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


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 m², HR: 0.21, 95% CI: 0.04–0.99) and good glycaemic control (HbA1c < 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.

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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
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 A1c (HbA1c), 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 HbA1c. 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 HbA1c 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 m²):

- 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 m² (CKD stages 3 and 4). Patients were
classified into three groups according to their urine albumin-to-creatinine ratio (ACR):

- normoalbuminuria = ACR < 30 µg/mg;
- microalbuminuria = 30 µg/mg ≤ ACR < 300 µg/mg;
- macroalbuminuria = ACR ≥ 300 µg/mg.

2.3. Study outcomes (endpoints)

The main kidney outcomes in the present study were ESRD and doubling of serum creatinine to at least 132.6 µmol/L (1.5 mg/dL). ESRD was defined as a persistent need for dialysis or kidney transplantation. Doubling of serum creatinine was defined as a sustained greater-than-two-fold increase in serum creatinine levels from baseline after taking several measurements.

2.4. Statistical analysis

Patients with T2D were compared for long-term kidney outcomes according to SU treatment (glimepiride or gliclazide). To minimize the effect of potential confounding and medication selection bias in this retrospective study, propensity score matching was used [16,17], and a subgroup of glimepiride-treated patients with similar baseline characteristics to the gliclazide-treated patients was also assessed. Materials describing details of the resulting models, and the propensity score method and their predictive characteristics, are shown in Figs. S1 and S2 (see supplementary material associated with this article online).

Student’s t and χ² tests were used to compare continuous and categorical characteristic variables, respectively, of the glimepiride- and gliclazide-treated patients before and after propensity score matching. Average levels of serum creatinine and HbA1c during follow-up were described graphically for the two treatment groups, and P values were derived from linear mixed models with repeated measures and an autoregressive covariance pattern. Two fixed effects – between-subjects group effect (glimepiride and gliclazide) and within-subject time effect (at baseline and every 12 months for serum creatinine, and every 6 months for HbA1c) – were included, while possible changes in serum creatinine and HbA1c levels across the follow-up periods were assessed according to time × group interactions, for which P values are given. In the propensity score-matched cohorts of patients receiving either glimepiride or gliclazide, Cox proportional-hazards regression models were used to estimate differences in kidney outcomes between these treatment groups, and to calculate the adjusted HRs and 95% CIs.

All models were adjusted for age, gender, HbA1c and total cholesterol levels at baseline, eGFR at baseline, history of hypertension at baseline, duration of medication (glimepiride or gliclazide) and use of metformin, thiazolidinediones, insulin analogues or angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs). Survival curves for the incidence of kidney outcomes were estimated by the Kaplan–Meier method and compared using the log-rank test. Continuous variables are expressed as means ± standard deviation (SD), and categorical variables as percentages (%).

The Cox proportional-hazards regression power calculation was carried out using Power Analysis and Sample Size (PASS) 13 for Windows software (NCSS, LLC, Kaysville, UT, USA). A two-sided P value < 0.05 was considered significant. Statistical analyses used SPSS version 20.0 for Windows (IBM Corp., Armonk, NY, USA) and R programming language, version 3.0.1.

3. Results

3.1. Study population characteristics

Between 2008 and 2012, a total of 4486 patients with T2D who were exclusively treated with either glimepiride (n = 3059) or gliclazide (n = 1427) for at least 2 years were included in the present study. The two treatment groups had different characteristics at baseline (Table S1; see supplementary material associated with this article online): patients treated with glimepiride had significantly higher baseline HbA1c levels and eGFR values, more hypertension and significantly increased serum creatinine levels compared with those taking gliclazide. Furthermore, more patients with impaired renal function (CKD stages 3–5; eGFR < 60 mL/min/1.73 m²) were treated with gliclazide (P < 0.001).

After 1:1 propensity score matching, there were 1427 matched pairs of patients (Table 1). Visual examination of the distributions of propensity scores between the two groups revealed good overlap (data not shown), and the average values of the propensity scores were similar. The average age of patients in the glimepiride-treated group was 62.0 years vs 62.4 years in the gliclazide-treated group. In this matched cohort, there were no longer any significant differences between the glimepiride- and gliclazide-treated groups for any baseline variables, including eGFR, HbA1c, serum creatinine levels, hypertension, CKD and albuminuria stage.

