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Original article

Comparing kidney outcomes in type 2 diabetes treated with different sulphonylureas in real-life clinical practice

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Abstract

Aim. – Although several sulphonylureas are widely used in type 2 diabetes (T2D), their differential impacts on long-term major kidney outcomes remain unclear. This study aimed to investigate the effects of the two most commonly prescribed sulphonylureas, glimepiride and gliclazide, on kidney outcomes in patients with T2D.

Methods. – A total of 4486 patients treated with either glimepiride or gliclazide for more than 2 years were followed for up to 5.5 years (median: 4.7 years). A propensity score based on baseline characteristics was used to match 1427 patients treated with glimepiride with 1427 gliclazide-treated patients; incidences of end-stage renal disease (ESRD) and sustained doubling of creatinine to > 132.6 μmol/L (1.5 mg/dL) were also compared.

Results. – In the matched cohort with 12,122 person-years of follow-up, there was no significant difference between groups in risk of ESRD [hazard ratio (HR): 0.57, 95% confidence interval (CI): 0.29–1.12] or doubling of creatinine (HR: 0.74, 95% CI: 0.44–1.26), although there was a trend towards higher risks in the glimepiride group. Subgroup analyses showed that, compared with glimepiride, gliclazide was associated with a lower risk of doubling of creatinine in patients with preserved renal function (glomerular filtration rate ≥ 60 mL/min/1.73 m^2, HR: 0.21, 95% CI: 0.04–0.99) and good glycaemic control (HbA_{1c} < 7%, HR: 0.35, 95% CI: 0.14–0.86), and in older subjects (≥ 62 years, HR: 0.52, 95% CI: 0.27–0.99).

Conclusion. – In a real-life setting, there was no significant difference in clinical outcomes of kidney disease for patients treated with glimepiride vs gliclazide. However, gliclazide appeared to protect against renal complication progression in certain populations.

Keywords: Chronic kidney disease; Gliclazide; Glimepiride; Type 2 diabetes

1. Introduction

Diabetic nephropathy is a major cause of diabetes-related morbidity and mortality, and places a large burden on both patients and public healthcare systems [1]. Its worldwide incidence has significantly increased over the past 10 years [2]. Diabetes and chronic kidney disease (CKD) synergistically increase the risks of all-cause and cardiovascular mortality [3]. Furthermore, diabetes is currently regarded as the leading cause of end-stage renal disease (ESRD) in the US, accounting for approximately 40% of all incident cases [1]. Considering the clinical and economic impact of kidney complications in people with type 2 diabetes (T2D), it is important to prevent and delay diabetic

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nephropathy, and the kidney function deterioration leading to ESRD.

Several clinical trials have shown that strict blood pressure control and intensive glucose-lowering can significantly improve microvascular complications, including nephropathy (major kidney outcomes), in patients with T2D [4–7]. To date, agents blocking the renin–angiotensin system (RAS) are first-line therapies, and the only effective treatment options for kidney disease in diabetic patients [8]. A recent meta-analysis suggested that thiazolidinediones reduce urinary excretion of albumin and protein in patients with diabetes [9], implying the possibility of renoprotection. However, there is a lack of evidence regarding the renal effects of other oral glucose-lowering drugs, including sulphonylureas (SUs).

SUs were the first oral medications available to treat T2D and have been widely used for more than 60 years. Glimepiride and gliclazide are the two most commonly prescribed SUs, accounting for 48% (glimepiride) and 34% (gliclazide) of all prescribed SUs in world markets in 2012. Despite their popularity in routine clinical practice due to their potent glucose-lowering efficacy, recent studies have shown that cardiovascular risk and mortality are significantly increased in T2D patients treated with SUs, and these effects depend on the type of SU [10]. In the ADVANCE study, those receiving gliclazide-based intensive glucose control (90% of study subjects) showed beneficial results for diabetic nephropathy, suggesting a possible renoprotective property of gliclazide. However, the ACCORD trial demonstrated no protective effect of glimepiride-based intensive glucose control in those with kidney complications (79% of subjects) [11]. Therefore, its impact on long-term major kidney outcomes in T2D patients compared with other SUs remains unclear. Moreover, as it is next to impossible to conduct a well-organized randomized controlled clinical study of the renal effects of SUs due to the huge expenditures and amount of time required, an observational study is invaluable for identifying how SUs affect kidney-related complications in real-life clinical practice.

The present observational study compared the long-term kidney outcomes in T2D patients treated with either glimepiride or gliclazide in a cohort from a university-affiliated tertiary-care hospital. Propensity score matching was adopted to minimize the effect of potential confounding factors and medication selection bias in the study. As a decrease in albuminuria is not considered solid evidence of clinically important renal benefit by many drug administration authorities [12], the use of albuminuria as a reliable surrogate endpoint for renal outcomes remains controversial [5,13]. Accordingly, in our study, reliable kidney-related parameters were applied, namely, new-onset ESRD and doubling of serum creatinine levels from baseline.

2. Materials and methods

2.1. Patients and data collection

A total of 4486 patients with T2D who visited the diabetes centre at Severance Hospital in Seoul, South Korea, between 1 January 2008 and 31 December 2012 were retrospectively enrolled and followed for kidney outcomes until 16 June 2013. The initiating date of follow-up for study participants was May 2009. Patients who satisfied the following criteria, based on their medical records, were included: age > 20 years old, with available laboratory data for serum creatinine and haemoglobin A_{1c} (HbA_{1c}), and prescribed glimepiride or gliclazide as an oral glucose-lowering drug for > 2 years. Patients were excluded for the following reasons: a medication history including both glimepiride and gliclazide; duration of drug treatment with glimepiride or gliclazide < 2 years; secondary causes of CKD, such as congestive heart failure with renal failure, septic shock, hepatic failure with hepatorenal syndrome, obstructive nephropathy with subsequent renal failure due to kidney stones, and cancer progression; or a history of kidney transplantation. As it is difficult to conclude whether glimepiride or gliclazide affected the renal outcome in subjects with a dual drug history during the follow-up period, these patients were excluded to minimize confounding factors and to better assess the independent effects of each drug.

The study protocol was approved by the institutional review board of Severance Hospital (No. 4-2013-0590). However, the patients' written informed consent to participate in this study was not required because the researchers only accessed the patient database for analytical purposes and no personal information was used.

2.2. Measurement of clinical and laboratory parameters

Using electronic medical records, demographic and clinical data were retrospectively collected for age, gender, blood pressure and medical history, including hypertension, medications, follow-up duration and time to either doubling of serum creatinine or ESRD. Patients regularly visited the clinic at intervals of 3 to 12 months, depending on their condition, and underwent routine examinations for serum creatinine and HbA_{1c}. Serum creatinine levels were determined with a Hitachi 7600-110 automated chemistry analyzer (Hitachi, Ltd, Tokyo, Japan), using an enzymatic method (CREA, Roche Diagnostics, Indianapolis, IN, USA), and HbA_{1c} was measured by high-performance liquid chromatography (Variant II; Bio-Rad, Hercules, CA, USA). Renal function was assessed using the estimated glomerular filtration rate (eGFR) derived from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; this index is more accurate than previous indices, such as the Modification of Diet in Renal Disease (MDRD) Study equation [14]. CKD stages were determined based on eGFR categories (mL/min/1.73 m^2):

- stage 1 ≥ 90;
- stage 2 = 60–89;
- stage 3 = 30–59;
- stage 4 = 15–29;
- stage 5 ≤ 15 [15].

Mild-to-moderate CKD was defined as an eGFR between 15 and 60 mL/min/1.73 m^2 (CKD stages 3 and 4). Patients were