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Comparative cardiovascular safety of insulin secretagogues following hospitalization for ischemic heart disease among type 2 diabetes patients: a cohort study

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ABSTRACT

Aim: To evaluate the association between insulin secretagogues and adverse cardiovascular sequelae in type 2 diabetes patients hospitalized for ischemic heart disease (IHD).
Methods: Administrative health records from Alberta, Canada between 1998 and 2010 were used to identify 2,254 gliclazide, 3,289 glyburide and 740 repaglinide users prior to an IHD-related hospitalization. Multivariable Cox regression models were used to compare the 30-day risk of a composite outcome of all-cause mortality or new onset of atrial fibrillation, stroke, heart failure or myocardial infarction according to insulin secretagogue use.
Results: Mean (SD) age was 76.1 (6.9) years, and 60.7% were men. The composite outcome occurred in 322 (30.2%) gliclazide users, 455 (28.1%) glyburide users and 81 (23.4%) repaglinide users within 30 days of IHD hospitalization. There were no differences in risk for glyburide use (adjusted hazard ratio [aHR] 0.91; 95% confidence interval [CI] 0.78–1.05) or repaglinide use (aHR 0.80; 95% CI 0.63–1.03) compared to gliclazide. Similar results were observed in analyses for each element of the composite outcome.
Conclusions: In older patients with type 2 diabetes hospitalized for IHD, prior use of gliclazide, glyburide, or repaglinide appears to be associated with a similar risk of adverse cardiovascular sequelae.

1. Introduction

The cardiovascular safety associated with insulin secretagogue (IS) use in patients with type 2 diabetes remains a contentious issue (Forst et al., 2013; Monami, Nardini, & Mannucci, 2014; Phung, Sobieraj, Engel, & Rajpathak, 2013). Two prevailing theories have been proposed to explain why IS use appears to be associated with an increased risk of adverse cardiovascular events. First, hypoglycemia, a common adverse reaction associated with these drugs, especially glyburide (Gangji, Cukierman, Gerstein, Goldsmith, & Clase, 2007), can prolong the QT interval and has been associated with cardiac ischemia (Desouza, Salazar, Cheong, Murgo, & Fonseca, 2003; Landstedt-Hallin, Englund, Adamson, & Lins, 1999). The second is an extension of the mechanism of action for IS. These oral antidiabetic drugs promote insulin secretion by binding to sulfonylurea receptors (SUR) and inhibiting ATP-sensitive potassium (K_{ATP}) channels in pancreatic beta cells (Ashcroft & Rorsman, 1989; Gromada, Dissing, Kofod, & Frøkjaer-Jensen, 1995). However, there may be important differences among IS based on SUR binding characteristics. Endocrine cells primarily express the SUR1 isoform while cardiac myocytes and smooth muscle cells primarily express SUR2 (Lang & Light, 2010). Some IS, like glyburide and the non-sulfonylurea IS repaglinide, will bind to both SUR1 and SUR2 isoforms when given at usual therapeutic doses and therefore also inhibit K_{ATP} channels located in the myocardium and vascular smooth muscle cells (Abdelmoneim et al., 2012). Animal models have shown that cardiac K_{ATP} channel opening is protective during ischemia–reperfusion injury and that K_{ATP} channel activity is essential for ischemic conditioning, an endogenous protective mechanism that promotes salvage of myocardial tissue during ischemia–reperfusion injury (Kristiansen et al., 2011; Tang et al., 2006). The extra-pancreatic cardiovascular effects of glyburide and repaglinide may potentially increase the risk of adverse cardiovascular events. In contrast, gliclazide appears to be more selective for SUR1, which may confer a better cardiovascular prognosis during acute

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ischemic events (Abdelmoneim et al., 2012; Kristiansen et al., 2011). Indeed, we have shown previously that gliclazide use is associated with a lower risk of acute coronary syndrome-related morbidity and mortality compared to glyburide use (Abdelmoneim et al., 2014).

In contrast to the hypothesized adverse cardiovascular effects affiliated with IS-mediated interference of ischemic conditioning, there may be beneficial effects in the atria (Baczkó, Husti, Lang, Leprán, & Light, 2011; Riveline, Danchin, Ledru, Varroud-Vial, & Charpentier, 2003). Inhibition of K_{ATP} channels in the atria increases action potential duration during ischemia–reperfusion injury and can reduce the occurrence of atrial fibrillation (Kantor, Coetzee, Carmeliet, Dennis, & Opie, 1990; Kim et al., 2012). In this regard, previous experimental and clinical studies have demonstrated that prolonged closure of cardiac K_{ATP} channels by glyburide decreases the effects of pro-arrhythmic substrates and reduces the risk of re-entry arrhythmias, such as atrial fibrillation (Baczkó et al., 2011; Furukawa, Kimura, Furukawa, Bassett, & Myerburg, 1991; Kim et al., 2012). As ischemic events in patients with diabetes can increase the likelihood of myocardial conduction anomalies (Ghuran & Camm, 2001; Pedersen, Bagger, Køber, & Torp-pedersen, 1999), it is important to determine the effects of IS on atrial fibrillation.