3.2. Follow-up

The median follow-up duration was 4.8 years (IQR: 3.6–5.1 years) for patients taking glimepiride and 4.8 years (IQR: 3.5–5.1 years) for gliclazide users (Table 1). In the full cohort during follow-up, ESRD developed in 25 (0.8%) patients treated with glimepiride and in 16 (1.1%) treated with gliclazide. Sustained doubling of serum creatinine to > 132.6 µmol/L (1.5 mg/dL) was seen in 47 (1.5%) patients treated with glimepiride and in 28 (2.0%) of those treated with gliclazide. In the propensity score-matched cohort, similar percentages of patients experienced kidney disease progression according to type of SU used (ESRD: 1.5% with glimepiride vs 1.1% with gliclazide, P = 0.408; doubling of serum creatinine: 2.1% vs 2.0%, respectively, P = 0.791). As regards glycaemic control, neither group showed any significant differences in mean HbA1c changes during follow-up (Fig. 1a). Average values of serum creatinine in the glimepiride-treated group were comparable to those in the gliclazide-treated group throughout the follow-up, with gradual increases over time (Fig. 1b).
Table 1
Adjusted hazard ratios (HRs) for end-stage renal disease (ESRD) and sustained doubling of serum creatinine to at least 132.6 μmol/L (1.5 mg/dL) in propensity score-matched cohorts treated with glimepiride (Glim; reference group) and gliclazide (Glic).

<table>
<thead>
<tr>
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<tr>
<td></td>
<td>Events/total (n)</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
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<td>Glic</td>
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<tr>
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Cox model was adjusted for age, gender, hypertension, estimated glomerular filtration rate, HbA1c at baseline, total cholesterol at baseline, duration of medication, use of metformin/thiazolidinediones/insulin or ACE inhibitors/angiotensin II receptor blockers at baseline; significant values (P < 0.05) are in bold; n: number of events (patients); CKD: chronic kidney disease.

* P values for interaction between treatment groups and indicated variables.

3.3. SU treatment and kidney outcomes in the propensity score-matched cohort

Fig. 2 shows the long-term outcomes related to kidney disease according to SU type in the propensity score-matched cohort. For the 1427 matched pairs with 12,122 person-years of follow-up, there was no significant difference between glimepiride and gliclazide treatment groups in the risk of ESRD (gliclazide HR: 0.57, 95% CI: 0.29–1.12) or in risk of sustained doubling of serum creatinine to >132.6 μmol/L (gliclazide HR: 0.74, 95% CI: 0.44–1.26).

CKD stage, glycaemic status and age had marginal interactions (all P < 0.20) with treatment group (Table S1). Subgroup analyses (Fig. 3, Table 1) showed that gliclazide treatment was associated with a significantly lower risk than glimepiride treatment for the development of sustained doubling of serum creatinine to >132.6 μmol/L in patients with preserved renal function (GFR ≥ 60 mL/min/1.73 m²; HR: 0.21, 95% CI: 0.04–0.99), well-controlled glycaemia [HbA1c < 7% (53 mmol/mol)]; HR: 0.35, 95% CI: 0.14–0.86 and older [age (≥ 62 years); HR: 0.52, 95% CI: 0.27–0.99]. In addition, the risk of ESRD was significantly lower in the gliclazide-treated group.

Fig. 1. Mean levels of (a) HbA1c and (b) serum creatinine during follow-up of treatment with gliclazide and glimepiride. P values are for time × group interactions derived by analyses of a linear mixed model. Error bars represent the standard error of the mean (SEM).
4. Discussion

In the present propensity score-matched analysis, long-term kidney outcomes with glimepiride and gliclazide treatment were compared in patients with T2D, and demonstrated that the risks of ESRD and sustained doubling of serum creatinine to > 132.6 μmol/L were not significantly different with either treatment in our matched cohort (Fig. 2, Table 1). However, further subgroup analyses revealed that the HRs for ESRD and sustained doubling of serum creatinine were significantly lower with gliclazide than with glimepiride among patients with preserved renal function (GFR ≥ 60 mL/min/1.73 m²), well-controlled glycaemia [HbA1c < 7% (53 mmol/mol)] and older age (≥ 62 years; Fig. 3, Table 1), suggesting that gliclazide may have a protective role against renal complication progression in early-stage or mild diabetic nephropathy.

The ADVANCE trial reported that patients in the intensive blood-glucose control group (HbA1c levels ~ 6.5%) treated with gliclazide showed a decreased risk of major kidney outcomes compared with the standard control group (HbA1c levels ~ 7.5%), which had taken glucose-lowering drugs other than gliclazide [5]. However, the effects of gliclazide and the other glucose-lowering agents could not be compared because the target level of glycaemic control was different between groups. Over a median duration of 5 years, there were only 27 cases (0.24%) of ESRD and 84 patients (0.75%) who had sustained doubling of serum creatinine. However, as more patients with CKD stages 3–5 were included in our present study, slightly larger proportions of patients developed ESRD (1.2%) and doubling of creatinine (2.1%). Nevertheless, the overall number of events was small while the 95% CIs were large. This suggests that a longer follow-up period and more patients need to be included in further studies to determine kidney outcomes.

