalizations due to hypoglycemia. To our knowledge, the relationship between population-wide use of blood glucose test strips and hospital admissions for hypoglycemia has never been examined.

The use of blood glucose testing strips is a major health care expenditure. In 2012, public and private drug plans in Canada spent an estimated $503 million on test strips alone, with $393 million of that attributed to patients who were not using insulin[7, 9]. In Saskatchewan, at least 50% of the costs of test strips are paid by the provincial drug plan[10]. Numerous provinces and federal payers have already imposed restrictions on the number of strips that are available as a benefit to patients with

diabetes that are not on insulin. Given the high cost of hospital inpatient treatment for hypoglycemia and the potential demands placed on emergency departments for acute events, an examination of the impact of SMBG and its role in healthcare utilization seems prudent.

The aim of this research is to determine if relationships exist between blood glucose test strip utilization and rates of hypoglycemia at the population level, and to explore the impact of blood glucose test strip use on the risk of being hospitalized for hypoglycemia.

Objective 1: To determine if utilization of blood glucose test strips at the provincial level result in lower rates of hospitalizations for hypoglycemia.
Objective 2: To determine if the individual risk of hospitalization for hypoglycemia is lower among patients who use blood glucose test strips compared to those who do not.

Chapter 2: Literature Review

Diabetes mellitus

Hyperglycemia is the primary manifestation of diabetes mellitus resulting from an absolute or relative insulin deficiency [2, 3]. Two distinct subtypes typically distinguish the disease[3]. Type 1 diabetes is caused by autoimmune destruction of pancreatic β-cells, which results in an absolute deficiency in insulin secretion [1]. Type 1 diabetes is diagnosed in younger patients and accounts for 5-10% of the total burden of diabetes in Canada [2, 3]. In contrast, type 2 diabetes accounts for the vast majority of cases and is characterized by insulin resistance[1], typically being diagnosed in older patients [3]. Other types of diabetes, such as gestational diabetes (i.e. diabetes during pregnancy) and drug-induced diabetes can also occur in select patient populations [1].

Pharmacologic Management

For individuals with type 1 diabetes, insulin is a lifesaving therapy started immediately at diagnosis [2]. Insulin is administered by subcutaneous injection or continuous subcutaneous infusion. Although initially isolated from animal sources (i.e. bovine or porcine derived insulin), modern insulin is manufactured using recombinant DNA technology to produce structurally identical human insulin or modified insulin analogues[2]. Insulins are categorized based on their duration of action and their time

to onset and peak effect.

Patients with type 1 diabetes are usually treated with multi-dose or basal-bolus insulin regimens in an attempt to mimic normal pancreatic insulin secretion [2]. For example, basal insulin levels are mimicked through the administration of an intermediate or long-acting insulin preparation (or insulin analogue) administered once or twice daily. Bolus or prandial insulin levels are mimicked by administering short- or rapid-acting insulin (or insulin analogue) at meal times. The exact dose of prandial insulin depends on several factors including the carbohydrate content of each meal, the glycemic index of the meal consumed, and the amount of physical activity or exercise around mealtimes [2]. Additional doses of short-acting/rapid-acting insulin analogues may also be used throughout the day to correct hyperglycemia [2]. Individuals diagnosed with type 1 diabetes must undergo significant education regarding insulin injections, dose titration based on diet and physical activity, sick-day management, avoidance of hypoglycemia, and management of hyperglycemia in order to effectively self-manage their condition[2]. Obviously, SMBG is an integral part of the successful management of this condition.

In contrast to those with type 1 diabetes, patients with type 2 diabetes form a much more heterogeneous group [11]. Pharmacologic treatment of type 2 diabetes varies significantly based on the duration and progression of the disease [2]. Type 2 diabetes is characterized initially by insulin resistance (i.e. relative insulin deficiency) but develops into an absolute insulin deficiency as pancreatic β-cell function declines over time [12]. Initially, some patients may be able to manage type 2 diabetes through lifestyle modifications (i.e. weight loss, dietary modifications, and increased physical activity), however the progressive nature of the disease will likely require pharmacologic therapy to be initiated when glycemic targets cannot be met through lifestyle interventions alone [1, 2]. Choice of pharmacologic therapy in patients with type 2 diabetes depends on the degree of hyperglycemia at diagnosis, the presence of microvascular or macrovascular complications, risk for developing hypoglycemia, concomitant medical conditions, medication side effects, the ability of the patient to self-manage, and patient preference [2].

Unlike the treatment of type 1 diabetes, type 2 diabetes may be managed using oral hypoglycemic agents as well as insulin. Oral hypoglycemic agents are categorized according to their mechanisms of action. They may increase pancreatic secretion of insulin (insulin secretagogues), decrease hepatic glucose production and/or increase sensitivity to insulin (biguanides and thiazolidiazones), block or delay uptake of dietary carbohydrates (alpha-glucosidase inhibitors), or mimic or enhance incretin secretion (GLP-1 agonists and DPP-4 inhibitors) [1].

Drug therapy is typically initiated using a single oral hypoglycemic agent, unless severe hyperglycemia and/or metabolic decompensation is present, in which case a combination of oral hypoglycemics or insulin may be initiated [1, 2]. Dosing of oral agents may be titrated to achieve target blood glucose levels, although combinations of different oral agents at submaximal doses have increased efficacy and reduced side effects as compared to maximal doses of single agents alone[2]. Insulin may be started at any time in the treatment of type 2 diabetes, but is typically reserved for patients receiving maximal doses of oral hypoglycemics and unable to meet glycemic targets, or for those with end-organ damage (i.e. end-stage renal disease), which renders oral hypoglycemics clinically inappropriate [1, 2]. Insulin also may be used in combination with oral hypoglycemics. The combination results in lower insulin doses that are able to effectively manage blood glucose levels, but with less weight gain and decreased risk of hypoglycemia when compared to insulin use alone [1]. Insulin therapy in patients with type 2 diabetes may be initiated as a once daily injection of a long-acting preparation or analogue in combination with oral hypoglycemic agents or as a basal-bolus regimen (in which case oral hypoglycemics are typically discontinued)[2].

Treatment Goals

Results of the Diabetes Control and Complications Trial (DCCT) were used to establish current management strategies and treatment goals in patients with type 1 diabetes. The DCCT was a multi-center, randomized clinical trial designed to compare intensive insulin therapy versus conventional diabetes therapy on the development and progression of microvascular complications of diabetes in 1,441 type 1 diabetic patients [13]. The conventional therapy arm administered insulin injections once or twice daily (along with once daily SMBG or urine glucose monitoring) with the main goal of therapy being the absence of symptoms attributed to hyperglycemia. The intensive therapy arm administered insulin injections three or more times daily (along with SMBG at least 4 times per day) titrated to achieve a pre-prandial (fasting) plasma glucose level of 3.9-6.7 mmol/L and a hemoglobin A1c (HbA1c) of 6.05% or less. After a mean 6.5 years follow-up, intensive therapy was associated with significantly lower hemoglobin A1c and plasma glucose profiles, a 76% risk reduction in development of primary retinopathy and 54% risk reduction in the progression of secondary retinopathy, and a reduction in nephropathy and neuropathy[13].

Numerous trials have examined the optimal level of glycemic control in patients with type 2 diabetes. The UK Prospective Diabetes Study (UKPDS) was designed to determine if intensive blood glucose control reduces the risk of micro- and macrovascular complications in patients newly

diagnosed with type 2 diabetes [14]. Subjects were assigned to receive either conventional therapy or intensive therapy. The conventional therapy arm aimed to achieve a fasting plasma glucose level of less than 15 mmol/L through dietary interventions, while avoiding symptoms of hyperglycemia. The intensive therapy arm aimed to achieve a fasting plasma glucose level of less than 6 mmol/L and received pharmacologic therapy with either insulin or sulfonylureas [14]. In the conventional arm, fasting plasma glucose and HbA1c increased steadily over the ten years after randomization. In the intensive arm, there was an initial decrease in fasting plasma glucose and HbA1c in the first year, followed by an increase in both fasting glucose and HbA1c similar to that seen in the conventional arm. The median HbA1c over ten years was 7.0% in the intensive arm, as compared to 7.9% in the conventional arm ($p<0.001$). The intensive arm showed a significant 25% relative risk reduction in microvascular endpoints compared with the conventional treatment group, which was primarily due to decreased retinal photocoagulation in the intensive arm. There was also a trend towards a reduction in myocardial infarction in the intensive arm ($p=0.052$), but no significant difference was noted between the two arms for diabetes-related mortality and all-cause mortality [14].

The Action to Control Cardiovascular Risk in Diabetics (ACCORD) trial attempted to determine if intensive diabetes therapy (with the goal of achieving a 'normal' HbA1c of <6.0%) reduced cardiovascular events in patients with type 2 diabetes and cardiovascular disease or risk factors for cardiovascular disease [15]. The trial was stopped after 3.5 years due to a 22% increase in all-cause mortality in the intensive diabetes therapy arm (HR 1.22; 95% CI [1.01,1.46], $p<0.04$). Also, there was no significant decrease in cardiovascular events between the control and intensive arms with an event rate of 6.9% per year in the intensive arm and 7.2% in the control arm (HR 0.90, 95% CI [0.78,1.02]; $p= 0.16$)[15]. In this population of high cardiovascular risk diabetic patients, intensive blood glucose lowering did not reduce cardiovascular events as originally postulated and actually increased the risk of adverse outcomes, including weight gain, hypoglycemia, and death[15].

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial also sought to assess the effects of intensive glycemic control in type 2 diabetics [16]. The intervention arm was able to achieve an HbA1c of 6.5% (compared to 7.3 % in the control arm), which was associated with a significant reduction in major microvascular events primarily due to a protective effect against nephropathy[16]. However, no significant differences were observed in the number of macrovascular events or deaths despite achieving a similar degree of HbA1c reduction as in ACCORD. Although there was no significant reduction in the development of retinopathy, the ADVANCE trial provides some additional evidence for benefits of intensive glycemic

control in reducing the risk of microvascular complications, despite no significant macrovascular benefit associated with intensive glycemic control.

Based on the evidence obtained from the aforementioned landmark trials, along with epidemiological data, the benefit conferred from intensive glycemic control varies according to the type of patient and treatment [2, 13, 15, 16]. Current Diabetes Canada (DC) guidelines recommend that glycemic targets should be individualized based on age, duration of disease, presence of comorbidities (especially cardiovascular disease), life expectancy, and risk of hypoglycemia [2]. In most patients with type 1 and type 2 diabetes, a target HbA1c of ≤7.0% is considered optimal in order to reduce the risk of microvascular complications. In selected patients, a more stringent HbA1c of ≤6.5% may be considered to further reduce risk of microvascular complications, however this must be balanced against an increased risk of hypoglycemia. In older patients with limited life expectancy or functional dependency, or in those with significant cardiovascular disease, a history of severe hypoglycemia and/or hypoglycemia unawareness, less aggressive HbA1c targets (i.e. 7.1%- 8.5%) may be considered [2].

Monitoring of glycemic control

Monitoring of glycemic status is fundamental to diabetes management as it enables an assessment of treatment efficacy and guides therapeutic adjustment to achieve glycemic targets[17]. In most patients, glycosylated hemoglobin (hemoglobin A1c or HbA1c) is a reliable measure of blood glucose concentrations over the preceding 90-120 days[2]. Current guidelines recommend measuring HbA1c every 3-6 months, depending on the patient's proximity to glycemic targets[2]. Results may be used by health care providers to assess mean glycemia, and as a measure of risk for developing long-term diabetic complications[17].

In contrast to HbA1c, which is typically performed and interpreted by health-care providers, self-monitoring of blood glucose is the measurement of blood glucose concentrations by patients with diabetes in their home environment [5]. The ultimate goal of self-monitoring of blood glucose is to collect blood glucose information at a number of different time points to construct a blood glucose profile which can then be used to create or modify a therapeutic regimen to optimize blood glucose control[18]. Self-monitoring can also be used by patients to help titrate medication dosing (e.g. insulin), detect or confirm hyper- and hypoglycemia, and to assess the effects of diet and lifestyle choices on their blood glucose levels [5, 18]. SMBG may also have a role in promoting patient empowerment as it may increase patients' ability to independently manage their disease, provide

motivation to remain adherent to therapy, or make healthy lifestyle choices [19].

Blood glucose self-monitoring technology is relatively recent, having only been utilized in the management of diabetes since the mid 1980's [17]. Prior to the availability of blood glucose testing strips, diabetes therapy was titrated to produce symptom relief (i.e. polydipsia, polyuria, and nocturia) rather than achieve specific blood glucose targets[17]. The first quantitative and semi-quantitative urine and blood glucose assays were difficult to interpret and therefore not suitable for home testing [4]. The first blood glucose meters required great precision to operate and were too cumbersome to be considered suitable for individual use[4]. As a result, the majority of blood glucose testing continued to be conducted in physician offices or other health care settings. Further improvements on these initial models decreased their size, improved their precision, and ultimately resulted in an end-product suitable for most patients to reliably measure their blood glucose at home[4].

Current blood glucose meters are palm-sized, equipped with a digital display and use test strips that are specific to the type of meter [4, 5]. Patients prick the skin (usually on the tip of the finger) using a lancet device to produce a small amount of blood that is applied to the test strip, which is inserted into the glucose meter. The concentration of glucose in the blood is quantified by a photometer and an output reading is provided to the user, usually within 30 seconds. The results can be stored in the device's digital memory for retrieval at a later time. Most modern meters are user-friendly, include alerts to warn of hypo- or extreme hyperglycemia, and may have additional software to allow individuals to record diet and exercise patterns to aid in interpreting blood glucose patterns [4, 17]. The test strip method is presently the only means by which an individual may accurately self-monitor their blood glucose concentrations [5]. It is worth noting that self-monitoring of blood glucose itself does not produce any meaningful clinical outcomes unless it is accompanied by changes in behaviors in response to blood glucose readings [5].

Trends in blood glucose test strip utilization

Blood glucose strips are emerging as a major source of health-care expenditure across the country. In a recent report of evidence based drug therapy, British Columbia identified a significant increase in test strip usage from 1996-2009. In 2009, total spending for blood glucose test strips was reported at $50 million, with an estimated $25 million attributed to test strip use in patients with type 2 diabetes[20]. In Ontario, blood glucose test strips represented the third largest expenditure to Ontario public drug plans, costing over $100 million and comprising 3.3% of total drug expenditures between 2007 and 2008 [21].

Test strip usage in Saskatchewan has also increased dramatically over the last two decades. In 2015, the Saskatchewan Drug Utilization and Outcomes Research Team (SDUORT) described trends and utilization patterns of test strip usage using Saskatchewan's administrative databases. In 1996, the crude number of strips dispensed was over 3.5 million attributed to 20,223 unique patients. In 2013, this increased to 16.8 million among 55,506 unique patients [10]. In each calendar year, approximately 20% of all test strip users had no record of blood glucose lowering medication use. An additional 26% of test strip users were receiving only oral hypoglycemic drugs with a low risk of causing hypoglycemia[10] . The total cost of strips increased from $3.5 million in 1996 to $16.8 million in 2013, of which the Saskatchewan government cost share was approximately $9 million[10] .

