EXPLORING THE DISTRIBUTION OF PRESCRIPTION FOR SULFONYLUREAS IN PATIENTS WITH TYPE 2 DIABETES ACCORDING TO CARDIOVASCULAR RISK FACTORS WITHIN A CANADIAN PRIMARY CARE SETTING

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ABSTRACT

Background
A growing body of evidence generated from observational studies and meta-analyses has begun to illustrate the potential adverse cardiovascular (CV) risk profile associated with sulfonylurea (SU) use. Specifically, the use of an SU has been demonstrated to be associated with increased mortality and a higher risk of stroke with more CV events associated with SU use having been reported in subgroups of patients with a history of CV disease, elderly and a higher body mass index.

Objective
The objective of the current study was to explore the distribution of established atherosclerotic CV disease and CV risk factors amongst patients with diabetes on an SU using a Canadian primary care dataset for the 2013 calendar year.

Methods
The Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which is a multi-disease surveillance system based on primary care electronic medical record data, was utilized for this research study. Patients with a diagnosis of diabetes and exposure to an SU were identified. Distribution/prevalence of CV risk profile amongst this sub-cohort was explored.

Results
In analyzing the CPCSSN database for the 2013 calendar year, 6150 patients were identified as having diabetes, at least one visit with their family doctor, and on an SU. For this sub-cohort, demographic data was as follows: age [mean (SD)] 65.4(12.8) years-old; 56.4% male and mean BMI 31.3(10.0). Established atherosclerotic CV disease was observed in 16.8% of the patients with the following distribution: 13.2% had ischemic heart disease/myocardial infarction or coronary artery disease; 2.4% had stroke; and 2.3% had peripheral vascular disease. Regarding the aggregation of CV risk factors, a large proportion (65%) of patients without established atherosclerotic CV disease presented with 2 or more CV risk factors including: hypertension (62%), dyslipidemia (33%), active smoking (13%), and obesity (43%). Almost half of the cohort (45%) were males older than 55 years of age or females older than 60 years of age with at least one of the following risk factors: dyslipidemia, hypertension or current smoking, but without established cardiovascular disease. A large proportion of patients (19.5%) had a diagnosis of cardiac-specific issues including ischemic heart disease/myocardial infarction/coronary artery disease, heart failure (not due to ischemic heart disease/myocardial infarction/coronary artery disease), or arrhythmia. Almost 82% of patients had either established atherosclerotic CV disease or 2 or more CV risk factors without established atherosclerotic CV disease.

Conclusion
This study illustrated that in this dataset of Canadian patients with diabetes in a primary care setting, a substantial proportion of patients treated with an SU in 2013 had established CV disease and/or an aggregation of multiple CV risk factors. In light of recent data reporting on an association between SU utilization and CV events and increased mortality, pharmacovigilance programs should actively monitor SU utilization in patients with diabetes and a high risk CV profile in real world clinical settings.

Key Words: *Diabetes, pharmacotherapy, sulfonylurea, cardiovascular risk, Canadian population*

Diabetes is a chronic disease with high incidence and prevalence, significant burden of illness due to complications, and presents a significant societal cost[1]. For the treatment of hyperglycemia, currently there are more than 10 classes of medications for patients with type 2 diabetes with each class having its own advantages and disadvantages from an efficacy and safety profile perspective.[2] In particular, there is an increasing need to define and understand the role of glycemic lowering medications on macrovascular disease and the implications of these medications in patients presenting with cardiovascular risk factors and established cardiovascular disease.[3;4] There is a growing body of evidence hypothesizing that off-target effects could potentially implicate and increase in cardiovascular risk.[5;6] Evidence generated from observational studies and retrospective meta-analyses has begun to illustrate the potential cardiovascular risk profile associated with sulfonylurea use.[7-11] However, this issue remains controversial.[3;4] The American Diabetes Association (ADA) clinical practice guidelines[12] lists "Disadvantages" of sulfonylurea utilization as follows: hypoglycemia, weight gain, and possibly blunts myocardial ischemic preconditioning. The Canadian Diabetes Association (CDA) 2013 clinical practice guidelines recommend that in the elderly patient with type 2 diabetes, sulfonylureas should be used with caution as the risk of severe or fatal hypoglycemia increases exponentially with age[1].

Currently there remains a lack of clarity regarding the prevalence of Canadian patients within the primary care setting with type 2 diabetes who have either present cardiovascular (CV) risk factors or established CV disease and who are being treated with a sulfonylurea. Data does exist on sulfonylurea utilization within the Canadian population. For instance, from a large database in Ontario spanning from 1995 to 2001, three-quarters of patients with diabetes receiving medications through a government supported medication program were receiving a sulfonylurea either as the primary medication or as one of a combination of medications.[13] However, no data on the cardiovascular risk profile of this patient population was reported.