Given the mixture of possible adverse and beneficial cardiovascular effects and potential differences in tissue-specific binding amongst the IS, we hypothesized that the risk of adverse cardiovascular sequelae, including mortality or new onset of atrial fibrillation, stroke, heart failure or myocardial infarction, would be different amongst patients using gliclazide, glyburide, or repaglinide prior to hospitalization for ischemic heart disease (IHD).

2. Methods

2.1. Subjects & setting

We conducted a population-based retrospective cohort study of all Alberta residents aged 65 years or older with one or more dispensations for an oral antidiabetic drug. The province of Alberta maintains administrative health records for this patient group while providing universal coverage for hospital care, physician services, and prescription drugs. These administrative health records are linkable through a unique anonymized number for each individual and have been used extensively in previous epidemiologic studies because of the high level of accuracy and completeness of data (Abdelmoneim et al., 2014; Gamble et al., 2011; Li, Evans, Faris, Dean, & Quan, 2008; Majumdar et al., 2013; So, Evans, & Quan, 2006). The University of Alberta Health Research Ethics Board approved the study protocol.

We employed a two-stage process to construct the main study cohort. First, we identified all subjects who received at least one dispensation for an IS between January 1998 and December 2010 and with at least one year of continuous coverage following the first IS dispensation record. Second, we restricted our cohort to subjects with an ischemic heart disease (IHD) hospitalization following their first IS dispensation record. A hospitalization was considered attributable to IHD if the primary diagnostic field contained the International Classification of Diseases, 9th revision (ICD-9) codes 410, 411, 412, 413, or 414, ICD-10 codes I20, I21, I22, I23, I24, or I25, or the patient received a percutaneous coronary intervention (PCI) based on procedure codes IJ50, 1IJ57GQ, 1IJ54GQAZ, or 360. If a patient had multiple IHD hospitalizations during the observation period, we only considered the first IHD admission following their first IS dispensation record. The index date was defined as the admission date for the first IHD hospitalization following the first IS dispensation record.

2.2. Exposure assessment

Exposure was determined based on dispensation records for an IS within 120 days before the index date. A 120-day exposure window was used because the provincial drug plan covers a 100-day supply for antidiabetic drugs, and we allowed for an average adherence rate of 80% (Abdelmoneim et al., 2014; Cramer, 2004). Five different IS were identified in the Alberta Blue Cross database during our study period: gliclazide, glyburide, repaglinide, tolbutamide, and chlorpropamide. We excluded patients with no IS dispensations as well as those with more than one type of IS dispensed within the 120-day exposure window. Subjects who received tolbutamide ($n = 22$) or chlorpropamide ($n = 46$) were also excluded due to low numbers (data available on request).

2.3. Outcome measures

The primary outcome was a composite of all-cause mortality or new onset of atrial fibrillation, stroke, heart failure or myocardial infarction within 30 days following the index date. If a patient experienced more than one component of the composite outcome (for example, developed new onset of atrial fibrillation and died), we only counted the first event. Secondary outcomes included individual components of the composite outcome as well as cardiovascular-related mortality. To identify a new onset of atrial fibrillation, stroke, heart failure or myocardial infarction, we excluded patients with a physician visit or hospitalization record for the specific outcome of interest within the previous 3 years of the index date.

For all analyses, follow-up of patients who did not have the outcome of interest was censored 30 days after the index date, when the patient moved out-of-province, or the end of our study observation period (December 31st, 2010). All-cause mortality and cardiovascular-related mortality were identified using the Vital Statistics database and ICD-9 or ICD-10 codes for the underlying cause of death. Atrial fibrillation, stroke, heart failure, and myocardial infarction were identified using ICD codes of the respective outcome of interest from any diagnostic field recorded in the hospitalization or emergency room visit records (Appendix; Table 1). These codes have been used in other studies to identify the outcomes of interest and have high positive predictive values (atrial fibrillation – 89%; stroke – 81%; heart failure – 90%; and myocardial infarction – 94%) (Jensen et al., 2012; Lee et al., 2013; Quan et al., 2005, 2008; Varas-lorenzo et al., 2008).

2.4. Covariates

All baseline characteristics were identified from administrative health records within the previous 3 years of the index date. In addition to sex, age, and index year, we identified dispensation information from Alberta Blue Cross for antihypertensive drugs, lipid lowering drugs, digoxin, antiplatelet drugs, oral anticoagulants, hormone replacement therapy, COX-2 inhibitors, anti-arrhythmia drugs, oral antidiabetic drugs and insulin. We used information from physician visits, emergency room visits and hospitalization records to identify a list of comorbid conditions (Elixhauser, Steiner, Harris, & Coffey, 1998), as well as hypoglycemia, cerebrovascular disease and hyperlipidemia. Comorbid conditions were collapsed into a single score representing the number of comorbidities (Abdelmoneim et al., 2014). To control for possible differences in management of patients using gliclazide, glyburide, or repaglinide, we identified physician service codes for guideline concordant procedures, which included retinopathy screening, lipid, blood glucose or renal function assessment Committee CDACPGE, as well as mammography and bone mineral densitometry screening.

2.5. Statistical analyses

Patients were grouped according to use of gliclazide, glyburide, or repaglinide prior to the index date, and descriptive statistics were calculated for baseline characteristics. Categorical variables were compared by χ^2 tests, and continuous variables were compared using one-way ANOVA.