A significant portion of test strip use in Saskatchewan is in patients who do not appear to benefit greatly from SMBG [10]. In October 2015, the Saskatchewan government limited the quantity of blood glucose test strips covered for patients not on insulin [22]. Prior to this date, patients in Saskatchewan were able to receive up to 900 strips every 3 months, regardless of their clinical situation [10, 22].

Evidence for the use of SMBG in Diabetes Mellitus

Glycemic Control

For those with type 1 diabetes, the benefits of intensive glucose control (i.e. maintaining normal or near-normal blood glucose levels) have been well documented in clinical trials [13]. However, while intensive glycemic control was associated with improved clinical outcomes such as decreases in HbA1c and microvascular complications, patients in the intensive arm of the DCCT also experienced a three-fold increase in episodes of severe hypoglycemia and coma [13]. As such, Canadian and American diabetes guidelines recommend frequent self-monitoring of blood glucose in this patient population [2, 6] to minimize the risk of drug-induced hypoglycemia.

Patients treated with intensive insulin regimens should perform SMBG at least 3 times per day, at different times per day (i.e. pre- and post-prandial, prior to exercise, at bedtime, prior to driving, if hypoglycemia is suspected) depending on the specific needs of the individual [2, 6]. Many of the major trials that have demonstrated the benefit of intensive glycemic control [13, 23] included SMBG as a component of the intervention arm, suggesting that SMBG is an important component of effective diabetes management [6, 24]; however, the direct effects of SMBG have rarely been studied in randomized trials [24]. The Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) conducted a systematic review and meta-analysis to determine the efficacy, safety, and optimal frequency of SMBG in type 1, type 2, and gestational diabetes. They determined that few studies have explored the optimal frequency of SMBG in patients with insulin-treated diabetes (type 1 or type 2). Based on low quality clinical data, the reviewers concluded that SMBG was associated with improvements in glycemic control [7]. None of the randomized studies in type 1 diabetes reported hypoglycemia as an outcome [7] and only one study reported hypoglycemia outcomes in type 2 diabetic patients using insulin [7]. However, despite the lack of robust clinical evidence, self-monitoring of blood glucose is considered the standard of care for patients who use insulin [7, 24].

Patients who are not treated with insulin do not typically titrate oral hypoglycemic agents in response to SMBG readings, although they may use blood glucose levels to adjust other health behaviors (i.e. diet and physical activity) [8]. As such, the efficacy of self-monitoring of blood glucose in patients with non-insulin treated type 2 diabetes has been the subject of considerable debate, generating numerous studies, systematic reviews, and meta-analyses. The 2009 systematic review and meta-analysis conducted by COMPUS pooled results from seven randomized controlled trials in non-

insulin treated patients. They reported a "statistically significant, albeit clinically modest" reduction in HbA1c of -0.25% (95% CI [-0.36, -0.15]) associated with SMBG (versus no SMBG) [7]. In subjects with worse glycemic control at baseline (i.e. HbA1c greater than 8%), subjects performing SMBG had greater improvements in HbA1c than those who did not perform SMBG [7]. The effect of SMBG on HbA1c was similar regardless of the intensity of patient education, which is contrary to the commonly held assumption that SMBG should be more effective with patient education and training [7].

A more recent review was published in 2012 by the Cochrane Collaboration to assess the effects of SMBG in patients with type 2 diabetes not using insulin [25]. Their primary outcomes were effects on glycemic control (as measured by HbA1c), health-related quality of life, and patient satisfaction in trials comparing SMBG based interventions with no SMBG (control) [8]. In trials that examined patients with diabetes duration greater than one year, SMBG was associated with a statistically significant reduction in HbA1c of 0.3% (95% CI [-0.4%, -0.1%]) within six months of follow-up. However, the benefit of SMBG on glycemic control appeared to be short-term, as trials with 6-12 months of follow up were associated with a non-significant decrease of 0.1% in HbA1c [8]. In newly diagnosed diabetic patients (i.e. disease duration less than 1 year), SMBG was associated with a significant 0.5% reduction in HbA1c, suggesting potential for clinical benefit in this patient population. However, the use of SMBG was not associated with any appreciable benefit on patient indices of well-being, treatment satisfaction, or health-related quality of life [8].

The evidence summarized in these reviews suggests that the effect of SMBG on glycemic control is small in patients not using insulin. There does seem to be evidence of benefit in certain patient subgroups, most notably in patients newly diagnosed with diabetes, and in those with poor metabolic control. However, SMBG did not increase patient treatment satisfaction, well-being indices, or other measures of self-care[7, 8].

Current North American guidelines do not provide clear recommendations on SMBG for diabetic patients not on insulin. The DC guidelines recommend that SMBG should be individualized for those on oral hypoglycemics and should be considered when glycemic targets are not being met, along with patient and provider education [2]. DC guidelines suggest that testing 1-2 times per week should suffice in most patients; however this may be increased in individuals who are at higher risk for hypoglycemia. Although recommending SMBG in patients at risk for hypoglycemia is clinically intuitive, it has not been supported by evidence in randomized trials [26-28].

Hypoglycemia

Drug-induced hypoglycemia (i.e., abnormally low plasma glucose) is the most common complication of diabetes management [2, 12, 29]. Drug-induced hypoglycemia occurs much more frequently in patients with type 1 diabetes than in those with type 2 diabetes, primarily due to the use of insulin [11, 12, 29-33]. The severity of hypoglycemia is clinically defined according to the patient's ability to independently manage the condition [2, 13, 30]. In mild to moderate hypoglycemia, patients are usually able to self-treat with administration of an oral carbohydrate [2]. Symptoms of mild hypoglycemia are typically autonomic (i.e. hunger, palpitations, sweating, trembling, anxiety) while moderate hypoglycemia may result in neuroglycopenic symptoms (i.e. drowsiness and confusion) in addition to autonomic symptoms [2, 11]. Severe hypoglycemia may result in extreme confusion, seizure, or coma, and requires third-party assistance or medical intervention for treatment and recovery [2, 11, 32, 34, 35]. If untreated, severe hypoglycemia can result in death; 2-4% of deaths in patients with type 1 diabetes have been associated with hypoglycemia [36].

Rates of overall hypoglycemia in patients with type 1 diabetes may range as high as 115 to 320 per 100 patient years [30, 34, 37]. Hypoglycemia in patients with type 2 diabetes has been reported to occur at rates of 35 to 70 events per 100 patient years [30, 34, 37]. However, the incidence of hypoglycemia in type 2 diabetes may approach that of type 1 in those with a long duration of disease or who are receiving intensive insulin therapy [12, 32, 34, 37]. Patients with an increased risk for severe hypoglycemia include those with prior episodes of hypoglycemia, hypoglycemia unawareness, a long duration of insulin therapy, and/or long duration of disease [29, 33, 38]. In patients with type 2 diabetes increasing age, cognitive impairment, higher HbA1c and low health literacy have also been associated with an increased risk of hypoglycemia [2, 29].

In individuals without diabetes, decreasing blood glucose levels will trigger a predictable physiologic response to quickly correct or prevent hypoglycemia from occurring [12]. Endogenous insulin secretion is reduced, while glucagon and epinephrine secretion increase in order to stimulate hepatic glycogenlysis and gluconeogenesis, and decrease skeletal muscle uptake of glucose [12]. In those with type 1 diabetes, the secretion of these counter-regulatory hormones is impaired. In patients with type 2 diabetes, the normal physiologic response to low blood glucose is preserved early in the course of the disease [12]. However, the progressive nature of the disease will cause individuals to becoming increasingly insulin deficient and develop dysfunctional glucose counter-regulation mechanisms similar to that seen in those with type 1 diabetes [12].

The reduced epinephrine response in patients with diabetes may decrease the initial autonomic

symptoms of hypoglycemia, resulting in 'hypoglycemia unawareness' [2, 11, 12]. As a result, the first signs of hypoglycemia may not occur until an individual is confused or has a reduced level of consciousness [33]. In addition, repeated episodes of hypoglycemia may cause the threshold for the epinephrine response to 'shift' to lower blood glucose concentrations [12], resulting in more frequent and severe episodes of hypoglycemia[12, 33]. From a practical point of view, recurrent episodes of hypoglycemia may also influence patients to avoid strict glucose control [33, 34]. This behavior may prevent patients from achieving the level of glycemic control necessary to decrease the risk of diabetic complications [33].

The 2009 COMPUS systematic review also explored the impact of SMBG on hypoglycemic episodes in patients with type 2 diabetes not using insulin[7, 8]. The risk of overall hypoglycemia was higher in patients performing SMBG compared to those who did not perform SMBG. Pooling the results of 3 randomized controlled trials that reported the effect of SMBG (compared to no SMBG) resulted in a higher relative risk of overall hypoglycemia in patients performing SMBG (RR 1.99, 95% CI [1.37, 2.89]). There was no significant difference noted for rates of severe hypoglycemia between SMBG and control arms, but very few severe hypoglycemic events were reported in the included trials[7]. The increased risk of hypoglycemia in subjects performing SMBG was thought to be due to increased detection. The review concluded that there is unlikely to be a significant effect of SMBG on the relative risk of overall hypoglycemia in patients using oral hypoglycemics alone [7].

The 2012 Cochrane review of SMBG in patients with non-insulin treated type 2 diabetes was also unable to find good evidence that SMBG reduced hypoglycemic events. In the four trials that reported hypoglycemia as an outcome, hypoglycemic episodes were reported more frequently in SMBG arms than in control arms. The authors stated this to be an expected finding, as subjects performing SMBG are able to definitively confirm both symptomatic and asymptomatic episodes of hypoglycemia [8]. However, they also noted that as different studies use different definitions hypoglycemia, it is difficult to distinguish between the severities of the events that may have been detected by SMBG [8], and thus the benefits of increased detection (or consequences of non-detection) may be underestimated. There appeared to be a benefit of SMBG in patients using insulin secretagogues, as detection of hypoglycemia with SMBG may reduce the progression of asymptomatic events [7, 39]. However, this was not a pre-specified outcome and was subjectively reported[7], providing only initial evidence about the degree of benefit in this patient population.

Conventional wisdom suggests greater uptake of SMBG will decrease the incidence of hypoglycemia among patients with diabetes. Although this theoretical association is widely accepted

by health care providers, surprisingly little evidence is available to confirm it. In fact, the vast majority of high quality studies suggest SMBG *increases* the incidence of hypoglycemic episodes, presumably through increased detection of asymptomatic events [7, 8, 26-28]. At the same time, a favourable effect of SMBG on severe hypoglycemia has not been demonstrated (Table 1). Most of the literature surrounding SMBG demonstrates improvements in glycemic control, with hypoglycemia reported as a secondary outcome. The *increased* detection of hypoglycemia among patients practicing SMBG either represents the pathway by which serious hypoglycemic emergencies can be avoided, or it may just be drawing attention to nuisance levels that are not clinically dangerous. Currently available data do not provide enough information to clarify the impact of SMBG on this issue.

Table 1: Summary of key studies providing evidence for SMBG and hypoglycemia outcomes

Author and Year	Population	Study aim/Intervention	Key Findings
Farmer et al, 2007[26]	Non insulin treated type 2 diabetes	To determine if self-monitoring (with or without additional instruction) more effective than usual care in improving glycemic control Primary outcome: HbA1c at 12 months Hypoglycemia not specified as outcome, but episodes of hypoglycemia reported each study visit and categorized according to severity	One or more mild hypoglycemic events experienced by 14 subjects in control arm, 33 participants in less-intensive SMBG arm, and 43 subjects in more intensive SMBG arm ($p<0.001$). One control group subject experienced an episode of moderate hypoglycemia. Increased reporting of hypoglycemia in the monitoring arms thought to be due to an increased awareness of hypoglycemia that could be confirmed using SMBG
O'Kane et al, 2008[28]	Newly diagnosed type 2 diabetes	To determine if self-monitoring improved glycemic control and attitudes and satisfaction with treatment as compared with usual care Primary outcome: differences in HbA1c, psychological indices and incidence of hypoglycemia at 12 months	Unable to detect a significant effect of SMBG on incidence of hypoglycemia SMBG arm: 18 subjects reported 33 episodes of hypoglycemia Control arm: 13 subjects reported 36 episodes of hypoglycemia Severity of episodes not defined and the difference between groups found to be non-significant at all time points
Barnett et al, 2008[39]	Type 2 diabetes receiving a sulfonylurea-based regimen	To determine contribution of SMBG to diabetes management Primary outcome: HbA1c at 27 weeks Hypoglycemia not prespecified outcome, however subjects in SMBG group also received instruction in managing suspected or SMBG-confirmed hypoglycemia All subjects kept diary to record symptoms suggestive of hypoglycemia	Significant reduction in symptomatic hypoglycemic events in SMBG arm. Total number of hypoglycemic events similar in both arms (51 events in the SMBG arm and 66 in the control arm), but number of symptomatic hypoglycemic events more than twofold less in SMBG arm (27 events versus 64 events) [39]
Guerci, et al 2003[27]	Type 2 diabetes poorly controlled on oral hypoglycemic therapy (i.e. HbA1c values between 7.5-11%)	To compare metabolic control in patients managed with standard care utilizing SMBG compared with standard care alone Primary outcome: change in HbA1c at 6 months Frequency of hypoglycemia (symptomatic and asymptomatic) reported as secondary outcome	Hypoglycemic episodes occurred in 78 subjects: 53 (10.4%) occurred in SMBG group and 25 (5.2%) in standard care group Difference between groups significant ($p=0.003$) and due to increased detection of asymptomatic hypoglycemia in the SMBG group No serious events of hypoglycemia in either group reported during study [27]

Hospitalizations and health care utilization

The increased rate of hypoglycemic events associated with SMBG is undoubtedly due to increased detection [7, 8]. Individuals who self-monitor are able to confirm suspected symptoms of hypoglycemia and self-treat, or be able to detect episodes of asymptomatic hypoglycemia, especially in those on sulfonylureas [39] or insulin. On this basis, it would seem reasonable that individuals employing SMBG may require fewer emergency department visits and/or subsequent hospitalizations for hypoglycemia. There has been substantial research examining the relationship between variables such as age, disease duration, and treatment modalities on hospitalization rates for hypoglycemia [29, 31, 32, 34, 40]. However, to our knowledge, SMBG has not been significantly explored as a factor for its potential to prevent hospitalizations for hypoglycemia.