The objective of the current study was to explore the distribution of established atherosclerotic CV disease and CV risk factors amongst patients with diabetes and being treated with a sulfonylurea using a Canadian primary care dataset for the 2013 calendar year.

METHODS

The Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which is a multi-disease surveillance system based on primary care electronic medical record data, was utilized for this research study. The system contains non-personally identifiable (i.e. de-identified, blinded) Electronic Medical Record (EMR) data for a subset of more than a million Canadian patients derived from a database of about 830 primary care providers (sentinels) across Canada. The data comes from physicians participating in 10 practice based research networks across Canada, extracted from multiple EMR systems across 7 provinces (Alberta, British Columbia, Manitoba, Newfoundland, Nova Scotia, Ontario and Quebec). Data is extracted quarterly, mapped to a common database structure then validated and coded. Case detection algorithms are run against the dataset to identify individuals with diabetes. CPCSSN data has been validated and had been

utilized extensively in the past for epidemiological studies.[14-17] For the current study, the database was accessed to flag patients with diabetes within the 2013 calendar year using ICD-9 coding (Appendix 1). Exposure of patients with diabetes to a sulfonylurea was determined through the Anatomical Therapeutic Chemical (ATC) classification system for the same period of time (Appendix 2). Utilization of sulfonylurea in a patient with diabetes was determinant of type 2 diabetes. Furthermore, a patient's cardiovascular risk profile was defined according to the patient inclusion criteria within the SAVOR clinical study[18] and was generated for each flagged patient with type 2 diabetes and exposure to a sulfonylurea. The cardiovascular risk profile definition included the following: established cardiovascular disease [defined as previous cardiovascular events/history of established CV disease (myocardial infarction, stroke), documented atherosclerosis (coronary, cerebrovascular, peripheral vascular disease)]; multiple cardiovascular risk factors without established cardiovascular disease [defined as being at least 55 years old (male) or 60 years old (female) and having at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking]. Beyond this definition, for the purposes of this study, obesity and other aspects of heart disease including arrhythmia or heart failure (excluding patients with coronary artery disease/myocardial infarction/ischemic heart disease) were obtained. Distribution or prevalence of CV risk profile amongst the aforementioned cohort was explored. Descriptive analyses were conducted to correlate cardiovascular risk profile to sulfonylurea use within the cohort. Data analyses were carried out using statistical software SAS 9.4 (Cary, NC, USA). This study was approved by the institutional review board at Queen's University, Kingston, Ontario, Canada.

RESULTS

In analyzing the CPCSSN database, 38,865 patients were identified as having had a diagnosis of diabetes and at least one visit with their family physicians within the 2013 calendar year. Of this population, 6,150 patients had a diagnosis of diabetes, and were being actively treated with a sulfonylurea (Table 1). For this cohort, the mean age was 65.4 (12.8) years-old and 56.4% were male. More than one-half of the cohort were elderly (greater than 65 years old). Furthermore, mean BMI was 31.3 (10.0) and more than 40% of patients were obese (Table 1).

TABLE 1 - Demographic/clinical data of diabetic patients in 2013 who utilized Sulfonylureas

Number of patients	6150
Mean age (SD)	65.4 (12.8)
% male	56.4%
Mean BMI (SD)	31.3 (10.0)
Active smoking	12.6%
Obesity	43.5%
CV risk factors combination according to SAVOR study[+]	45.1%

+CV risk factors combination according to SAVOR study: Males ≥ 55 years of age and females ≥ 60 years of age with at least one of the following risk factors: dyslipidemia, hypertension (HTN) or current smoking, but without established CV disease.

Regarding the aggregation of CV risk factors, of the 6,150 patients having a diagnosis of type 2 diabetes and being actively treated with a sulfonylurea, a large proportion (65%) of patients had 2 or more CV risk factors without having established atherosclerotic CV disease (Table 3) including: hypertension (62%), dyslipidemia (33%), active smoking (13%), and obesity (43%) (Table 2). When considering age, almost half of the cohort (45%) were males older than 55 years of age or females older than 60 years of age with at least one of the following risk factors: dyslipidemia, hypertension or current smoking, but without established atherosclerotic CV disease (Table 1). Established atherosclerotic CV disease was found in 16.8% of patients with the following distribution: 13.2% had ischemic heart disease/myocardial infarction or coronary artery disease; 2.4% had stroke; and 2.3% had peripheral vascular disease (Table 2). When considering these two risk populations together, almost 82% of patients had either established atherosclerotic CV disease or 2 or more CV risk factors without established atherosclerotic CV disease (Table 3).