The present study has several important strengths. First, this was the very first evaluation of the long-term effects of gliclazide and glimepiride, two commonly prescribed oral glucose-lowering drugs, on the development of renal impairment in patients with T2D. To date, the differential effects of SUs have been compared in several studies looking at the risks of all-cause, cardiovascular and cancer mortality [10,18,19], but no data have been available for kidney outcomes in T2D. Patients whose duration of treatment was <2 years or who had a history of treatment with both drugs were excluded. Second, the propensity score matching method was used to overcome the inherent limitations of a retrospective observational cohort study design [16], and a large number of patients treated in a “real-life” situation were included, with a long follow-up duration (median: 4.8 years). Third, the incidences of ESRD and sustained doubling of serum creatinine to > 132.6 μmol/L were defined and evaluated as major kidney outcomes in our study population instead of albuminuria-related parameters, considered to be inaccurate surrogate indices [5,12,13].

Subgroup analyses suggested a possible renoprotective role of gliclazide over glimepiride in patients with preserved GFR, well-controlled glycaemia and older age. Also, several studies have shown that gliclazide has antioxidant actions [20] that can reduce oxidative stress markers and improve endothelial function [21], as well as ameliorate diabetic nephropathy, in animal models [22]. The unique amino azabicyclo-octane ring
Fig. 3. Kaplan–Meier survival analysis of the cumulative incidence of kidney-related complications in patients treated with glimepiride and gliclazide: (a) sustained doubling of serum creatinine to at least 132.6 μmol/L in patients with CKD stages 1 and 2; (b) sustained doubling of serum creatinine to at least 132.6 μmol/L in patients with CKD stages 3–5; (c) ESRD in patients with HbA1c < 7%; (d) ESRD in those with HbA1c ≥ 7%; (e) sustained doubling of serum creatinine to at least 132.6 μmol/L in those with HbA1c < 7%; and (f) sustained doubling of serum creatinine to at least 132.6 μmol/L in those with HbA1c ≥ 7%. P values are from Cox proportional-hazards regression models.
in glimepiride has been demonstrated to scavenge diabetes-induced free radicals in human studies [23,24] and in vitro [25]. Excessive oxidative stress caused by hyperglycaemia plays a crucial role in the pathogenesis of diabetic nephropathy [26]. Although antioxidant contributions to the treatment and amelioration of CKD are still in dispute, some antioxidants, including N-acetyl cysteine, have shown benefits in CKD [11]. However, considering that glimepiride itself is not a potent antioxidant, this effect is likely to exert a favourable influence only in specific patients with diabetes. Also, it is plausible that the critical pathological condition of patients with advanced stages of renal impairment (such as CKD stages 3–5) or severe hyperglycaemia may not be improved by the mild antioxidant activity of glimepiride, which is consistent with our present findings. In addition, CKD in younger patients is generally more affected by genetic predisposition or underlying structural susceptibilities [27]. Thus, glimepiride could selectively have kidney-protective actions only in elderly people who are not at high risk of CKD.

The major limitation of the present study is that it was a retrospective observational analysis and, thus, potentially subject to selection bias and effects of confounding factors. The decision to prescribe oral glucose-lowering medication was at the discretion of the patient and/or physician. In the full cohort, the glimepiride-treated group included more people with impaired kidney function (eGFR < 60 mL/min/1.73 m²) than the gliclazide group. This may be because physicians tend to prescribe glimepiride for patients with CKD, which is according to clinical guidelines [28], or it may indicate that glimepiride is the preferred drug for patients with renal impairment, as it has a lower risk of hypoglycaemia than glimepiride [29]. To minimize these possible biases and confounders, propensity score matching was used [17], which restricted the study cohort to patients with similar likelihoods of taking glimepiride or gliclazide according to their observed characteristics at baseline. Nevertheless, cautious interpretation of our present results is strongly recommended, given the possibility of unexpected biases due to concurrent comorbidities and the relatively low power of our subgroup analyses. The estimated power of our study was 75%, 92% and 71% for subgroups with CKD stages 1–2, HbA1c < 7% and age ≥ 62 years, respectively, whereas they were < 60% for the other subgroups.

In addition, urinary albuminuria was not evaluated in our study due to a large proportion of missing data for urine ACR. However, the reliability of albuminuria as an alternative indicator for renal outcome remains a matter of debate [5,13]. Furthermore, it was not possible to examine the duration of diabetes, physical activity, diet or history of medications, such as fenofibrates, which affect kidney disease outcomes, because of a lack of data.

In a real-life clinical practice setting, our results suggest that, in a matched cohort of T2D patients, glimepiride and glimepiride treatment groups had similar long-term rates of ESRD and sustained doubling of serum creatinine to > 132.6 μmol/L. However, in patients with GFR ≥ 60 mL/min/1.73 m², HbA1c < 7% and older age, glimepiride use was significantly associated with lower risks of ESRD and doubling of creatinine compared with glimepiride. Future prospective studies are now warranted to verify the effects of SUs on long-term kidney outcomes in patients with T2D.

**Author contributions**


**Disclosure of interest**

The authors declare that they have no conflicts of interest concerning this article.

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**Appendix A. Supplementary data**

Supplementary data (Figs. S1 and S2, and Table S1) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabet.2015.01.004.

**References**


