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Original Research

Mortality and Cardiovascular Risk of Sulfonylureas in South Asian, Chinese and Other Canadians with Diabetes

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ABSTRACT

Objectives: Sulfonylureas have been inconsistently associated with increased cardiovascular mortality in patients with type 2 diabetes mellitus. However, there are no existing studies of long-term risk in South Asian and Chinese populations. Our objective was to determine whether sulfonylureas are associated with increased mortality or cardiovascular disease in a population cohort of South Asian, Chinese and other Canadian patients with incident diabetes.
Methods: We studied a population-based cohort of adults 35 years of age or older who had diabetes and had been diagnosed between April 2004 and March 2014 by using administrative databases from British Columbia. The primary outcome was time to death from any cause or from a major cardiovascular event (MACE) with sulfonylurea treatment within each ethnicity. Propensity score modelling was applied using inverse probability of treatment weights. Results were stratified by agent and adjusted for age, sex, comorbidities, income and other medications.
Results: We included 208 870 patients: 13 755 South Asians, 22 871 Chinese, 172 244 other Canadians. Mortality and MACEs were higher in other Canadian patients for whom sulfonylureas had been prescribed (adjusted HR = 2.0; 95% confidence interval 1.9 to 2.2; and HR = 1.9, 1.7 to 2.2). Among Chinese and South Asian patients who had been prescribed sulfonylureas, mortality (HR = 2.6, 2.0 to 3.5; and HR = 2.4, 1.7 to 3.4, respectively) and MACEs (HR = 2.3; 1.4 to 4.0; and HR = 2.0, 1.2 to 3.2, respectively) were elevated.
Conclusions: Considering the widespread use of sulfonylureas, there is a significant signal for increased mortality in all patients. In particular, increased mortality and MACEs were observed in South Asian and Chinese patients. These results should be confirmed in other studies, and patients of Asian descent should be included in clinical trials concerning diabetes.

Mots clés :
sulfonylurées
groupe ethnique
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risque cardiovasculaire
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diabète de type 2

RÉSUMÉ

Objectifs : Les sulfonylurées ont été associées de manière contradictoire à l'augmentation de la mortalité cardiovasculaire chez les patients atteints du diabète sucré de type 2. Toutefois, les études actuelles ne démontrent pas le risque à long terme auquel sont exposées les populations sud-asiatique et chinoise. Notre objectif était de déterminer si les sulfonylurées sont associées à l'augmentation de la mortalité ou des maladies cardiovasculaires dans une cohorte populationnelle de nouveaux cas de diabète chez des patients canadiens d'origines sud-asiatique, chinoise et autre.
Méthodes : Nous avons étudié une cohorte populationnelle d'adultes de 35 ans et plus ayant le diabète dont le diagnostic avait été posé entre avril 2004 et mars 2014 en utilisant les bases de données administratives de la Colombie-Britannique. Le critère de jugement principal était le moment du décès toutes causes confondues ou à la suite d'un événement cardiovasculaire majeur (ÉCIM) lors du traitement

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aux sulfonylurées au sein de chaque groupe ethnique. La modélisation du score de propension était appliquée en utilisant la pondération par l'inverse de probabilité de traitement. Les résultats étaient stratifiés selon l'agent et ajustés selon l'âge, le sexe, les comorbidités, le revenu et les autres médicaments.

Résultats : Nous avons inclus 208 870 patients canadiens : 13 755 d'origine sud-asiatique, 22 871 d'origine chinoise, 172 244 d'autres origines. La mortalité et les ÉCIM étaient plus élevés chez les patients canadiens d'autres origines qui prenaient des sulfonylurées (RR ajusté=2,0; intervalle de confiance à 95%, 1,9 à 2,2; RR=1,9, 1,7 à 2,2). Parmi les patients d'origines chinoise et sud-asiatique qui prenaient des sulfonylurées, la mortalité (RR=2,6, 2,0 à 3,5; et RR=2,4, 1,7 à 3,4, respectivement) et les ÉCIM (RR=2,3; 1,4 à 4,0; et RR=2,0, 1,2 à 3,2, respectivement) étaient élevés.

Conclusions : Compte tenu de l'utilisation généralisée des sulfonylurées, une augmentation importante de la mortalité est signalée chez tous les patients. En particulier, l'augmentation de la mortalité et des ÉCIM était observée chez les patients d'origines sud-asiatique et chinoise. Ces résultats devraient être confirmés au cours d'études ultérieures. De plus, les patients d'origine asiatique devraient être inclus dans les essais cliniques sur le diabète.