Beyond the above population definitions, one-quarter of patients had both hypertension and dyslipidemia (Table 3). A large proportion of patients (19.5%) had a diagnosis of cardiac specific issues including ischemic heart disease/myocardial infarction/coronary artery disease, or heart failure not due to ischemic heart disease/myocardial infarction/coronary artery disease, or arrhythmia (Table 3).

TABLE 2 – Distribution of cardiovascular risk factors

IHD/MI/CAD*	13.2%
Stroke	2.4%
PVD	2.3%
HTN	61.8%
Dyslipidemia	32.8%
Heart (other)**	9.5%

*IHD/MI/CAD: ischemic heart disease/myocardial infarction/coronary artery disease;
**Heart (other): heart failure (not due to ischemic heart disease/myocardial infarction/coronary artery disease), or arrhythmia.

TABLE 3 – Combined cardiovascular risk factors

Patients with established CVD (CAD/MI/IHD or Stroke or PVD)	16.4%
Patients with 2 or more risk factors and no established CVD	65.1%
Patients with hypertension and dyslipidemia	24.8%
Patients with cardiac specific issues: (CAD/MI/IHD) or (Heart (other))	19.6%
Patients with established CVD or with 2 or more risk factors and no established CVD	81.6%

DISCUSSION

Pathophysiological evidence demonstrates that sulfonylureas bind to the subunit of adenosine triphosphate (ATP)–sensitive potassium channels within pancreatic beta cells that keeps these channels closed. This causes an influx of calcium ions into the cell that result in an increased release of insulin via exocytosis of insulin-containing granules. Sulfonylurea drugs are not specific for pancreatic beta cells and can also bind to ATP-sensitive potassium channels in cardiomyocytes and vascular smooth-muscle cells. Channel binding by sulfonylureas in cardiac tissue prevents three otherwise beneficial mechanisms: the vascular smooth-muscle cell relaxation that improves coronary blood flow; the limitation of myocardial damage during ischemia; and the protection in cardiomyocytes of energy-generating mitochondria[11].

It is well-established that sulfonylurea use is associated with hypoglycemia risk and weight gain[1;12]. Furthermore, a growing body of evidence generated from observational studies and meta-analyses has begun to illustrate the potential cardiovascular risk profile associated with sulfonylurea use[8]; although this observation remains controversial.[19] Simpson and colleagues published an analysis of administrative data for 4138 patients with type 2 diabetes taking glyburide monotherapy and 1537 patients taking metformin monotherapy.[7] The authors found that an association between higher daily doses and increased risk of death existed with the use of first-generation sulfonylureas and with glyburide but not with metformin use. A study using National Veterans Health Administration databases linked to Medicare files found that among 253,690 patients initiating treatment (98,665 with sulfonylurea therapy and 155,025 with metformin therapy), crude rates of the composite outcome (hospitalization for acute myocardial infarction or stroke, or death) were 18.2 per 1000 person-years in sulfonylurea users and 10.4 per 1000 person-years in metformin users.[9] Results were consistent for both glyburide and glipizide in subgroups by CVD history, age, body mass index, and albuminuria in both a propensity score–matched cohort analysis and in sensitivity analyses.[9] A German study examined the association of sulfonylurea treatment with all-cause and cardiovascular mortality through a systematic review and meta-analysis of observation studies which included 19 cohort and observational registries with 551,912 patients.[20] In 13 of these studies which analyzed all-cause mortality, patients treated with sulfonylureas, either as monotherapy or in combination treatment, had a 92% increased all-cause mortality risk compared with those who received treatment with a non-sulfonylurea. In five of the reported studies, individuals treated with sulfonylureas alone or in combination had a nearly threefold increased risk of cardiovascular mortality.[20] Finally, in considering comparative risk between drug classes, a recent meta-analysis of RCTs demonstrated that in type 2 diabetes, the use of sulfonylureas versus DPP4 inhibitors and other classes of medication is associated with increased mortality and a higher risk of stroke.[10]

On the other hand, a meta-analysis and trial sequential analysis of 47 randomized clinical trials involving 37,650 patients found no association between sulfonylurea use and increased mortality or cardiovascular mortality.[21]

The current study demonstrated that a large proportion of Canadian patients diagnosed with type 2 diabetes within a primary setting and utilizing sulfonylureas have clusters of cardiovascular risk factors with and without established atherosclerotic CV disease. These patients are treated with sulfonylureas, irrespective of their high CV risk factors. The consequential impact of treating these high risk patients with a sulfonylurea remains to be seen. However, in the absence of this connection, more work is required to understand the implications of treating these patients with this class of medications. In light of the discussed recent controversy on the association between sulfonylureas utilization and CV events, pharmacovigilance programs should actively monitor sulfonylureas utilization in patients with diabetes and high risk CV profile in real world clinical settings.