In order to determine risk factors for hospital admission due to hypoglycemia in patients with type 2 diabetes on oral hypoglycemics, Quilliam performed a nested case-control study in a cohort of type 2 diabetic subjects who received at least one oral hypoglycemic agent [40]. A total of 1,339 patients with a first hospital admission for hypoglycemia were identified as cases and matched to controls based on cohort entry date. Overall, cases had more comorbidities and cardiovascular disease than controls, and the presence of macrovascular and microvascular complications of diabetes were independent predictors of hospital admission. Previous emergency department and outpatient visits for hypoglycemia were also strong predictors of hospital admission for hypoglycemia. Metformin was associated with a reduced risk of hospital admission, while sulfonylureas and insulin use were associated with increased risk. Age was not a predictor of admission in the adjusted model. The use of blood glucose monitoring supplies was associated with a slight reduction in risk for admission (adjusted OR 0.83; 95% CI [0.71,0.96]), however this was non-significant in the unadjusted model (OR 1.02; 95%CI [0.9,1.15])[40]. A related case-control study by the same authors examined factors associated with Emergency Department (ED) visits for hypoglycemia in patients with type 2 diabetes using oral hypoglycemics. Factors increasing the risk of ED admission were similar to that of hospital admission, although female sex and lower age were associated with an increased risk. Use of blood glucose strips was low in both cases and controls (25.6% of cases and 21.4% of controls), and model results for SMBG utilization was not reported [31].

The 2011 Survey on Living with Chronic Diseases in Canada-Diabetes Component (SLCDC-DM) surveyed 2,862 respondents identified as having type 2 diabetes in order to determine the prevalence, frequency, and correlates of SMBG in this patient population [41]. In addition to obtaining self-reported testing prevalence and frequency information for SMBG, respondents were also asked if

they had visited an emergency department for hypoglycemia within the last year. The prevalence of SMBG did not differ between respondents on insulin alone, insulin with oral hypoglycemics, or oral hypoglycemics alone. SMBG was performed more frequently by those who reported a hypoglycemia-related emergency department visit than those who did not; the mean number of tests per week for respondents reporting a hypoglycemia-related emergency department visit within the last year was 18.4, compared to 10.2 tests per week in respondents who denied having a hypoglycemia-related emergency department visit ($p<0.05$)[41]. More frequent SMBG did not decrease the risk of hypoglycemia-related emergency department visits in this survey; however data was self-reported, vulnerable to selection bias, and was cross-sectional and therefore was likely unreliable to truly explore the relationship between SMBG and hospital or emergency department visits for hypoglycemia.

Although not designed to examine the association between test strip utilization and hypoglycemia hospitalizations, Booth et al. conducted a population-based time series analysis to determine trends in hospital admissions and emergency department visits for hypo- and hyperglycemia in Ontario from 1994-1998 [42]. After adjusting for fiscal year, age, sex, and various socioeconomic factors, they noted a marked 76% decline in the number of hospital admissions for hypoglycemia over the 5-year period (-18.7 per 100,000/year). Over the same time period, ED visits for hypo- and hyperglycemia (combined) also declined (-307.8 per 100,000/year). The authors postulated that as both indices declined simultaneously, the results suggest a true decline in the number of episodes of hypoglycemia [42], rather than a change in admitting thresholds or practices over the time period and may have been the result of improved diabetes care and management.

A second Ontario-based study provided preliminary insight into the relationship between test strip utilization and ED visits for hypoglycemia [43]. In 2017, Gomes et al. conducted a cross-sectional time series among Ontario drug plan beneficiaries to examine the impact of test strip quantity restriction on ED visits for hypoglycemia. Despite a 20% reduction in test strip utilization after the imposition of test strip reimbursement limits, no significant impact was observed on the rate of ED visits for hypoglycemia [43]. This effect was similar when patients were stratified according to mode of diabetes therapy and in a subgroup of heavy test strip users.

These types of analyses have not been formally carried out in Saskatchewan. Anecdotal and internal data suggests that hospitalizations for hypoglycemia in Saskatchewan may also declined over the last two decades. Given the dramatic increase in test strip usage over the same time period, it is possible that the two factors are related. SMBG has been associated with increased detection of hypoglycemia in clinical trials, which could theoretically lead to a decrease in serious events through

early detection. However, current evidence suggests SMBG may have no impact on the risk of hypoglycemia hospitalization in lower-risk patients.

As the majority of test strip use in Saskatchewan is in patients at low risk of hypoglycemia[10], it appears as though substantial resources are being invested with little potential for benefit. Therefore, the purpose of this project was to determine the relationship between blood glucose test strip use and rates of hypoglycemia-related healthcare utilization in Saskatchewan, and to explore the degree to which blood glucose test strip use affects the risk of being hospitalized for hypoglycemia.

Objectives

1. To determine if utilization of blood glucose test strips at the provincial level result in lower rates of hospitalizations for hypoglycemia.

2. To determine if the individual risk of hospitalization for hypoglycemia is lower among patients who use blood glucose test strips compared to those who do not.

Hypothesis

- A crude inverse association between test strip use rate and hospitalization rates will be observed when no adjustment is made for confounding factors.
- The use of blood glucose test strips does not reduce the risk for a hypoglycemia hospitalization except for those taking high doses of insulin.

Chapter 3: Methods and Procedures

Data source

The Saskatchewan Ministry of Health maintains several databases containing health services information including a population registry, vital statistics information, hospital discharge abstracts, physician claims, and prescription drug claims. Each Saskatchewan resident is assigned a unique patient identifier (i.e. Health Services Number, or HSN) that remains unchanged over time. The HSN is included in all health service records allowing information in each database to be electronically linked. The population registry contains demographic information, dates of coverage (i.e. entry and exit dates) and location of residence. The population registry includes approximately 99% of the population; people with federally funded health care (i.e. Canadian Forces, Royal Canadian Mounted Police, and inmates of federal penitentiaries) are excluded from the registry. The registry is verified by routine computer and manual checks to maintain its accuracy and currency [44, 45]. Vital statistics captures all births, marriages, deaths, and name changes that occur in the province of Saskatchewan. The adjudicated prescription drug claim database covers approximately 90% of the population with the exception of those who have drug coverage under a federal program (i.e., registered First Nations, federal inmates, Canadian military officers and veterans, and Royal Canadian Mounted Police). The

prescription database records all outpatient dispensations for medications from an extensive formulary and some drugs receiving prior authorization. Dispensations for drugs available without a prescription (i.e. over-the-counter), professional samples, and hospital inpatient drug use are generally not captured. For each medication dispensed, the Prescription Drug Database captures the generic and brand name, Drug Identification Number (DIN), drug class (by American Hospital Formulary System) date of dispensation, strength, dosage form, quantity, and prescriber and cost information of each dispensed drug [46]. Dispensations for drugs not approved for coverage have been captured in a separate, non-adjudicated claims database since 2006. There is no information on clinical indication, dosage regimen, or adherence available in the prescription claims database [44].

The medical services database includes all fee-for-service physician claims in Saskatchewan. Most medically necessary services are considered a benefit and all members of the eligible population are covered. The majority of physicians in Saskatchewan are reimbursed by the fee-for-service model; however, physicians paid by other means (e.g. salary) are encouraged to submit shadow claims for services performed [44, 47]. Each claim in the medical services database contains patient and provider identifiers, provider specialty, International Classification of Diseases (ICD) codes for primary diagnosis (coded to 3 digits), fee codes for procedures, and the location of service (e.g. physician office, hospital inpatient, hospital outpatient, emergency room, and home visit) [44, 48]. Submitted claims are cross-checked to determine validity and eligibility within the population registry [44].

The hospital discharge database contains a unique record for every discharge, transfer, or death occurring in all hospitals in the province. Each record includes demographic information (age, gender, and HSN) and information related to their hospital stay, such as admission and discharge date, main diagnosis, secondary diagnoses (up to 25), an accident code, length of stay, hospital identification, and their disposition (i.e. home, transfer to another hospital or term care facility, or death) [46, 49]. Diagnoses coding is done at the local level by health records administrators according to ICD standards and is recorded up to 6 digits [46, 49]. Since 2001, Saskatchewan has reported diagnosis according to the International Classification of Diseases (Tenth Revision, Canada) (ICD-10-CA) classification; prior to 2001, the International Classification of Diseases (Ninth Revision)(ICD-9) classification was used [45]. Limited routine validation of coding accuracy is also performed centrally. Data from the hospital discharge database is supplied to the Canadian Institute for Health Information (CIHI) and is collated in the Discharge Abstract Database (DAD). CIHI collects and analyzes health and health care information in Canada for statistical purposes, rather than for billing and remuneration [49]. The DAD includes demographic, clinical, and administrative data on inpatient hospital discharges that is supplied

to CIHI from hospitals across Canada. All hospitals, with the exception of those in the province of Quebec, are required to submit discharge information to CIHI [49]. CIHI conducts annual data re-abstraction studies to assess the ongoing quality of the coding and abstracting of clinical and non-clinical data contained within the DAD [49]. The most currently available data quality re-abstraction study evaluated 2009-2010 data, at both the national and provincial level. For the province of Saskatchewan, the authors reported that 86% of ICD-10-CA coded significant diagnoses reported in the DAD were confirmed in chart review, 77% of significant diagnoses recorded in chart review were present in the DAD, and an ICD-10-CA coding consistency of 86% [49]. Validation studies of the Saskatchewan Health Databases have been done for a wide range of medical conditions [44, 45] and its accuracy for use in research has been demonstrated in numerous studies [50-53].

Study data was accessed in the Saskatchewan Health Quality Council (HQC) via a secure virtual private network connection to a data warehouse located in eHealth Saskatchewan's servers. HQC's access to and use of these data are regulated by a data sharing agreement (DSA) between the Ministry of Health and HQC. An exemption from ethics approval for research was obtained from the University of Saskatchewan Biomedical Research Ethics Board (BIO 16:35), February 22, 2016.

Objective 1: To determine if utilization of blood glucose test strips at the provincial level result in lower rates of hospitalizations for hypoglycemia.

- Sub-objective 1.a--Conduct a time-series analysis to determine if an association exists between population-level usage of blood glucose test strips and hospitalizations for hypoglycemia

Sub-objective 1.a – Conduct a time-series analysis to determine if an association exists between population-level usage of blood glucose test strips and hospitalizations for hypoglycemia

Study Design

A retrospective, observational study design was used. Time series analyses were constructed for a) the number of hospitalizations for hypoglycemia and; b) the number of glucose test strips dispensed annually between January 1st, 1996 and December 31, 2014. Only beneficiaries of the Saskatchewan drug plan were included as drug and strip usage data for individuals with federal drug coverage was not captured in the prescription drug database (i.e., adjudicated claims database).

Identification of hypoglycemia cases

In each calendar year, starting from 1996, the total number of cases of hypoglycemia were measured using the following endpoints: a) Number of individuals with at least one hospital admission for hypoglycemia; b) Number of hospital admissions for hypoglycemia; c) number of individuals with at least one physician service claim for hypoglycemia; and d) number of physician service claims for hypoglycemia.

Hospitalization for hypoglycemia was identified using ICD-9 and ICD-10-CA codes indicating a diagnosis of hypoglycemia in the DAD in any diagnostic field (Table 2). To avoid capture of events occurring during the hospital stay, all hypoglycemic events designated as 'Type 2' diagnoses (i.e. post-admit comorbidities) were excluded [54, 55]. Ginde et al validated an ICD-9 based algorithm to accurately identify hospitalizations for hypoglycemia. The algorithm (adapted in Table 2) was found to have an overall positive predictive value of 89% (95% CI 86-92) for identifying hospitalizations for hypoglycemia [56]. Although we were not aware of a similar algorithm using ICD-10-CA codes, ICD-10-CA codes were examined to ensure correspondence with ICD-9 diagnosis codes. Neonatal

hypoglycemic events (i.e. ICD-9 codes 775.0 and 776.0) were excluded as they were not clinically relevant to the analysis.

Table 2: Diagnostic codes (ICD-9 and ICD-10-CA) used to identify hypoglycemia hospitalizations [42, 56, 57]

ICD Classification	Code	Description
ICD-9	251.0	Hypoglycemic coma
ICD-9	251.1	Other specified hypoglycemia
ICD-9	251.2	Hypoglycemia, unspecified
ICD-9	270.3	Leucine-induced hypoglycemia
ICD-9	250.8 (in absence of other contributing diagnoses: 259.8 272.7 681.xx, 682.xx, 686.9x 707.1-707.9 709.3 730.0-730.2, 731.8	Diabetes with other specified manifestations, excluding: Secondary diabetic glycogenosis Diabetic lipidosis Cellulitis Ulcers of the lower extremity Oppenheim-Urbach syndrome Osteomyelitis
ICD-10-CA	E10.63	Type 1 diabetes mellitus with hypoglycemia
ICD-10-CA	E11.63	Type 2 diabetes mellitus with hypoglycemia
ICD-10-CA	E13.63	Other specified diabetes mellitus with hypoglycemia
ICD-10-CA	E14.63	Unspecified diabetes mellitus with hypoglycemia
ICD-10-CA	E15.0	Non-diabetic hypoglycemia coma
ICD-10-CA	E16.0	Drug induced hypoglycemia
ICD-10-CA	E16.1	Other hypoglycemia
ICD-10-CA	E16.2	Hypoglycemia unspecified

Physician visits for hypoglycemia were recorded from the medical services database and identified by the ICD-9 code 251 in the diagnosis field. The medical services database captures a single, three-digit ICD-9 diagnosis code collected for remuneration purposes and may not be completely representative of the reason for the visit. In addition, the three-digit code describes the diagnosis in broad terms only; no further detail regarding specifics of the disease or condition can be obtained. To our knowledge, use of the physician claims database to identify hypoglycemia has not been validated; however, it was felt to be a measure that should be recorded to provide a comprehensive picture of health services claims over time.

Additional secondary endpoints

Additional endpoints were also tracked during the observation period to provide context for the observed trends in hypoglycemia events. All-cause hospitalizations consisted of the annual number of hospitalizations resulting in at least one night's stay. In addition, hypoglycemic medication utilization consisted of the annual number of individuals receiving at least one dispensation for a hypoglycemic medication. Trends over time were examined independently for each endpoint.

Emergency Department (ED) visits for hypoglycemia

The annual rate of hospitalization for hypoglycemia may be influenced by changes in admitting thresholds in provincial emergency departments (ED). For example, decreases in hypoglycemia hospitalizations could result if a higher percentage of these cases were managed and released directly from the ED (i.e., without hospital admission). To estimate the impact of ED activities on hypoglycemia-hospitalization trends, ED databases from the two largest urban centres in Saskatchewan were accessed (Saskatoon and Regina). Visits for hypoglycemia were identified from ICD-10-CA codes (Table 2) indicating hypoglycemia as the main reason for the ED visit. The annual number of ED visits for hypoglycemia were described along with the percentage of individuals who were subsequently hospitalized.

