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Gliclazide monotherapy increases risks of all-cause mortality and has similar risk of acute myocardial infarction and stroke with glimepiride monotherapy in Korean type 2 diabetes mellitus

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Abstract

Sulphonylureas (SUs) subclasses have different risks of all-cause mortality, acute myocardial infarction (AMI), and stroke. Therefore, we assessed these risks in patients with type 2 diabetes mellitus administered gliclazide, glimepiride, or metformin monotherapy with retrospective cohort study design. Total 195,235 subjects were included in the study who were ≥20 years' old and prescribed monotherapy for at least 1 year as a first-line therapy for incident diabetes from January 01, 2009 to December 31, 2013 in the National Health Insurance Service Claim data. Incidence and hazard ratios (HRs) of all-cause mortality, AMI, and stroke were compared with glimepiride monotherapy as a reference. Gliclazide monotherapy increased all-cause mortality compared with glimepiride monotherapy. However, the gliclazide and glimepiride groups showed no difference in AMI and stroke incidences. In line with previous studies, metformin monotherapy showed significant clinical benefits in reducing risks of all-cause mortality, AMI, and stroke compared with glimepiride. This population-based cohort study suggested that gliclazide increases risks of all-cause mortality and has similar risk of AMI and stroke with gliclazide monotherapy in Korean.

Abbreviations: AMI = acute myocardial infarction, CI = confidence interval, HR = hazard ratio, NHIS = National Health Insurance Service, SUR = SU receptor, SUs = Sulphonylureas.

Keywords: gliclazide, glimepiride, metformin, mortality, myocardial infarction, stroke

1. Introduction

Type 2 diabetes mellitus is a very common chronic disease worldwide that is associated with increased risk of mortality and cardiovascular mortality.[1,2] Intensive glucose control demonstrates decreased development of microvascular complications[3] and even macrovascular complication with early intervention.[4]

Sulphonylureas (SUs) are one of the common second-line agents for the management of type 2 diabetes mellitus; however, they are associated with a higher risk of cardiovascular events than metformin.[5,6] Glimepiride and gliclazide are common SUs marketed in Korea for use in patients with type 2 diabetes mellitus. They have different properties including tissue selectivity, risk of hypoglycemia, SU receptor (SUR) selectivity, and effects on myocardial ischemic preconditioning. Gliclazide is a pancreas-specific and rapidly reversible inhibitor of Kir6.2/SUR1 expressed in beta-cells. However, glimepiride inhibits not only beta-cell-specific SUR1-type KATP channels but also cardiac and smooth muscle SUR2-type KATP channels and only slowly, reversibly inhibits Kir6.2/SUR1.[7] In previous studies, glibenclamide has been shown to increase overall and cardiovascular mortality compared with other SUs such as gliclazide and glimepiride,[8–11] suggesting that SUs have different properties. Moreover, gliclazide is considered the SU associated with the lowest risk of hypoglycemia[12] and, therefore, it is often the first choice clinically.

Recently, Douros et al[12] demonstrated that the long-acting SUs, glyburide, and glimepiride, have similar risk of cardiovascular adverse events to those of short-acting SUs such as gliclazide, glipizide, and tolbutamide except for increased risk of

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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severe hypoglycemia. Another study showed no differences in the risk of all-cause mortality or first-ever acute myocardial infarction (AMI) between current gliclazide users with their most recent prescription in the previous 90 days and current nongliclazide SU monotherapy users.[13]

Currently, few reports have compared the mortality and cardiovascular risks between gliclazide and glimepiride monotherapy initiated for at least for 1 year. Therefore, we performed a nationwide retrospective cohort study to compare the all-cause mortality and cardiovascular risks of gliclazide monotherapy compared with glimepiride along with metformin monotherapy in patients with low cardiovascular risk as defined by no previous AMI or stroke in Korea.

2. Methods

2.1. Study subjects

The National Health Insurance Service (NHIS) in Korea is an obligatory single-payer system that provides coverage for all Koreans and, therefore, includes data of > 99% of the population. NHIS obtains information on patient demographics, medical use and transaction information, insurers' payment coverage, and patients' deduction as well as claim data including medical information. Thus, NIHS data have been used as a population-based resource in nationwide studies of many diseases.[14] We extracted the data of 1,334,426 subjects with incident diabetes from January 01, 2009 to December 31, 2013 NHIS data.

We selected 210,963 subjects who were ≥20 years' old, prescribed monotherapy with metformin or an SU (gliclazide or glimepiride) at least for 1 year as a first-line antidiabetic therapy for incident diabetes in 2009 to 2013. We excluded 3302, 11,142, and 1284 subjects with missing data; previous history of AMI and stroke; and who experienced an AMI, stoke, or mortality within the first year of diabetes, respectively. A total of 1,952,35 subjects were eligible by meeting the inclusion criteria of incident diabetes without previous or current history of AMI and stroke diagnosis (Fig. 1).

