

## SULFONYLUREA AND THE HEART: THEORETICALLY A COMPOUNDED QUESTION FROM A PATHOPHYSIOLOGICAL PERSPECTIVE

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### ABSTRACT

Evidence from literature illustrates that from a pathophysiological perspective, sulfonylureas (SU) may impact the heart three ways: directly by intrinsic properties from a pharmacological receptor perspective, indirectly by adverse effects related to hypoglycemia, and obesity.

From a pharmacological receptor perspective, SU can bind to ATP-sensitive potassium channels in cardiomyocytes. Channel binding by SU in cardiac tissue may prevent ischemia myocardial protective mechanisms. From a pathophysiological perspective, obesity is associated with cardiac issues such as pulmonary hypertension, left ventricular hypertrophy, arrhythmia, and atrial fibrillation. From a pathophysiological perspective, hypoglycemia is associated with cardiac sympathetic activation and QT prolongation.

With the high prevalence and incidence of diabetes, obesity and aging, future basic and clinical studies should further explore the questions related to the pathophysiology of SU utilization and potential cardiac impact in randomized clinical trials and real-world outcome research settings.

**Key Words:** *diabetes, sulfonylurea, hypoglycemia, obesity, elderly, cardiovascular risks*

### BACKGROUND

Sulfonylureas (SU) are associated with documented efficacy, lower cost, and decades of clinical experience in diabetes management. However, SU usage is associated with risk of hypoglycemia and weight gain. Hypoglycemia and obesity are associated with a lower health-related quality of life and an increased burden of disease. In the past 2 decades, a growing body of evidence has begun to illustrate the potential adverse cardiovascular (CV) risk profile associated with SU use, especially glyburide.<sup>1-4</sup> This issue has been particularly demonstrated in subgroups of patients with a history of CV disease, elderly patients, and patients with a higher body mass index.

From a pathophysiological perspective, obesity is associated with hypertension, dyslipidemia, pro-inflammatory state, pro-thrombotic state, endothelial dysfunction, sleep apnea, pulmonary hypertension, systemic hypertension, left ventricular hypertrophy, arrhythmia, and atrial fibrillation.<sup>5,6</sup> Hypoglycemia is

associated with sympathetic activation, endothelial dysfunction, vasoconstriction, QT prolongation, pro-inflammatory and pro-thrombotic state.<sup>7,8</sup>

From a pharmacological and receptor perspective, SU can bind to ATP-sensitive potassium channels in cardiomyocytes and vascular smooth-muscle cells.<sup>9</sup> Channel binding by SU 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.

Therefore, a theoretical impact of SU on myocardium may be a threefold issue – intrinsic pharmacological and receptor properties, adverse effects related to hypoglycemia, and obesity. As a consequence, SU use has the potential to impact the heart with ischemia and arrhythmia.

### SU UTILIZATION PATTERN IN CANADA

A report from the Canadian Primary Care

Sentinel Surveillance Network (CPCSSN) found that 40% of primary care patients were prescribed SU as part of their anti-hypoglycemic regimen. SU represented the second largest class of medications after metformin. The data were derived from patient EMR records over a 2-year period between January 1, 2011 and December 31, 2012.<sup>10</sup>

A published report in 2003 from the Institute for Clinical Evaluative Sciences (ICES) (using administrative health care data in Ontario, Canada) reported that from 1995 to 2001, three-quarters of patients with diabetes receiving medications through a government supported medication program were receiving a SU either as the primary medication or as one of a combination of medications.<sup>11</sup>

Furthermore, a more recent population-based cross-sectional analyses of older adults (mean age 75 years) with treated diabetes in Ontario from 2002 until 2013 utilizing ICES data examined the percentage prescribed diabetes medication.<sup>12</sup> It was found that prescriptions for glyburide steadily declined over the last decade whereas those for gliclazide have increased. This change was reported to be consistent with clinical practice guidelines,<sup>13</sup> which have endorsed avoiding glyburide in older patients in favour of newer SUs including gliclazide that have a lower risk for hypoglycemia.

Collectively, all data illustrate that SUs are still one of the most utilized classes of medication for diabetes management, specifically in older adults, although there is a change towards pharmacologically safer SU utilization.

#### **SU USE AND CHARACTERISTICS OF PATIENTS IN CANADIAN CLINICAL SETTINGS**

CPCSSN data, which is a multi-disease surveillance system based on primary care electronic medical record data in Canada, demonstrated that a large number of patients with diabetes in Canada who are exposed to SU have myocardial issues.<sup>14</sup> In analyzing the CPCSSN database for the 2013 calendar year, for 6150 patients who had prescribed SU, the average age was 65.4 years, mean BMI was 31.3, and 43% of patients were obese. Established atherosclerotic CV disease was observed in 16.8%

of the patients with 13.2% having ischemic heart disease, or myocardial infarction, or coronary artery disease. A total of 19.5% of the patients had a diagnosis of cardiac-specific issues including ischemic heart disease or myocardial infarction or coronary artery disease, heart failure (not due to ischemic heart disease or myocardial infarction or coronary artery disease), or arrhythmia.

#### **EPIDEMIOLOGY OF OBESITY AND DIABETES IN CANADA**

Being overweight or obese is an important risk factor for type 2 diabetes and its complications.<sup>13</sup> A rising percentage of Canadians who fall into these categories could increase the prevalence of diabetes.<sup>15-17</sup> Sixty-one percent of Canadians are overweight or obese and approximately 80-90% of people with type 2 diabetes are overweight or obese.<sup>13,15-17</sup> The Prospective Studies Collaboration indicated that each 5 kg/m<sup>2</sup> higher body mass index (BMI) above 25 kg/m<sup>2</sup> was associated with a 30% higher overall mortality.<sup>18</sup>

#### **EPIDEMIOLOGY OF AGING IN OLDER ADULTS AND DIABETES IN CANADA**

The aging of the population has been one of the factors contributing to the increase in the number of Canadians living with diagnosed diabetes.<sup>15-17</sup> In recent years, the highest increase in the number of individuals with diabetes was seen in the 60-64 year old age group. The aging population is the most important demographic change affecting diabetes prevalence worldwide.<sup>19</sup> As diabetes in the elderly is metabolically distinct from diabetes in younger people, the approach to therapy should be different as well.<sup>13</sup>

#### **FUTURE DIRECTIONS FOR BASIC AND CLINICAL RESEARCH ON SU**

Overwhelming demographic trends of aging and increasing rates of overweight and obesity drive the prevalence in the growth of diabetes which leads to the rising costs for treatment and its complications. Therefore, one of the most important factors in diabetes pharmacotherapy should stem from avoidance of hypoglycemia and weight

gain, particularly in older adults and patients with cardiac disease. Future studies both in basic science and clinical/outcome research should explore the relevant pathophysiology and outcomes of SU utilization regarding both cost and effectiveness/safety in comparisons to newer classes of therapies with potentially safer hypoglycemia profiles, weight neutral/weight loss profiles. Comparative real-world studies are needed that particularly focus on older patients with cardiac issues and excessive weight.

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None.

### **Conflict of Interest**

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