Test Strip Utilization

Blood glucose test strip use was measured annually according to the following endpoints: a) the total number of test strips dispensed; b) total number of individuals receiving at least one strip; and c) total number of test strip dispensations. Test strip dispensations were identified by their DIN and captured from the adjudicated prescription claims database. Test strip brand names (and associated DINs) identified as a benefit under the Saskatchewan Drug Plan Formulary are given in Table 3. This analysis was conducted in the same manner as the previous SDUORT analysis of test strip utilization, with additional drug data that had become available [10].

Table 3: Blood glucose test strip products listed as benefits under the Saskatchewan Drug Plan (by name and DIN) from 1996-2014 [22]

DIN	Test strip name	DIN	Test strip name
00950599	ACCU-CHEK	97799597	FREESTYLE LITE
00950926	ACCU-CHEK ADVANTAGE	97799596	FREESTYLE LITE
00950949	ACCU-CHEK AVIVA	00950894	FREESTYLE PRECISION STRIP
00950900	ACCU-CHEK COMPACT	97799373	GE200 BLOOD GLUCOSE STRIP
00951190	ACCU-CHEK INFORM II	97799372	GE200 BLOOD GLUCOSE STRIP
97799497	ACCU-CHEK MOBILE	00950378	GLUCOFILM
00950432	ACCUTREND	00950878	GLUCOMETER DEX
00950661	ADVANTAGE	00950408	GLUCOSTIX
00950883	ADVANTAGE COMFORT	00950956	ITEST
00950878	ASCENSIA AUTODISK	97799594	LIFE BRAND
00950960	ASCENSIA BREEZE 2	97799595	LIFE BRAND PORTABLE
00950924	ASCENSIA CONTOUR	00951177	MEDISURE
00950878	ASCENSIA DEX	97799458	MYGLUCOHEALTH TEST STRIPS
00950924	ASCENSIA MICROFILL	97799583	NOVAMAX
00950911	BD LATITUDE STRIP	00950889	NOVO-GLUCOSE
00950911	BD TEST	97799582	ON-CALL PLUS
97799465	BGSTAR	00950459	ONE TOUCH
97799478	BIONIME RIGHTEST GS100	00950893	ONE TOUCH ULTRA
97799394	BRAVO BLOOD GLUCOSE TEST	00950459	ONE TOUCH ULTRA
00950960	BREEZE 2	97799476	ONETOUCH VERIO
00950068	CHEMSTRIP BG	00950912	PRECISION EASY
00950924	CONTOUR	00950300	PRECISION PLUS
97799459	CONTOUR NEXT	00950894	PRECISION XTRA
97799460	CONTOUR NEXT	00950831	PRESTIGE
00950572	ELITE	97799451	RAPID RESPONSE
00950505	ENCORE	00950948	SIDEKICK
00950122	EXACTECH	00950902	SOF-TACT
97799564	EZ HEALTH ORACLE	00950734	SURESTEP
00950882	FASTTAKE	97799355	SURETEST
00950907	FREESTYLE	97799532	TRUETEST
		00950957	TRUETRACK SMART SYSTEM

Data Analysis

Test strip dispensations and hypoglycemia endpoints were graphed annually to show the trend of use over the study period. In order to account for changes in population demographics over time, all endpoints were standardized by age group (5-year intervals) and sex [58, 59]. The 2005 population of active beneficiaries was used as the reference population to directly standardize hospitalizations and test strip use per calendar year. The crude number of test strips (or hypoglycemic events) in each age-sex group was converted to a rate and multiplied by the corresponding reference/standard population in that age-sex group. The sum of the standardized endpoint across all age-sex groups for a given year gave the age-sex standardized measure of test strip use and hypoglycemic events [59].

Unadjusted changes in each endpoint were estimated over the study period using least squares regression models. Graphs of each endpoint versus time (i.e. calendar year) were constructed to visualize initial trends and relationships between variables. Quantile-quantile plots of standardized residuals were constructed to assess the distribution of residuals. Independence of errors was assessed using the Durbin-Watson test [60]. The coefficient of determination (i.e. adjusted R^2 statistic) was reported for each model to estimate the degree to which the model fit the observed data [60, 61]. The least squares regression model for each outcome was given by the equation $Y= \beta_0 + \beta_1 x + \varepsilon$, with the equation variables given in Table 4.

Table 4: Variables included in least squares regression model

Variable	Definition
Y	Outcome (i.e. age and sex standardized number of hypoglycemia events and age-sex standardized test strip use)
β_0	Regression Y-intercept
β_1	Coefficient representing impact of time (x)(Regression slope)
x	Time period represented by number of years since beginning of observation period (0, 1, 2….x)
ε	Error term

Generalized estimating equations (GEE) fit within a generalized linear model (GLM) framework were used to test the association between test strip use and hypoglycemic events at the population level. As hospitalizations for hypoglycemia and test strip dispensations were measured repeatedly in the study population, it was unlikely these would represent independent endpoints.

Therefore, GEEs were used to model the trend of hypoglycemia admissions over time, while accounting for potential autocorrelation within the data [62-64].

Individuals were stratified by age group, sex, and year. Age group categories were by 5-year intervals, except for the youngest and oldest (i.e. less than 1 year and greater than 95 years). Independent variables in the analysis were test strip usage and the total number of hospitalizations (all-cause) for each strata (Table 5). The population of each stratum was included as a constant in the model. The dependent variable (i.e. total number of hospitalizations for hypoglycemia) was obtained for each age/sex/year strata. The model was used to determine if test strip use was an independent predictor of total annual hospitalizations for hypoglycemia, while controlling for year, age, sex and overall healthcare utilization [62].

In order to determine the distribution of the dependent variable, the intercept-only model was tested with both a Poisson and negative binomial distribution. The ratio of variance to degrees of freedom was used to establish which distribution best represented that of the dependent variable [63] . Both autoregressive and exchangeable correlation structures were postulated to be a reasonable estimate of the correlation that may exist within the data. The correlation structure that resulted in lower values of the quasi-likelihood information criteria (QIC) was chosen for model construction [63].

Table 5: Variables included in the GEE model

Variable	Definition
Y	Outcome (total number of hospitalizations for hypoglycemia in the strata)
$\mathbf{x_1}$	Year
$\mathbf{x_2}$	Test strip utilization in each stratum
$\mathbf{x_3}$	All-cause hospitalization in each stratum
k	Constant (natural logarithm of the population in each stratum)

Objective 2: To determine if the individual risk of hospitalization for hypoglycemia is lower among patients who use blood glucose test strips compared to those who do not.

Methods

A nested case control study was used to identify the impact of blood glucose test strip use on the risk for hypoglycemia requiring hospitalization. Individuals were entered in the cohort if they satisfied all the following criteria: a) were a beneficiary of the Saskatchewan drug plan; b) met the Canadian Chronic Disease Surveillance System (CCDSS) case definition for diabetes after January 1st 1996; and c) were at least 20 years of age at cohort entry. The CCDSS case definition was met if individuals received two outpatient physician claims for diabetes within 730 days or one hospitalization indicating a diagnosis of diabetes [65] [Table 6]. For those meeting the case definition through outpatient physician claims, the cohort entry date corresponded to the date of the second claim. For those hospitalized with diabetes, the cohort entry date was the discharge date.

Table 6: Diagnostic codes (ICD-9 and ICD-10-CA) used to identify diabetes cases

ICD Classification	Code	Description
ICD-9	250.xx	Diabetes mellitus
ICD-10-CA	E10.xx	Type 1 diabetes mellitus
ICD-10-CA	E11.xx	Type 2 diabetes mellitus
ICD-10-CA	E12.xx	Malnutrition-related diabetes mellitus
ICD-10-CA	E13.xx	Other specified diabetes mellitus
ICD-10-CA	E14.xx	Unspecified diabetes mellitus

According to the CCDSS definition, women with gestational diabetes mellitus were excluded from the analysis. As drug usage data could not be obtained for persons under federal coverage programs prior to 2006, individuals with federal drug coverage were not included in the analysis. In addition, those with less than 1 year of continuous beneficiary status prior to their cohort entry date were excluded. All subjects were followed from the cohort entry date until the earliest occurrence of death, termination of provincial health benefits, or the end of the study period (December 31, 2014).

The CCDSS definition of diabetes has been validated in individuals ≥ 20 years of age [66]. Although it is not able to differentiate between type 1 and type 2 diabetes, it was found to have a sensitivity of over 95% upon its first validation in Manitoba using the provincial diabetes education database [47, 66]. It has been further validated using various 'gold standards' in different jurisdictions across the country [66]. In Saskatchewan, the sensitivity of the case definition has been estimated at

92% [47]. The inclusion of hypoglycemic agents in the case definition does not appear to improve its sensitivity or specificity [47].

Identification of cases and controls

Cases were defined by the first occurrence of a hospital admission for hypoglycemia during the follow-up period (i.e., January 1st, 1996 to December 31, 2014). Hospitalizations for hypoglycemia were identified from DAD records listing ICD-9 or ICD-10-CA codes indicating a diagnosis of hypoglycemia [Table 1] in any diagnosis field. To avoid capture of hypoglycemic events occurring in hospital, all hypoglycemic events designated as 'Type 2' diagnoses (i.e. post-admit comorbidities) were excluded [54, 55]. Cases were assigned an index date corresponding to the admission date for their first hospitalized hypoglycemic event [31, 40]. To ensure all patient exposures could be evaluated for six months preceding the event, patients experiencing hypoglycemic events within 180 days of cohort entry were excluded for the primary analysis. However, they were re-introduced in sensitivity analyses to determine if their presence affected final estimates.

Controls were selected using incidence density sampling [67]. As incidence density sampling estimates the entire at-risk experience of all those in the risk set, this approach is considered the most efficient and least biased sampling design for case-control studies [68]. For each case, four controls [69] were randomly selected from the study cohort and assigned an index date that corresponded to the date of admission for their matched case. Controls were matched according to their cohort entry date (year), by age category at cohort entry**,** and sex. A control for one case may have been selected as a control for another case occurring at a later date, providing they remained in the study cohort and therefore continued to be at risk of becoming a case. Accordingly, controls may have also become cases at a later date [68, 70, 71]. Matching by age at cohort entry in 5-year age categories resulted in multiple cases that failed to match with a single control; thus, matching criteria for age was subsequently increased to 10-year intervals to allow for inclusion of all cases.

Identification of Variables / Confounders

The primary independent variable was the use of blood glucose test strips in the 180 days preceding the index date. Test strip use was identified from the Saskatchewan Drug Plan database using their DIN [Table 3]. Cases and controls were categorized as test strip 'users' or 'non-users' based on the presence (i.e. user) or absence (i.e. non-user) of test strip dispensations in the 180-day period prior to the index date. In sensitivity analyses, total number of test strips 'on-hand' was

categorized into an ordinal variable representing intensity of test strip use.

Numerous possible confounders were identified either on the cohort entry date or during the exposure period. Covariates were identified within the following categories: patient factors, treatment/drug factors, disease factors, and health care utilization and system factors. Treatment/drug factors were identified by dispensations captured from the Prescription Claims database. Disease factors were identified using ICD-9 and ICD-10-CA codes recorded in the Medical Services database and Discharge Abstract database. Health system and healthcare utilization factors were identified using administrative variables obtained from the Medical Services database and DAD. Covariates are described in detail in Table 7.

Table 7: Variables included in conditional logistic regression analysis [31, 32, 34, 40, 72, 73]

Covariate Category	Covariate	Covariate Definition	Variable Name	Variable Coding
Primary Dependent Variable	Outcome	Hospitalization for hypoglycemia	CACO	0=Control 1=Case
Primary Independent Variable	Test Strip Use	Dispensation of test strips in 180 days prior to index date	STRIP_USER	0=No 1= Yes
Patient Factors	Location of residence	Subject residence (rural or urban) according to postal code at index date	URB_RUR	0= Urban 1= Rural
Treatment Factors	Mode of diabetes therapy	Category of diabetes treatment according to risk of hypoglycemia (Table 8) in 180 days prior to index date	DIAB_TX	0= No drugs 1= Low risk oral hypoglycemic 2= High risk oral hypoglycemic 3= Insulin
Disease Factors	Comorbidity Score	Charlson score[72] in 1 year period prior to index date	CHARL_CAT	0=Charlson score 0 1=Charlson score 1-4 2=Charlson score 5 or more
	Previous outpatient visits for hypoglycemia	Medical services claim indicating outpatient visit for hypoglycemia (i.e. ICD-9 code 251) in 180 days prior to index date	MSB_HYPO	0= No 1=Yes
Healthcare utilization and system factors	Specialty Physician Care	Medical services claim indicating specialist visit for treatment of diabetes in 180 days prior to index date	SPEC_DIAB_VISIT	0= No 1=Yes
	Outpatient health care utilization	Total number of outpatient visits occurring in 180 days prior to index date	OUTPT_VISITS	0= 0-3 outpatient visits 1=4-6 outpatient visit 2=7-10outpatient visits 3= ≥ 11 outpatient visits

Table 8: Classification of patients according to mode of diabetes therapy [10, 22]

Treatment Category	Definition	Category specific medications available as a benefit under the Saskatchewan Drug Plan
Insulin	At least one dispensation of insulin with or without an oral antihyperglycemic medication during the 180 days prior to the index date	Rapid Acting: Insulin Lispro Insulin Aspart Insulin Glulisine Short Acting/Regular: Humulin R (Regular) Novolin ge Toronto Hypurin Regular Intermediate Acting: Humulin N Novolin ge NPH Hypurin NPH Long Acting: Insulin glargine Insulin determir Premixed: Humulin 30/70 Novolin ge 30/70 Novolin ge 40/60 Novolin ge 50/50
High risk oral hypoglycemic medication	At least one dispensation for an oral agent with a high potential to cause hypoglycaemia without claims for insulin during the 180 days prior to the index date	Tolbutamide Chlorpropamide Glyburide
Low risk oral hypoglycemic medication	At least one dispensation for an oral agent with a lower potential to cause hypoglycaemia without claims for insulin or high risk oral agent during the180 days prior to the index date	Gliclazide Nateglitinide Repaglitinide Metformin Acarbose Rosiglitazone Pioglitazone Sitagliptin Saxaglitpin Linagliptin Rosiglitazone/Metformin Sitagliptin/Metformin
No hypoglycemic medications received	No claims for diabetes medications in the 180 days prior to index date	N/A

Analysis

A conditional logistic regression model was developed to test if test strip use (the primary independent variable of interest) was independently associated with risk of hospitalizations for hypoglycemia. Variables that were considered for inclusion in the model are given in Table 7. The distributions of all independent variables were examined. For categorical variables, contingency tables of the outcome against the levels of categorical variable were constructed. Covariates were examined to determine if multicollinearity existed between independent variables and test strip use. Potential collinear relationships were identified by pairwise correlation coefficients greater than 0.8 or Variance Inflation Factors (VIF) greater than five [74].