2.2. Operational definition of diabetes

We used the operational definition of diabetes suggested in the Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association.[14] For the NHIS claim data, individuals were defined as having diabetes if antidiabetic drugs were prescribed with the presence of *ICD-10* codes E11, E12, E13, or E14 as either principal diagnosis or first to fourth additional diagnosis at least once a year. The incidence of type 2 diabetes was estimated by confirming the incident cases that did not meet the criteria of type 2 diabetes mellitus (eg, no claims under *ICD-10* codes E11–14 or antidiabetic medication prescriptions) previously from January, 01, 2002 to December, 31, 2008 and their diabetes diagnosis. Thus, the incident cases were identified after January 1, 2000 with at least a 7-year disease-free observational period.

Participants with low income were defined subjects who corresponded to the bottom 20% of annual family income. The presence of hypertension was operatively defined as >1 claim for antihypertensive medication under the *ICD-10* code I10-I13, I15 at the year of diagnosis of diabetes. Subjects with ≥1 claim/year for antidyslipidemic agents under *ICD-10* code E78 at the year of diagnosis of diabetes were considered to have dyslipidemia. Information on mortality was available for all subjects in the NHIS data received from the Korean National Statistical Office.

Individuals with AMI were defined as those with at least 2 outpatient clinic visits or inpatient admission under *ICD-10* code I121 or I122. Stroke was defined based on the inpatient record under ischemic stroke with *ICD-10* code 63, I64 and claims for

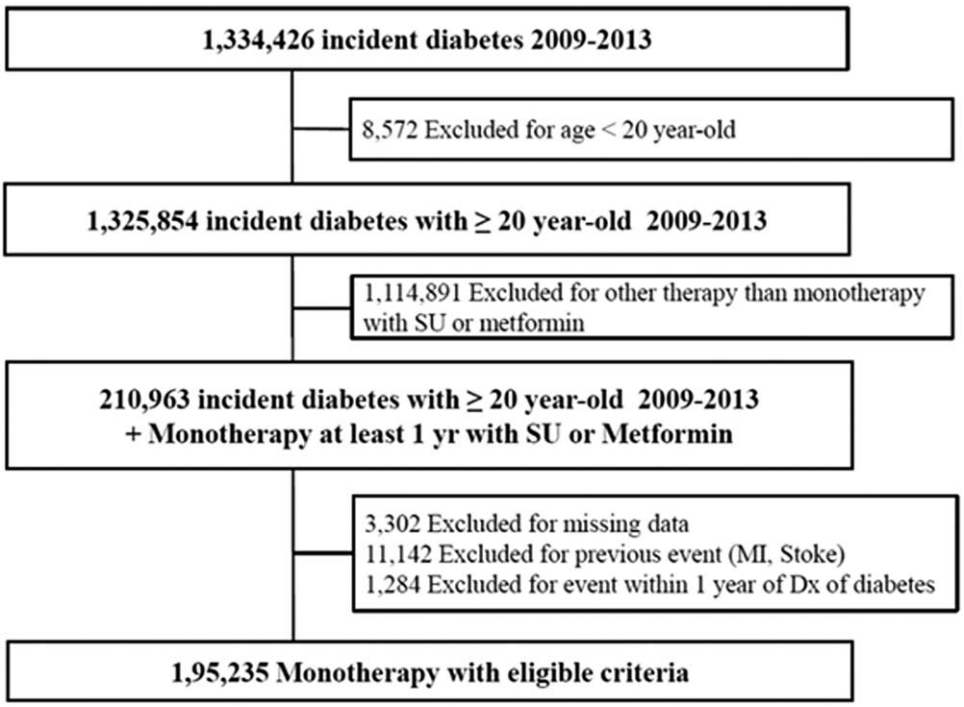

Figure 1. Selection of eligible monotherapy participants.