As aforementioned, the 2013 Canadian Diabetes Association (CDA) clinical practice guidelines have recommended that in the elderly

patient with type 2 diabetes, sulfonylureas should be used with caution as the risk of severe or fatal hypoglycemia increases exponentially with age.[1] These guidelines explain that the definition of "elderly" varies, with some studies defining the elderly population as ≥60 years of age and administrative guidelines frequently classify people >65 years of age as elderly. The current study illustrated that more than 50% of the patients with diabetes within the CPCSSN database who were exposed to a sulfonylurea in 2013 were older than 65. Hypoglycaemia is a concern in diabetes management.[22;23] It is associated with a lower health-related quality of life, an increased burden of depression, a variety of undesirable compensatory behaviours by patients, and continues to be a major treatment limiting factor in achieving optimal glycaemic control.[24-28] Furthermore, emergency treatment for hypoglycaemia is associated with significant economic costs.[29] Given this spectrum of adverse consequences, studies and guidelines continue to emphasise the importance of individualising therapy with accounting each patient's clinical features, such as significance of hypoglycemia and weight gain avoidance.[30-32]

All sulfonylureas have been associated with weight gain and thus, may not be the optimal first choice for obese patients.[1;12] The current study illustrated that amongst patients with diabetes on a sulfonylurea, mean BMI was 31.3 and more than 40% of patients were obese. The categorization of overweight and obese increase an individual's risk of other chronic diseases, such as cardiovascular disease, arthritis, sleep and breathing disorders, depression, and some cancers.[33] In addition, overweight and obesity in patients with diabetes is associated with poorer control of blood glucose, blood pressure and lipids, thus increasing the risk of diabetes related comorbidities.[34] Between 1985 and 2011, the prevalence of adult obesity in Canada increased from 6.1% to 18.3%.[35] The study[35] predicted that, by 2019, the prevalence of obesity will increase significantly and that half of the Canadian provinces will have more overweight or obese adults than normal-weight adults.

This study is unique by way of providing new and novel data from a robust, Canadian multi-disease surveillance system based on primary care electronic medical record data to describe the cardiovascular risk profile of a Canadian population of patients with diabetes who are exposed to sulfonylureas. This study, does however, have data limitations. Namely, instances where incomplete patient demographic and risk factor data is captured within the CPCSSN database by contributing physicians. This can lead to more conservative estimates (i.e. under-estimation) of CV risk profile for this cohort. Additionally, as the study population is limited to only select sentential networks within 7 provinces, this may limit the generalizability of these findings from a pan-Canadian perspective.

CONCLUSIONS

Sulfonylureas are associated with a documented efficacy, low cost and decades of clinical experience in diabetes management. However, in recent decades, a growing body of evidence has raised concerns regarding the possible association between sulfonylureas usage and increased cardiovascular risk, beyond side effect of weight gain and risk of hypoglycemia. The current study illustrated that using a robust, Canadian primary care database, a substantial proportion (81.6%) of patients with diabetes and treated with a sulfonylurea have established CV disease and/or an aggregation of multiple CV risk factors. More than 40% of patients were obese and one-half of the cohort were greater than 65 years-old. In light of recent data on the possible association between sulfonylureas utilization and CV events and increased mortality, pharmacovigilance programs should actively monitor sulfonylureas utilization in patients with diabetes and high risk CV profile in real world clinical settings. These findings call for further comprehensive, longitudinal research studies with larger sample size in the future.

Acknowledgements
This study was supported by a research grant from AstraZeneca Canada Inc.

Conflict of interests: Pendar Farahani: Research Grants: AstraZeneca Canada; Consulting: AstraZeneca Canada, Amgen Canada; Shahriar Khan: None; Mark Oatway & Alison Dziarmaga are employees of AstraZeneca Canada Inc.

Appendix A - ICD9 codes were utilized
CAD/MI/IHD: 410, 411, 412, 413, 414
Stroke: 436, 437, 438
PVD: 443, 997, 999
Heart (other): 402, 404, 427, 428, 429
Hypertension: 401, 405
Dyslipidemia: 272
Obesity: 278
Active Smoking: 305

Appendix B - ATC codes were utilized
A10BB01
A10BB02
A10BB03
A10BB04
A10BB05
A10BB06
A10BB07
A10BB08
A10BB09
A10BB10
A10BB11
A10BB12
A10BB31

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