The conditional logistic regression model was constructed utilizing a theoretical-based approach. Sets of covariates (Table 7) were added to the model sequentially to determine the effect of clinically related variables on the relationship between the primary independent variable and outcome. In order to maximize control for confounding, a model containing all covariates in Table 7 was constructed.

The covariates in the main effects model were then assessed for any clinically relevant interactions with the primary outcome variable. Clinically relevant interactions identified a priori that were tested included those between strip use and mode of diabetes therapy, strip use and comorbidity score, and strip use and previous outpatient visits for hypoglycemia. Statistically significant interactions were added to main effects models and evaluated using the Akaike Information Criterion (AIC) [75] and Bayesian Information Criterion (BIC) [76] to identify best candidate models that fit the data well, while including clinically relevant variables. The unadjusted and adjusted odds ratios (along with 95% confidence intervals and corresponding p-values) for test strip use and other predictors of hospitalizations were reported.

Sensitivity analyses were conducted with exposures being characterized in the 90-day period prior to the index date (i.e., versus 180 days) and with the inclusion of subjects with events occurring within the first 180 days of cohort entry that had previously been excluded from the analysis. Additional sensitivity analyses that were conducted also included categorization of strip use to represent levels of use (i.e. none, lowest users, intermediate users, and highest users) [10], and according to drug use (i.e. therapeutic class of hypoglycemic). A subgroup analysis in insulin users was also conducted, with insulin use stratified by average daily consumption (DACON) [77] of insulin. In the insulin-user subgroup, an interaction

between test strip use and insulin dosage (by DACON quartile) was also examined to determine if the relationship between test strip use and hospitalizations for hypoglycemia differed according to the intensity of insulin therapy.

All statistical analyses were conducted using SAS version 9.4.

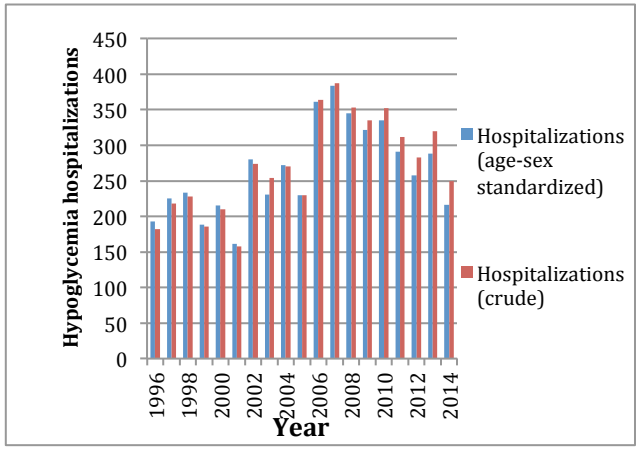
Chapter 4: Results

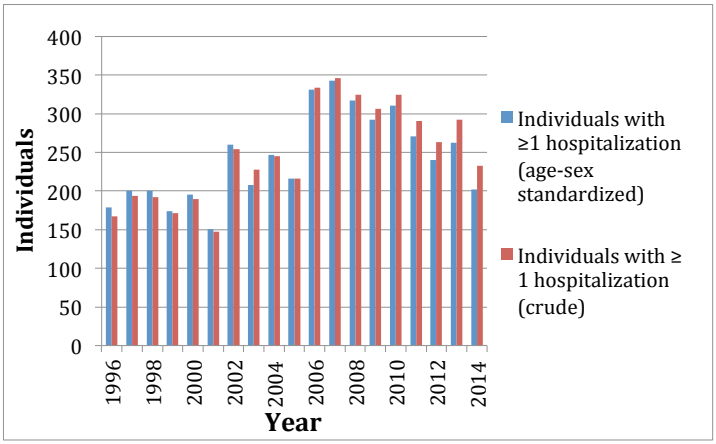
Hospital admissions for hypoglycemia

Between January 1, 1996 and December 31, 2014, a total of 5,166 hospitalizations for hypoglycemia were recorded in Saskatchewan. The average annual crude rate was 272 hypoglycemia admissions among 1,039,150 beneficiaries, or 26.2 hypoglycemia admissions per 100,000.

On visual inspection, no consistent trend was evident in hypoglycemia hospitalizations between 1996 and 2014 (Figure 1). The lowest number of hospitalizations for hypoglycemia occurred in 2001 (158 hospitalizations among 147 individuals) and the highest number was recorded in 2007 (387 hospitalizations among 346 individuals - Figures 1a and 1b). Linear regression analysis was not applied to the entire study period due to non-linear trends in the endpoint over the study period. A similar trend resulted when the outcome was changed to the number of individuals with at least one hospital admission (Figure 1b). Quantile-Quantile plots of residuals indicated that distribution of errors were approximately normal for hypoglycemia and hospitalization endpoints, but not for test strip endpoints. For all endpoints, the Durbin-Watson test indicated that positive autocorrelation was present in all models.

Figure 1a and 1b: Total number of hospitalizations for hypoglycemia (left) and total individuals with ≥1 hospitalization for hypoglycemia in Saskatchewan (right) from 1996-2014



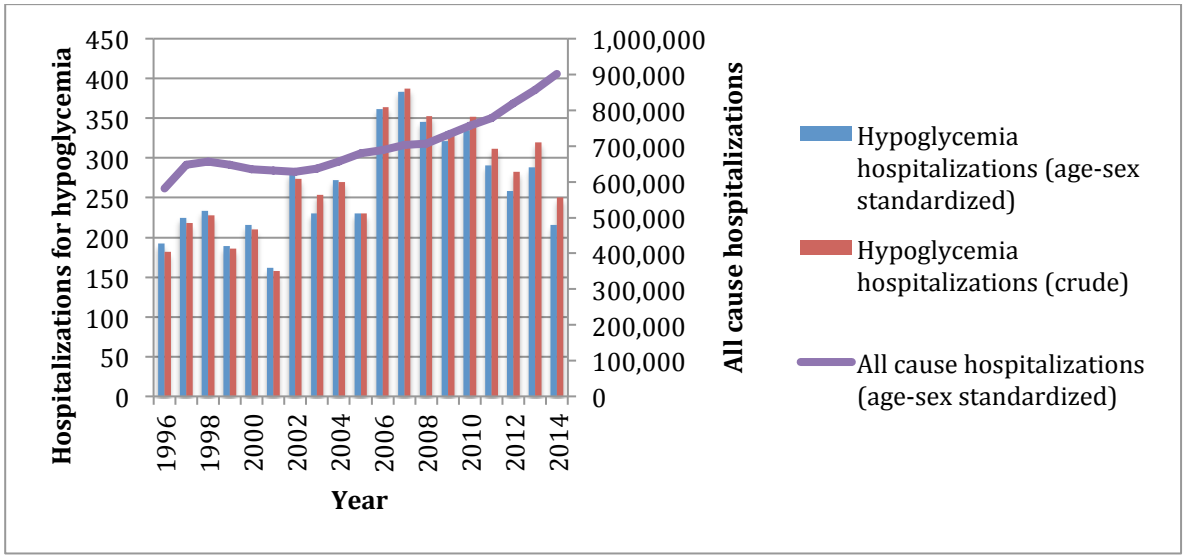


Additional investigations were undertaken to understand the descriptive results (including the poor model fit). First, a review of drug policy, provincial drug availabilities, and coding practices did not reveal any obvious factors that might have explained the apparent increase in hospitalizations

between 2005 and 2006. Second, the analysis was reproduced after restricting the cases of hypoglycemia to those specified as type 1 or type M (for most responsible) as well as restricting to those diagnoses occurring in the first two diagnostic positions. All of these sensitivity analyses produced results consistent with the primary results. The results were then stratified by time periods (i.e. 1996 to 2005, and 2006 to 2014) corresponding to visual inspection of the original time series (Figure 1). After performing separate linear regression analyses on each time period, the change in the number of hypoglycemia hospitalizations from 1996 to 2005 was non-significant ($p=0.20$), while the number of hypoglycemia hospitalizations significantly decreased from 2006 to 2014 (annual decrease -17.9; 95% CI [-24.47, -11.31], $p<0.01$, adj. $R^2=0.83$), which coincides with the qualitative trends described by Figure 1.

All-cause hospitalizations were plotted to provide context relating to overall health care trends across the province (Figure 2). The crude number of hospitalizations for any cause that resulted in at least one night's stay increased from 591,391 hospitalizations in 1996 to 1,047,069 hospitalizations in 2014, indicating an overall increasing trend in health care utilization over the study period (annual increase +13,879, 95% CI [10,638, 17,121], $p<0.01$,adj. $R^2=0.82$). Of note, trends in all-cause hospitalizations were not consistent with those observed for hypoglycemia, especially in the latter part of the study period.

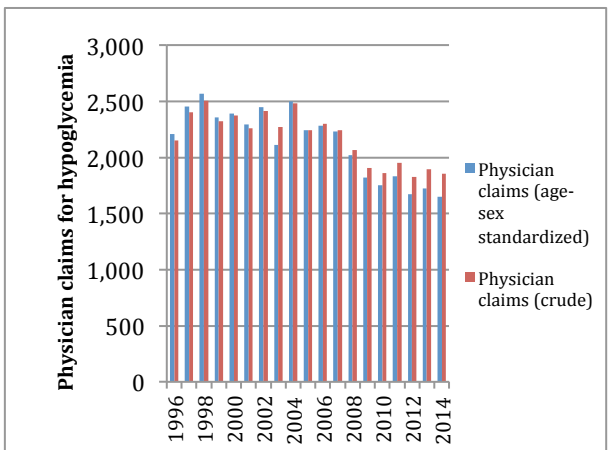
Figure 2: Total number of hospitalizations for hypoglycemia and all-cause hospitalizations in Saskatchewan from 1996-2014

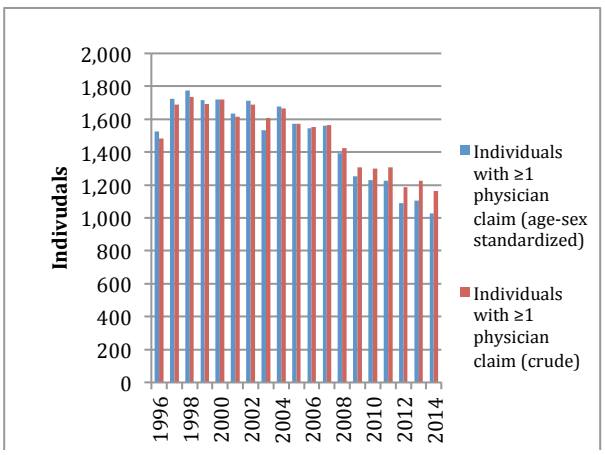


Physician claims for hypoglycemia

The frequency of physician claims for hypoglycemia during the observation period was much higher than that of hospitalizations. Between 1996 and 2014, a total of 41,322 claims for hypoglycemia were recorded. Overall, physician claims for hypoglycemia declined over the study period (Figures 3a and 3b). The highest number of claims (2,504) was observed in 1998 representing 1,735 individuals. In 2014, the crude number of physician claims for hypoglycemia was 1,856 resulting from 1,664 individuals. The decline was significant over the study period (annual decrease -46.7, 95% CI [-60.87, -32.60], $p<0.01$, adj. $R^2=0.73$). The number of individuals with at least one physician claim for hypoglycemia also exhibited a similar declining trend over the study period (annual decrease -38.8, 95% CI [-48.83, -28.75], $p<0.01$, adj. $R^{2=}$ 0.78).

Figure 3a and 3b: Total number of physician claims for hypoglycemia (left) and total individuals with ≥1 physician claim for hypoglycemia (right) in Saskatchewan from 1996-2014





Blood glucose test strip utilization

Blood glucose test strip utilization increased annually over the study period, both in terms of an increase in the number of test strips dispensed and the number of individuals receiving test strips. In 1996, 3.9 million strips were dispensed to 15,756 distinct users (59,493 dispensations). In 2014, 18.2 million test strips were dispensed to 42,051 distinct users (150,958 dispensations - Figures 4-6). The increases in all measures of test strip utilization were statistically significant over the study period. The annual estimated increase in the total number of strips dispensed was +758,171 (95% CI [674,587, 841,754], $p<0.01$, adj. $R^2 = 0.95$), the annual increase in the total number of test strip dispensations was +4,418 (95% CI [3,419, 5,415], $p<0.01$, adj. $R^2 =0.83$) and the annual increase in the number of individuals receiving at least one test strip was +1,216 (95% CI [1,009,1,424], $p<0.01$, adj. $R^2 = 0.89$).

Figure 4: Total number of blood glucose test strips dispensed in Saskatchewan from 1996-2014

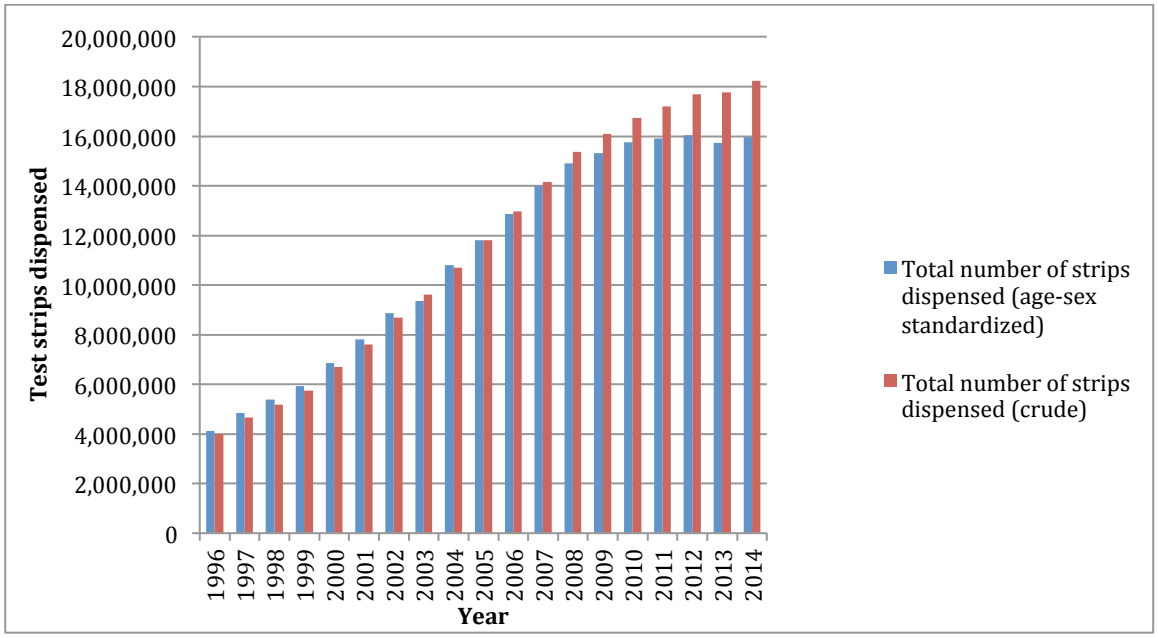


Figure 5: Total blood glucose test strip dispensations in Saskatchewan from 1996-2014