Introduction

Sulfonylureas have been promoted by international guidelines as a glycemia-control medication for patients with type 2 diabetes. However, the safety of sulfonylureas has been called into question for decades, ever since the University Group Diabetes Program study reported an increased mortality risk with tolbutamide in 1970 (1). Since then, numerous observational studies and randomized control trials have reported conflicting findings of increased cardiovascular and all-cause mortality (2–5).

Specifically, Forst et al (5) performed a meta-analysis of observational cohort studies evaluating all-cause and cardiovascular mortality among patients with type 2 diabetes treated with sulfonylureas vs. non-sulfonylurea diabetes medications. They reported that odds ratios for all-cause and cardiovascular mortality were higher, but findings were limited by the lack of randomized control trial (RCT) data to control for confounding by indication. A meta-analysis of RCTs comparing sulfonylureas to nonsulfonylurea treatments showed that sulfonylureas were associated with significantly increased odds ratios for all-cause mortality but not for major cardiovascular events (MACEs) (acute myocardial infarction, congestive heart failure or stroke) (3). A repeat meta-analysis of RCTs by Du et al (4) excluding first-generation sulfonylureas found that MACEs, cardiovascular mortality and all-cause mortality were not significantly increased. A meta-analysis combining RCT and observational studies of sulfonylureas found an increased relative risk for cardiovascular mortality and MACEs in patients treated with sulfonylureas compared to non-sulfonylurea treatment or metformin treatment (2). This increased risk was not demonstrated after excluding observational studies. These mixed findings, while altogether suggestive, are limited by the inherent heterogeneity of comparing studies in differing patient populations.

Furthermore, most of the studies evaluating sulfonylureas were conducted in primarily Caucasian populations, with very limited evidence in specifically Asian populations. One study of Chinese patients reported a higher hazard ratio of major cardiovascular events (1.8; 1.1 to 3.3) when comparing those treated with glipizide to those treated with metformin (6). However, patients were followed for only 3 years, and a mortality difference was not detected at this duration. The A Diabetes Outcome Progression Trial (ADOPT), 1 of the largest RCTs reporting no mortality difference with a sulfonylurea, included only 2.4% of patients of Asian ethnicity (7). The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial included a subset of 37% Asian patients and reported that intensive glycemic control using gliclazide did not increase mortality over 5 years (8). However, this trial may not be representative of the general population with diabetes because it included only patients with established macrovascular or microvascular disease or an additional vascular disease risk factor. The ADVANCE trial also did not distinguish South Asian vs. Chinese patients, which is critical, considering that genes related to sulfonylurea clearance occur at differing frequencies depending on ethnicity (9). Moreover, the experience with gliclazide may differ from that of earlier sulfonylureas, which are still widely used in Asian countries globally (10).

Sulfonylureas are used routinely in Asian patients both in Canada (11) and worldwide. There remains considerable uncertainty regarding long-term safety in Chinese and South Asian patients, and it is unlikely that further large RCTs specifically investigating these populations will be conducted. This gap is especially concerning in light of the fact that sulfonylureas are hugely popular in Asia, given their cheap cost; they are prescribed for 65% of Japanese patients with type 2 diabetes and not on insulin (12), and are included in 48% of oral hypoglycemia prescriptions in Taiwan (13). We conducted a population-based cohort study to determine whether sulfonylureas are associated with increased mortality and MACEs in a cohort of South Asian, Chinese and other Canadian patients with newly diagnosed diabetes.

Methods

Study population

We analyzed adults aged 35 years of age or older living in British Columbia, Canada, who had diabetes that was diagnosed during the period between April 1, 2004, and March 31, 2013. We defined diabetes diagnosis by using a validated algorithm (92.3% sensitivity and 96.9% specificity (14)) consisting of an International Classification of Diseases (ICD) -9 or -10 code for diabetes for at least 1 hospital discharge abstract or 2 physician claims within 2 years (ICD-9-CM: 250.x; ICD-10: E109, E119, E139, E149, E101, E111, E131, E141, E105, E115, E135 and E145). We set a washout period of a minimum of 3 years to identify incident cases of diabetes. The index date was defined as the first encounter with a documented diabetes diagnosis.

Patients were categorized by income quintile and Charlson comorbidities. Income was estimated based on Canadian census data by assigning median incomes derived from postal codes. In our patient population, up to two-thirds of patients who were prescribed sulfonylureas by 5 years after diagnosis were initially started within the first year. Therefore, within each ethnicity, patients were classified as having been treated with a sulfonylurea (gliclazide, glyburide, glipizide, glimepiride) if they received a prescription within 1 year after diagnosis. We excluded patients who died within 1 month of prescription.

Data sources

We analyzed de-identified datasets for the province of British Columbia, Canada (total population 4.6 million, including 210 400