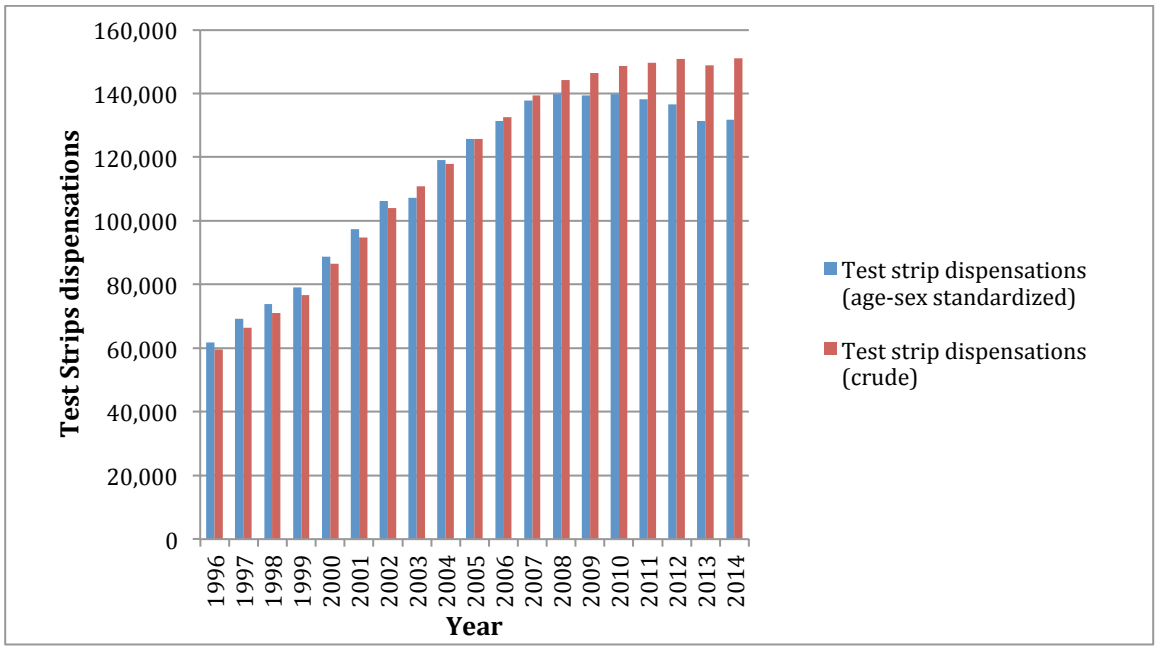
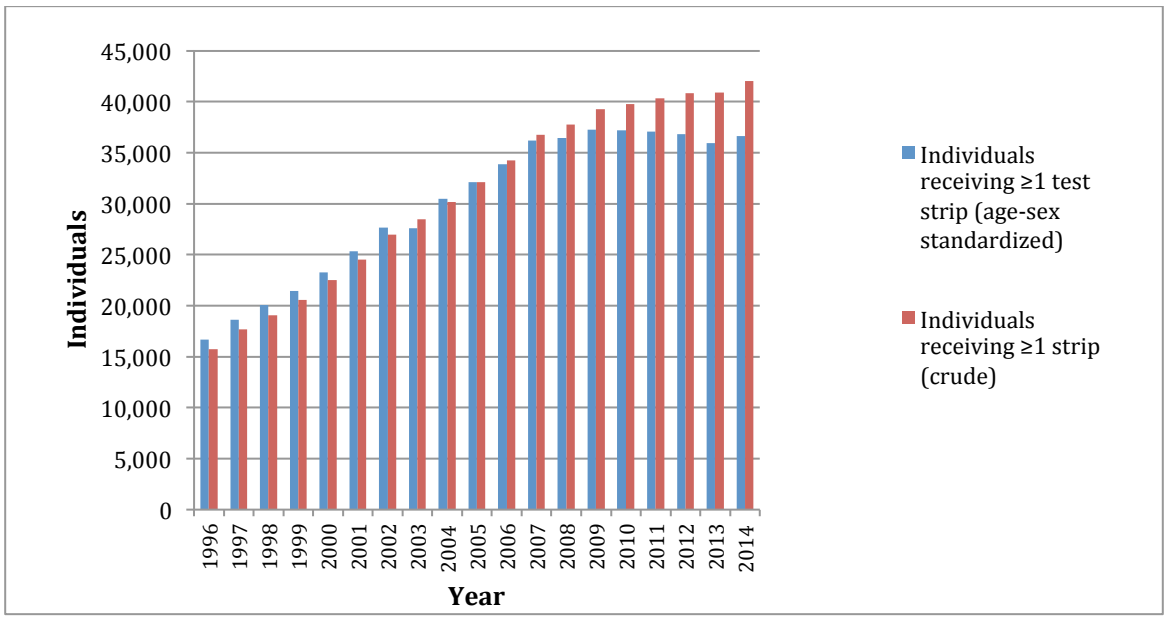


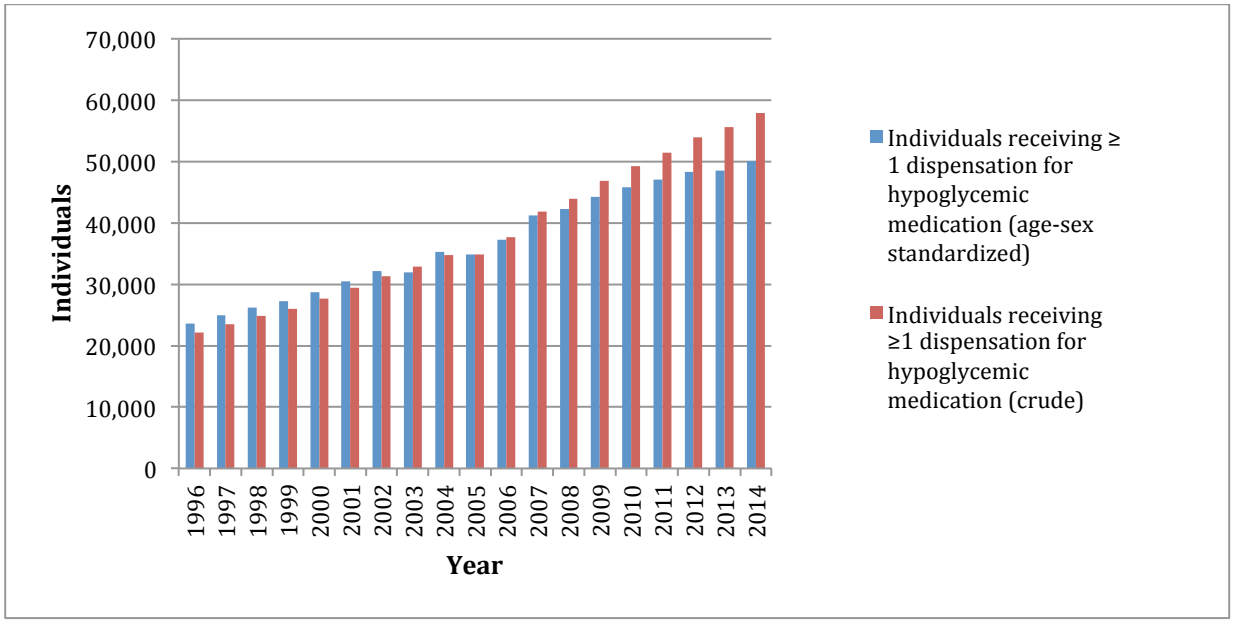
Figure 6: Total number of individuals receiving at least one blood glucose test strip in Saskatchewan from 1996-2014



Hypoglycemic medication utilization

The number of individuals receiving at least one hypoglycemic medication increased annually over the study period from 22,197 individuals in 1996 to 57,877 individuals in 2014 (Figure 7) (annual increase +1,565, 95% CI [1476,1653], $p<0.01$, adj. $R^2=0.98$).

Figure 7: Total number of individuals receiving at least one hypoglycemic medication in Saskatchewan from 1996-2014



ED visits for hypoglycemia

Data for emergency department visits in Saskatchewan were only available from 2012 onwards (Table 9). Of all patients presenting to the ED for hypoglycemia during this period (n=608), only 15% (n=101) were admitted to hospital on the same day. An additional 5% were admitted to hospital within 7 days of an ED visit for hypoglycemia.

Table 9: ED visits for hypoglycemia in SHR and RQHR from 2012 to 2014

Year	Total ED Visits	Admitted to hospital on same day of ED visit	Admitted to hospital within 7 days of ED visit
2012	223	33	<6
2013	191	39	10
2014	194	29	12

Association between test-strip utilization and hospitalizations for hypoglycemia

To obtain a reliable estimate of the relationship between hypoglycemia hospitalizations and blood glucose test strip usage, a GEE model was fit to account for autocorrelation within the time series. When initially fit with a Poisson distribution, the resulting model possessed a ratio of variance to degrees of freedom of 6.30, indicating over-dispersion was present. When fit with a negative binomial distribution, the resulting model possessed a ratio of variance to degrees of freedom of 1.12, indicating a better fit to distribution of the dependent variable. The negative binomial distribution (and corresponding log link function) was therefore used for model construction [63]. Both the autoregressive and exchangeable correlation structure appeared to fit the data reasonably well, however the exchangeable correlation structure resulted in smaller values of the QIC and was chosen for model construction [63].

After controlling for the number of all-cause hospitalizations and changes in population size, the total number of test strips dispensed was not associated with a significant change in the rate of hospitalizations for hypoglycemia ($p=0.41$) (Table 10). The test strip utilization endpoint in the model was also measured in terms of the total number of test strip dispensations. This made little difference to the overall association between test strip use and hospitalizations for hypoglycemia. The average annual rate of change for hypoglycemia hospitalizations was estimated as +3% over the study period (multiplicative rate increase 1.03 [95% CI 1.01-1.05], $p<0.01$).

Table 10: Hypoglycemia hospitalizations as a function of year, the total number of test strips dispensed (in millions), and all-cause hospitalizations (in millions)

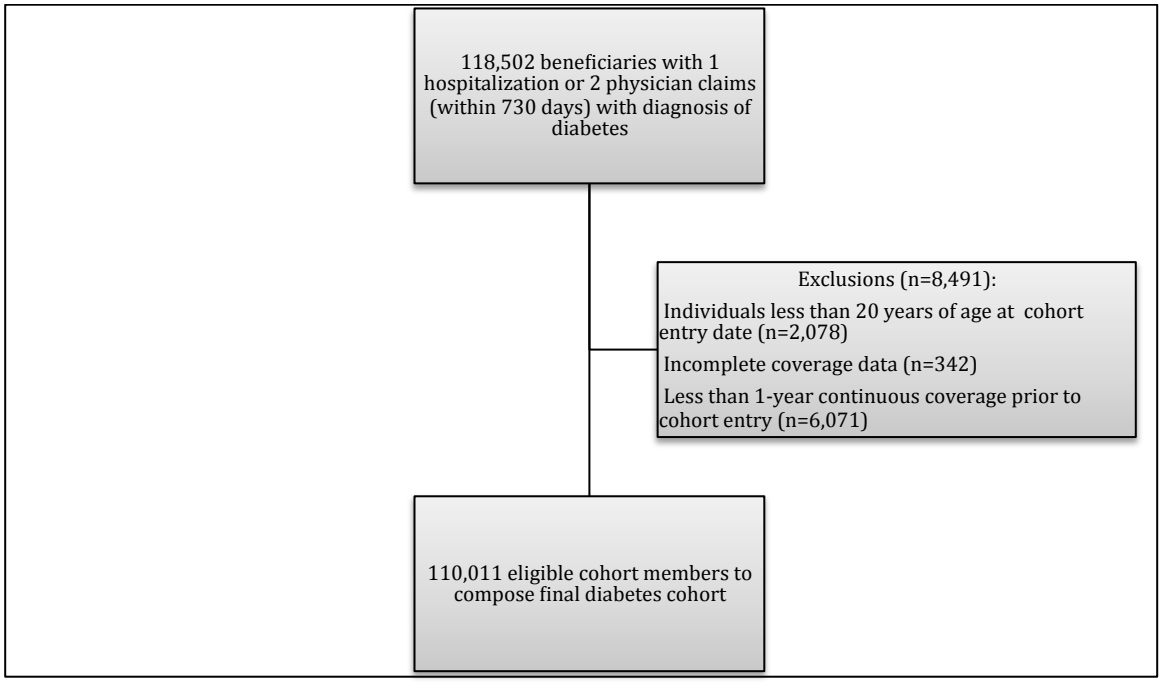
Parameter	Estimate	Empirical Standard Error	95% Confidence Limits	p-value
Intercept	-7.84	0.24	(-8.30, -7.38)	<0.01
Year	0.03	0.01	(0.01, 0.05)	<0.01
Test strips dispensed (millions)	0.18	0.22	(-0.25, 0.60)	0.41
All-cause hospitalizations (millions)	-5.80	7.11	(-19.74, 8.14)	0.41

Objective 2: To determine if the risk of hospitalization for hypoglycemia is lower among patients who use blood glucose test strips compared to those who do not.

Cohort Definition

Between January 1, 1996 and December 31, 2014, a total of 118,502 beneficiaries of the Saskatchewan Drug plan met the CCDSS case definition for diabetes (Figure 8). As the CCDSS case definition has not been validated in individuals younger than 20 years of age, those who were less than 20 years of age at cohort entry were excluded. An additional 342 beneficiaries were excluded from the overall cohort due to incomplete coverage records, while 6,071 beneficiaries were excluded due to having less than 1 year of continuous coverage prior to cohort entry. The final cohort consisted of 110,011 beneficiaries. The mean age at cohort entry was 62.1 years (SD 15.1) and 54.6% of cohort members were male.

Figure 8: Construction of overall diabetes cohort



During a mean follow-up of 7.8 years, 2.6% of the diabetes cohort (2,827/110,011) was hospitalized for hypoglycemia. Of these, 197 individuals were excluded because their hypoglycemic event took place within the first 180 days of cohort entry and as a consequence, their exposure period could not be fully characterized. Thus, 2,630 cases were identified. Compared to patients who did not experience hypoglycemia, cases were slightly older (mean age at index 72.8 years vs. 71.7 years), received more hypoglycemic medications (90.1% vs. 73.9%), had a higher comorbidity burden, and visited their physicians more often.

Cohort members hospitalized for hypoglycemia (i.e., cases) were randomly matched to 4 controls by sex, age category, and cohort entry date (+/- 1 year). Ultimately, 10,520 matched controls were selected to achieve a final study cohort of 13,150 individuals. Descriptive characteristics of cases and controls are given in Table 11.

Important differences were observed between cases and controls. Over 80% of cases were dispensed insulin or high-risk oral hypoglycemic agents in the 180 days prior to index date, as compared to less than 50% of controls. Similarly, 90% of cases received a dispensation for any diabetes medication in the exposure period compared to less than 75% of controls. Cases also had more frequent outpatient physician claims, and higher comorbidity. Outpatient claims for hypoglycemia were recorded in 12.7% of cases compared to less than 1% of controls. Furthermore, approximately 25% of outpatient claims for hypoglycemia occurred within one day of a hospitalization for hypoglycemia. As such, it was postulated that having a previous outpatient claim for hypoglycemia may be in the causal pathway for a subsequent hospitalization for hypoglycemia and the variable was subsequently removed from the analysis.

Table 11: Descriptive characteristics and exposures of cases and controls

Covariate	Controls (n=10,520)	Cases (n=2,630)	Total (n=13,150)
		Mean (SD)	
Age at cohort entry			
	63.2 (13.1)	64.4 (14.3)	63.6 (13.4)
Age at index			
	71.7 (12.9)	72.8 (14.1)	71.9 (13.2)
Follow up time (years)			
	7.8 (4.9)	7.8 (4.9)	7.8 (4.9)
		n (%)	
Sex			
Male	5,548 (52.7)	1,387 (52.7)	6,935 (52.7)
Diabetes Medications received in the exposure period (180 days prior to the index date)			
Insulin	2,716 (25.8)	1,359 (51.7)	4,075 (31.0)
High risk oral hypoglycemic	2,541 (24.2)	826 (31.4)	3,367 (25.6)
Low risk oral hypoglycemic	2,516 (23.9)	185 (7.0)	2,701 (20.5)
No drugs	2,747 (26.1)	260 (9.9)	3,007 (22.9)
Location of residence at index date			
Urban	6,616 (62.9)	1,576 (59.9)	8,192 (62.3)
Rural	3,809 (36.2)	1,027 (31.1)	4,836 (36.8)
Missing	95 (0.9)	27 (1.03)	122 (0.93)
At least one outpatient claim for hypoglycemia in the exposure period (180 days prior to the index date)			
Yes	77 (0.7)	335 (12.7)	412 (3.1)
Number of outpatient physician claims in the exposure period (180 days prior to the index date)			
0-3	3,593 (34.2)	479 (18.2)	4,072 (30.9)
4-6	2,810 (26.7)	562 (21.4)	3,372 (25.6)
7-10	2,171 (20.6)	630 (22.5)	2,801 (21.3)
≥11	1,946 (18.5)	959 (26.4)	2,905 (22.1)
At least one specialist claim for diabetes in the exposure period (180 days prior to the index date)			
Yes	516 (4.9)	191 (7.3)	707 (5.4)
Charlson Comorbidity Index in the 1-year period prior to the index date			
Score of 0	8,156 (77.5)	1,120 (46.0))	9,366 (71.2)
1 to 4	2,086 (19.8)	1,076 (40.9)	3,162 (24.0)
5 or more	278 (2.6)	344 (13.1)	622 (4.7)

In the 180 days preceding the index date, 63% of cases received at least one test strip dispensation compared to 51.3% of controls (Table 12).

Table 12: Test strip dispensations in the 180 days prior to index (main analysis)

	Controls n (%)	Cases n (%)	Total n (%)
Test strip dispensation	5,393 (51.3)	1,657 (63.0)	7,050 (53.6)

Substantial clinical differences between cases and controls were found in the overall cohort of diabetes patients. Due to the high degree of heterogeneity, we elected not to proceed with modelling in the overall diabetes cohort. Rather, the case-control analysis was repeated in two nested subgroups expected to consist of more homogeneous populations: patients using insulin (representing those at highest risk of developing hypoglycemia) and also a subgroup of patients taking low-risk oral hypoglycemic medications only (representing those at lowest risk of developing hypoglycemia).

Insulin Subgroup

Patients with at least one prescription claim for insulin within a year of their cohort entry date made up the insulin subgroup (n=10,617). During a mean follow-up of 7.3 years, 8.3% of the insulin user subgroup (884/10,617) was hospitalized for hypoglycemia. Of these, 79 individuals were excluded because their hypoglycemic event took place within the first 180 days of cohort entry. Thus, 805 cases were matched to 4 controls (with the exception of 1 case for which only 2 suitable controls could be identified) for a total sample of 4,023 subjects. The mean age of the overall insulin subgroup was 57.1 years (SD 18.3) at cohort entry and 52.1% of subgroup members were male.

In the 180 days preceding the index date, 88% of subgroup members received at least one prescription for insulin (Table 13). Most were receiving insulin therapy alone, however approximately 18% were receiving both insulin and an oral hypoglycemic agent. Intensity of insulin usage (as estimated in units/day) [77] was similar between cases and controls. Cases had more outpatient physician claims than controls, and a higher Charlson Comorbidity Index. Outpatient physician claims for hypoglycemia were not included in the final model, due to the potential of being in the causal pathway for hypoglycemia hospitalization.

Table 13: Descriptive characteristics and exposures of insulin subgroup

Covariate	Controls (n=3,218)	Cases (n=805)	Total (n=4,023)
		Mean (SD)	
Age at cohort entry			
	58.5 (15.6)	59.6 (16.4)	58.7 (15.7)
Age at index			
	66.4 (15.5)	67.6 (16.4)	66.7 (15.7)
Follow up time (years)			
	7.3 (5.1)	7.3 (5.1)	7.3(5.1)
		n (%)	
Sex			
Male	1,690 (52.5)	423 (52.5)	2,113 (52.5)
Daily insulin consumption [77] in the exposure period (180 days prior to index)			
First quartile (<29.8 units/day)	801 (24.9)	185 (23.0)	986 (24.5)
Second quartile (29.8-50.3 units/day)	781 (24.3)	202 (25.1)	983 (24.4)
Third quartile (50.3-77.8 units/day)	805 (25.0)	212 (26.3)	1,017 (25.2)
Fourth quartile (>77.8 units/day)	831 (25.8)	206 (25.6)	1,037 (25.7)
Diabetes medications received in the exposure period (180 days prior to index date)			
Insulin alone	2,247 (69.8)	613 (76.2)	2,860 (71.1)
Insulin + high risk oral hypoglycemic	68 (2.1)	24 (2.9)	92 (2.3)
Insulin + low risk oral hypoglycemic	507 (15.8)	115 (14.3)	622 (15.4)
Oral hypoglycemic only	170 (5.3)	21 (2.6)	191 (4.7)
No drugs	226 (7.0)	32 (4.0)	258 (6.4)
Location of residence at index date			
Urban	2,061 (63.9)	491 (60.6)	2,552 (63.4)
Rural	1,157 (35.0)	314 (38.4)	1,471 (35.6)
Missing	6 (0.1)	<6 *	
At least one outpatient physician claim for hypoglycemia in exposure period (180 days prior to the index date)[+]			
Yes	62 (1.9)	129 (16.0)	191 (4.8)
Number of outpatient physician claims in the exposure period (180 days prior to the index date)			
0-3	975 (30.3)	165 (20.5)	1,140 (28.3)
4-6	848 (26.3)	158 (19.6)	1,006 (25.0)
7-10	723 (22.5)	204 (24.3)	927 (23.0)
≥11	672 (20.9)	277 (34.5)	950 (23.6)

At least one specialist claim for diabetes in the exposure period (180 days prior to index date)			
Yes	317 (9.8)	84 (10.4)	401 (10.0)
Charlson Comorbidity Index in the 1-year period prior to index date			
Score of 0	2,367 (73.6)	377 (46.8)	2,744 (68.2)
1 to 4	731 (22.7)	334 (41.5)	1,065 (26.5)
5 or more	120 (3.7)	94 (11.7)	214 (5.3)

*Indicates that the frequency of the variable was less than 6 and cannot be reported

[+] Variable not included in final model as it was considered to be an intermediate factor between the independent variable and the outcome

Model Results

In the 180 days preceding the index date, 77% of cases and 73% of controls received at least one dispensation for test strips (Table 14). In univariate analysis, test strip dispensation was associated with a significant increase in the odds of hospital admission for hypoglycemia (unadjusted OR 1.25, 95% CI [1.04,1.50], p=0.02)(Table 15). However, after covariate adjustment, test strip dispensations became non-significant (adjusted OR 1.08, 95% CI [0.88,1.31], p=0.48).

The model was tested for pre-specified interactions between test strip dispensation and clinical characteristics. No significant interaction was found between test strip dispensation and diabetes therapy (p=0.96), between test strip dispensation and Charlson Comorbidity Index (p=0.31), or test strip dispensation and intensity of insulin use (p=0.93).

Table 14: Test strip dispensations within 180 days of index (Insulin subgroup)

	Controls n (%)	**Cases n (%)**	**Total n (%)**
Test strip dispensation	2350 (73.0)	620 (77.0)	2970 (73.8)

Table 15: Predictors of hospitalizations for hypoglycemia (insulin subgroup)

Covariate	Unadjusted OR	95% CI	p-value	Adjusted OR*	95% CI	p-value
Test strip dispensation in the exposure period (180 days prior to index date)						
No	1.0					
Yes	1.25	1.04-1.50	0.02	1.08	0.88-1.31	0.48
Diabetes Medications received in the exposure period (180 days prior to index date)						
No drugs	1.0					
Oral hypoglycemic alone	0.89	0.50-1.61	0.71	0.81	0.44-1.49	0.50
Insulin + Low risk oral hypoglycemia	1.65	1.07-2.53	0.02	1.78	1.09-2.92	0.02
Insulin + High risk oral hypoglycemic	2.58	1.40-4.73	<0.01	2.42	1.26-4.65	0.01
Insulin alone	1.99	1.35-2.94	<0.01	2.25	1.44-3.52	<0.01
Estimated daily insulin consumption (units/day) in the exposure period (180 days prior to index date)						
<29.8	1.0					
29.8-50.3	1.13	0.90-1.41	0.30	0.87	0.67-1.14	0.31
50.3-77.8	1.15	0.92-1.44	0.23	0.87	0.67-1.14	0.32
>77.8	1.08	0.86-1.36	0.50	0.81	0.62-1.06	0.13
Location of residence at index date						
Rural	1.0					
Urban	0.89	0.75-1.03	0.11	0.85	0.72-1.01	0.07
Number of outpatient physician claims in the exposure period (180 days prior to index date)						
0-3	1.0					
4-6	1.15	0.91-1.47	0.24	0.98	0.76-1.25	0.85
7-10	1.76	1.39-2.22	<0.01	1.36	1.06-1.75	0.01
≥11	2.61	2.08-3.27	<0.01	1.76	1.37-2.26	<0.01
Specialist claim for diabetes in the exposure period (180 days prior to index date)						
No	1.0					
Yes	1.07	0.83-1.39	0.62	0.87	0.66-1.15	0.33
Charlson Comorbidity Index in the 1-year period prior to the index date						
Score of 0	1.0					
1 to 4	2.99	2.51-3.57	<0.01	2.69	2.24-3.23	<0.01
5 or more	5.43	4.00-7.38	<0.01	4.46	3.24-6.14	<0.01

*Adjusted for all covariates in the table AIC =2334.86 BIC=2429.37

Sensitivity analyses that were pre-specified for the main analysis were subsequently conducted within the insulin subgroup. In the first sensitivity analysis, cases that had been previously excluded from the insulin subgroup analysis due to their hypoglycemic event occurring in the first 180 days after cohort entry were entered into the analysis. This resulted in a study cohort of 4,418 individuals (884 cases, 3,534 controls). In this analysis, the distribution of covariates and subsequent model results were consistent with that of the primary analysis (unadjusted OR for strip use 1.24, 95% [CI 1.04,1.48], p= 0.02; adjusted OR 1.08, 95%CI [0.89,1.31], p=0.42). In a second sensitivity analysis, exposures were characterized in the 90 days prior to the index date. Again, test strip dispensation was not a significant predictor of hypoglycemia hospitalizations after covariate adjustment (unadjusted OR 1.28, 95% CI [1.09,1.52], p<0.01; adjusted OR 1.14, 95% CI [0.95,1.35], p=0.16). A third sensitivity analysis with diabetes therapy classified according to the therapeutic class of hypoglycemic agent could not be carried out due to the low numbers of patients on oral hypoglycemic agents in this subgroup.

In a final sensitivity analysis, test strip dispensation was categorized based on the number of strips dispensed in the 180 days prior to the index date. Test strip dispensations were categorized based on approximate quartiles of use as follows: 1) no test strips dispensed; 2) 1-100 test strips dispensed; 3) 101-200 test strips dispensed; or 4) more than 200 test strips dispensed. In the univariate logistic model, the risk of hospitalization for hypoglycemia did not differ between those receiving 1 to 100 or 101 to 200 strips and those not receiving test strips in the 180 days prior to index (Table 16). However, receiving more than 200 test strips was associated with an increased risk for hospitalization for hypoglycemia when compared to those not receiving test strips. After adjusting for covariates in the main effect model, this effect became non-significant. The model also included two-way interaction effects between test strip use and (a) mode of diabetic therapy, (b) Charlson Comorbidity Index, and (c) intensity of insulin use (by DACON quartile), of which none were significant (p=0.87, p=0.71, and p=0.65, respectively).

Table 16: Predictors of hospitalizations for hypoglycemia (insulin subgroup) with test strip use in the 180 days prior to index categorized according to quartiles of use

Number of test strips dispensed	n (%)	Unadjusted OR	95% CI	p-value	Adjusted OR*	95% CI	p-value
0	1,053 (26.2)	1.0			1.0		
1-100	690 (17.2)	0.99	0.77-1.29	0.99	0.89	0.68-1.17	0.42
100-200	550 (13.7)	1.10	0.84-1.44	0.48	0.90	0.68-1.20	0.47
>200	1,730 (43.0)	1.43	1.17-1.75	<0.01	1.23	0.99-1.53	0.06

* Adjusted for covariates in Table 6

Low risk oral hypoglycemic agent subgroup

The next subgroup analysis was conducted in patients receiving low-risk hypoglycemic agents. Individuals were included in the low-risk oral subgroup if they had at least one prescription claim for an oral hypoglycemic agent with a low risk of causing hypoglycemia within 1 year of cohort entry. Patients were followed until the earliest of: receiving insulin or a high-risk oral hypoglycemic agent, loss of coverage, death, or end of follow-up period. During a mean follow-up of 3.8 years, 0.2% of the low-risk oral hypoglycemic user subgroup (113/47,501) was hospitalized for hypoglycemia. The mean age of the low-risk hypoglycemic user subgroup was 64.5 years (SD 11.7) at cohort entry and 50.7% of subgroup members were male.

Of the 113 subgroup members that were hospitalized for hypoglycemia (i.e. cases), 38 were excluded as their event occurred within the first 180 days of cohort entry. The remaining 75 cases were successfully matched to 4 controls. Approximately 80% of subgroup members had a dispensation for a low-risk oral hypoglycemic agent during the 180 days prior to index, while approximately 20% did not have a dispensation for any diabetic medications during the exposure period (Table 17). Similar to the previous analyses, cases were more likely to have a higher Charlson Comorbidity Index than controls and visited their physicians more often.

Table 17: Descriptive characteristics and exposures of low risk oral hypoglycemic user subgroup

Covariate	Controls (n=300)	Cases (n=75)	Total (n=375)
		Mean (SD)	
Age at cohort entry			
	66.1 (12.3)	67.2 (13.0)	66.3 (12.4)
Age at index			
	71.7 (12.7)	72.9 (13.8)	72.0 (12.9)
Follow up time (years)			
	5.6 (4.0)	5.7 (4.0)	5.6 (4.0)
		n (%)	
Sex			
Male	136 (45.3)	34 (45.3)	170 (45.3)
Diabetes medications received in the exposure period (180 days prior to the index date)			
Low risk oral hypoglycemic	241 (80.3)	57 (76.0)	298 (79.5)
No drugs	59 (19.7)	18 (24.0)	77 (20.5)
Location of residence			
Urban	174 (58.0)	47 (62.7)	221 (58.9)
Rural	126 (42.0)	28 (37.3)	154 (41.1)
At least one outpatient physician claim for hypoglycemia in the exposure period (180 days prior to the index date)[+]			
Yes	0 (0)	<6*	*
Number of outpatient physician claims in the exposure period (180 days prior to the index date)[°]			
0-3	109 (36.3)	11 (14.6)	120 (32.0)
4-6	88 (29.3)	17 (22.7)	105 (28.0)
7-10	52 (17.3)	17 (22.7)	69 (18.4)
≥11	51 (17.0)	30 (40.0)	81 (21.6)
At least one specialist claim for diabetes in the exposure period (180 days prior to the index date)			
Yes	8 (2.7)	<6*	*
Charlson Comorbidity Index in the 1-year period prior to the index date			
Score of 0	240 (80.0)	32 (42.7)	272 (72.5)
1 to 2	42 (14.0)	13 (17.3)	55 (14.7)
3 or more	18 (6.0)	30 (40.0)	48 (12.8)

[+] Variable not included in model due to zero cell value for controls

[*] Censored due to small cell size

[°] Variable not included in model due to zero cell sizes

Table 18: Test strip dispensations within 180 days of index (low risk oral hypoglycemic user subgroup)

	Controls N (%)	Cases N (%)	Total N (%)
Test strip dispensation	104 (34.7)	29 (38.7)	133 (35.5)

Model Results

In the 180 days preceding the index date, 38.7% of cases and 34.7% of controls received at least one dispensation for test strips (Table 18). Test strip dispensation was not a significant predictor of hospital admission for hypoglycemia (adjusted OR 1.04, [95% CI 0.55,1.94], p= 0.91) (Table 19). Interactions between test strip use and disease-related factors were non-significant (p=0.16 for test strip use and Charlson Comorbidity Index), however a statistically significant interaction between test strip use and diabetic therapy was noted (p=0.03), indicating that risk of hospitalization for hypoglycemia was reduced in low risk OHA users with a test strip dispensation when compared to non-drug users with a test strip dispensation. This interaction may represent a spurious statistically significant result due to small sample size given the wide confidence interval (OR 0.17, [95% CI 0.04, 0.62]. The clinical significance of this interaction was also deemed questionable as patients not on diabetic therapy should have a negligible risk of experiencing hypoglycemia, regardless of blood glucose test strip use.

Table 19: Predictors of hospitalizations for hypoglycemia (low risk oral hypoglycemic user subgroup)

Covariate	Unadjusted OR	95% CI	p-value	Adjusted OR*	95% CI	p-value
Test strip dispensation in the exposure period (180 days prior to index date)						
No	1.0					
Yes	1.19	0.70-2.03	0.51	1.04	0.55-1.94	0.91
Diabetes Medications received in the exposure period (180 days prior to index date)						
No drugs	1.0					
Low risk oral hypoglycemic	0.73	0.38 -1.43	0.36	0.52	0.24 -1.14	0.10
Location of residence						
Rural	1.0					
Urban	1.22	0.72 -2.04	0.46	1.03	0.57-1.89	0.92
Number of outpatient physician visits in the exposure period (180 days prior to the index date)°						
0-3	1.0					
4-6	1.82	0.80-4.10	0.15	1.90	0.78-4.63	0.16
7-10	3.29	1.46-7.42	<0.01	2.28	0.91-5.70	0.09
≥11	5.70	2.64-12.34	<0.01	3.12	1.25 -7.77	0.02
Charlson Comorbidity Index in the 1-year period prior to the index date						
Score of 0	1.0					
1 to 2	2.47	1.16-5.27	0.02	1.99	0.90-4.38	0.09
3 or more	13.00	6.03-28.02	<0.01	10.01	4.39-22.83	<0.01

*AIC=195.40 BIC=226.82

Chapter 5: Discussion

Saskatchewan health-administrative databases were used to construct a population-based, retrospective study examining trends in blood glucose test strip utilization and their impact on hospitalization for hypoglycemia. All measures of blood glucose test strip use increased over the course of the study (i.e. from 1996 to 2014). In contrast, no obvious trends in hospitalizations for hypoglycemia were observed until 2007, when a clear decreasing rate persisted until 2014. As a result, no association was found province-wide use of blood glucose test strip use and hospitalization rates for hypoglycemia. Similarly, blood glucose test strip use was not associated with a reduced risk of hospitalizations for hypoglycemia using a case-control study design. This finding was consistent among patients using insulin and those using low-risk oral hypoglycemic agents.

All measures of blood glucose test strip utilization increased over the study period in a manner consistent with previously published studies [10]. The number of dispensed test strips increased approximately 300% from 1996 to 2010, while the number of test strip users increased by over 150% during the same time period. In Manitoba, blood glucose test strip use increased by 170% from 2000 to 2013 [78]. In Ontario, blood glucose test strip use increased 250% from 1997 to 2008 ([79]. In the current study however, test strip utilization stabilized from 2010 to 2014, presumably due to a heightened awareness of test strip over-use reported in numerous publications questioning the clinical utility and cost effectiveness of SMBG ([7, 8, 80]. A similar trend was also identified in British Columbia. Despite an overall 28% increase in test strip utilization from 2004 to 2012, test strip use decreased by 4% per year from 2010 to 2012 [81]. Beginning in 2013, provinces across Canada began implementing restriction limits for blood glucose test strip reimbursement. In 2013, Ontario imposed limits that were associated with a 20% reduction in costs [82]. British Columbia and Saskatchewan imposed limits starting in 2015 [83] [22]. To date, no published studies have reported cost savings in either of those provinces.

There was no clear trend in hospitalizations for hypoglycemia between 1996 and 2005; however, a decreasing trend was observed between 2008 and 2014 (annual decrease -17.9/year; $p<0.01$). One of the most striking results was a substantial spike in hospitalizations for hypoglycemia between 2005 and 2006. Reasons for this abrupt change remain unclear. Changes in coding practices were not likely the cause because Saskatchewan changed its hospital discharge coding system in 2001-2002 (i.e., from ICD-9 to ICD-10-CA) [45]. Also, the elevated trend between 2005 and 2006 persisted when only the most responsible diagnosis code or codes in the first two diagnostic positions were used

to identify hypoglycemia. However, trends in the individual diagnosis codes for hypoglycemia were not tracked over the study period, so it was not possible to determine which (if any) diagnostic codes were specifically contributing to the increase in recorded events. Finally, no major changes in hypoglycemic drug or insulin formulary listings occurred from 2006 to 2008 [22].

Changes in the incidence of hypoglycemia hospitalizations may have been a result of diabetes management strategies rather than coding practices. The DC guidelines published in 2003 recommended aggressive glycemic targets for most patients [84, 85], which may have resulted in the increased number of hypoglycemia hospitalizations between 2006 and 2007. In 2008, the ACCORD trial demonstrated that tighter glycemic control in patients with a long-standing history of diabetes or cardiovascular disease resulted in increased mortality[15]. The DC guidelines released the same year recommended less stringent glycemic targets[85] which may have translated into less aggressive blood glucose management (thereby reducing the risk of hypoglycemia in potentially high risk patients). As well, new insulin products (such as long and rapid-acting insulin analogues) that may result in less hypoglycemia [86] became widely used due to formulary inclusion status in 2009 and 2010 [22], which also may have explained the decline in hospitalizations for hypoglycemia. Of note, the number of physician visits for hypoglycemia (which greatly outnumbered hospitalizations for hypoglycemia) did not exhibit the same trend over study period. In addition, this trend was not observed in Ontario where ED visits and hospitalizations for hypoglycemia have exhibited a general declining trend in several studies [42, 43].

Although available emergency department data was limited to visits occurring in Saskatchewan's largest urban hospitals within a three-year time span (2012 to 2014), it appears that only a fraction of all patients presenting to hospital with hypoglycemia (15%) are admitted for at least one night. Thus, it is highly possible that changes in the clinical management of these patients in the emergency department could have impacted the observed rate of hospitalization. However, due to the short time frame of available data, it was not possible to determine if this preliminary trend was consistent over the study period. In Ontario, emergency department visits for hypoglycemia exhibited an overall declining trend over a similar time frame [42, 43]. Therefore, the impact of emergency department visits for hypoglycemia on hospitalization rates remains unanswered.

Population-wide test strip utilization was not associated with hospitalizations for hypoglycemia in this study. A similar finding from Ontario has recently been published. Gomes and colleagues reported no significant changes in emergency department hypoglycemia visits following test strip quantity limit implementation [43]. Follow-up was limited to 18 months only so longer-term studies

should be conducted to confirm these observations. In the current study, the association between test strip utilization and hypoglycemia endpoints was directly tested over an 18-year time frame and in a broader segment of the diabetic patient population. This study provides additional, longer-term evidence to suggest that blood glucose test strip use does not affect hypoglycemia healthcare utilization rates.

The association between test-strip use and hypoglycemia hospitalizations was also examined at the patient level using a nested case-control study design. The initial cohort was comprised of all patients with diabetes; however, substantial differences in clinical characteristics between cases and controls were observed despite matching on age, sex, and cohort entry date. Therefore, the study was repeated within two subgroups: insulin users and patients receiving low-risk oral hypoglycemic medications. Both groups were expected to demonstrate a more uniform risk of hypoglycemia (insulin users = high risk versus oral hypoglycemic patients = low risk). Among insulin users, test strip use was associated with an increased risk of hospitalization in unadjusted analysis (OR 1.25, 95% CI [1.04,1.50], p=0.02) but this association became non-significant after covariate adjustment (adjusted OR 1.08, 95% CI [0.88,1.31], p=0.48). This finding was consistent across several pre-specified sensitivity analyses and the relationship between test strip use and hospitalizations for hypoglycemia did not change according to the intensity of insulin use (p=0.93). Similar results were observed when patients were categorized by the number of test strips dispensed during the exposure period. In the unadjusted analysis, no differences were observed between patients in the three lowest exposure categories of test strip use; however the highest category of test strip use (i.e. more than 200 strips dispensed in the 180 days prior to index) had an increased risk of hypoglycemia hospitalization. Again, this risk became non-significant after covariate adjustment. In low-risk oral hypoglycemic users, test strip use was not associated with hospital admission for hypoglycemia in both unadjusted and adjusted analyses (p=0.51 and p=0.91, respectively).

An increased risk of hypoglycemic events among frequent test strip users has been reported in previous studies reporting unadjusted results [7, 8, 26-28]. Because covariate adjustment attenuated the risk estimate, it is likely the crude association resulted because patients who are already at a higher risk of developing hypoglycemia perform testing more frequently than those at lower risk [7, 8, 41]. None of the risk estimates for blood glucose testing indicated a protective effect against hypoglycemia hospitalizations. However, it should be noted that very high levels of test-strip use were observed in individuals at greatest risk of developing hypoglycemia; approximately three-quarters of the insulin user cohort had a dispensation for test strips in the exposure period. As a result, it is possible that a

lower threshold of test strip use does increase the risk for hypoglycemia but very few patients at increased risk of developing hypoglycemia in current practice reach it. Our findings suggest that patients exhibiting low levels of test strip use in the current context of diabetes management do not experience a high risk of hypoglycemia.

Large differences between cases and controls observed in this study have also been reported previously [31, 40]. Cases in the present study were more likely to use insulin or high risk oral hypoglycemic agents, had a higher comorbidity burden, and had more outpatient physician visits. In fact, previous outpatient claims for hypoglycemia were excluded from the final model because more than a quarter occurred within one day of the index event (i.e., hospitalization for hypoglycemia). As a result, this variable appeared to represent the actual case event rather than serve as an independent risk factor.

Strengths and Limitations

The strengths of this study include its population-based design that captured virtually all residents of Saskatchewan regardless of income or employment status. It has previously been demonstrated that hospital discharge records are a sensitive and specific measure of hypoglycemia hospitalizations [45, 49]. This endpoint is clinically important from both a resource and patient safety perspective. However, several limitations should be noted. Individuals with federal drug coverage (most notably registered First Nations), were not included in this study as their test strip utilization could not be captured prior to 2006. Although the high prevalence of diabetes in First Nations has been well-established [87], to our knowledge the comparable risk of hypoglycemia has not been defined in this patient population. This may limit the generalizability of this study, as its findings may not be comparable in this patient population. Test strip utilization endpoints were based solely on dispensing information; patients may not have actually used the test strips dispensed or may have purchased test strips without a prescription. Numerous factors that have been shown to increase the risk for hypoglycemia could not be accounted for, including type of diabetes, precipitating events (e.g. dietary indiscretions, exercise, minor illness), degree of glycemic control, previous episodes of hypoglycemia, renal function, and cognitive status [30, 32, 34, 36]. The impact of these factors, plus other possible unmeasured confounders may change the relationship between test strip use and hospitalizations for hypoglycemia beyond the findings of this study. In addition, severe hypoglycemic events that did not result in hospitalization, such as events occurring at home, or those treated solely by emergency medical services or the emergency department could not be captured throughout the study period. Previous studies have suggested only 10% of severe episodes of hypoglycemia result in hospital

treatment [32, 34], therefore this study may only represent a small proportion of hypoglycemic events. Finally, hypoglycemia hospitalization rates changed dramatically during the observation period and could not be explained with existing sources.

Chapter 6: Conclusion

Population-wide use of blood glucose test strips is not associated with the rate of hospitalizations for hypoglycemia. The province-wide increase in test strip utilization over the study period did not translate into a reduction of hospitalizations for hypoglycemia over the same time frame. At the individual level, blood glucose test strip use did not reduce the risk of hospitalization for hypoglycemia in diabetic patients both at high and low risk of developing drug-induced hypoglycemia. This study adds to the body of evidence that suggests test strip use has a marginal impact on patient outcomes in most diabetic patients, and that policies that limit the reimbursement of blood glucose test strip are unlikely to be detrimental in terms of effects on patient safety.

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