Table 1

Demographic data at baseline and follow-up.

n (195,235)	Total 195,235 (100%)	Metformin 160,370 (82.1%)	Glimepiride 33,322 (17.1%)	Gliclazide 1,543 (0.8%)	*P*
Age (mean ± SD)	58.9 ± 11.2	58.6 ± 11.1	60.0 ± 11.4	61.2 ± 11.3	
Age group, y, n (%)					<.0001
≤49	45,729 (23.4)	38,041 (23.7)	7414 (22.3)	274 (17.8)	<.0001
50–69	117,693 (60.3)	97,378 (60.7)	19,387 (58.2)	928 (60.1)	
≥70	31,813 (16.3)	24,951 (15.6)	6521 (19.6)	341 (22.1)	
Sex (men) n, (%)	96,241 (49.3)	78,492 (48.9)	16,900 (50.7)	849 (55.0)	<.0001
Low income, n (%)	46,435 (23.8)	37,107 (23.1)	8979 (27.0)	349 (22.6)	<.0001
Hypertension, n (%)	123,576 (63.3)	100,931 (62.9)	21,575 (64.8)	1070 (69.4)	<.0001
Dyslipidemia, n (%)	100,073 (51.3)	86,096 (53.7)	13,187 (396.)	790 (51.2)	<.0001
Event of acute myocardial infarction, n (%)	1,627 (0.8)	1,166 (0.7)	440 (1.3)	21 (1.4)	<.0001
Event of stroke, n (%)	2,008 (1.0)	1,413 (0.9)	572 (1.7)	23 (1.5)	<.0001
Event of mortality, n (%)	4,508 (2.3)	2,900 (1.8)	1,520 (4. 6)	88 (5.7)	<.0001
Mean FU duration ± SD, y					
Duration of incident acute myocardial infarction	4.28 ± 1.4	4.08±1.33	5.25±1.29	4.77±1.45	<.0001
Duration of incident stroke	4.28 ± 1.4	4.08±1.33	5.24±1.3	4.77 ± 1.45	<.0001
Duration of incident mortality	4.3 ± 1.4	4.09 ± 1.33	5.27 ± 1.27	4.79 ± 1.44	<.0001

FU = follow-up, SD = standard deviation.

brain computed tomography (CT) or magnetic resonance imaging (MRI). The index date was set on the first prescribed date of metformin, glimepiride, or gliclazide administration, and subjects enrolled in the study were those who were prescribed monotherapy at for least 1 year from the index data. Follow-up was terminated when the subjects first develop clinical study outcomes (death, AMI, or stroke), or at the end of the study period (December 31, 2015).

2.3. Statistical analyses

We determined the number and percentage of category variables to describe the distribution of each monotherapy group. The total and demographic-specific incidences of developing mortality, AMI, and stroke were calculated based on per 1000 person-years. The Cox proportional hazards regression model with crude model and adjustment for potential confounding factors, including age, sex, location, hypertension, dyslipidemia, and income status, were used to estimate the hazard ratio (HR) and confidence interval (CI) for the incidence of mortality, AMI, and stroke in 3 monotherapy groups.

Data management and analysis were performed using the SAS 9.4 software (SAS Institute, Cary, NC), and the cumulative incidence curve was constructed using the R software (3.2.4 version, R Foundation for Statistical Computing, Vienna, Austria). The significance level was set at a P value $<.05$ for 2-sided testing.

2.4. Ethics

The study was approved by the Institutional Review Board (IRB) of the Kangwon National University Hospital (IRB number: KNUH-2016-06-007) and an informed consent exemption was granted by the board.

3. Results

The total number of monotherapy cohorts treated for at least 1 year was 195,235. The monotherapy cohorts were composed of 160,370 (82.1%), 33,322 (17.1%), and 1543 (0.8%) in the metformin, glimepiride, and gliclazide groups, respectively, with a mean age of 58.6 ± 11.1, 60.0 ± 11.4, and 61.2 ± 11.3, respectively (Table 1). The number of male patient was higher in the gliclazide cohort (55.0%) than it was in metformin (48.9%) and glimepiride (50.7%) cohorts. The proportion of hypertension was 62.9% to 69.4% in the 3 cohorts.

3.1. All-cause mortality

The overall event rate of all-cause mortality was the highest for patients treated with gliclazide (11.91 per 1000 person-years, Table 2), followed by those administered glimepiride and metformin (8.65 and 4.42 per 1000 person-years, respectively). A total of 4508 all-cause mortalities occurred in 2900 (160,370 [1.81%]), 1520 (33,322 [4.56%]), and 88 (1543 [5.70%]) patients in the metformin, glimepiride, and gliclazide groups, respectively, during the whole study period.

Metformin monotherapy had decreased risk of mortality (adjusted HR [AHR] = 0.76) compared with those administered glimepiride as the reference after adjustment for age, sex, location (urban or rural), income status, concurrent hypertension, and dyslipidemia history at baseline. In both men and women and all age groups, metformin monotherapy showed a significantly lower risk of developing mortality than the other agents did. However, the gliclazide monotherapy appeared to tend toward increased all-cause mortality (AHR = 1.32) compared with glimepiride monotherapy. However, in the subgroup analysis, the gliclazide monotherapy group demonstrated no significant differences in all-cause mortality relative to the glimepiride group in both men and women, and the 3 age groups.

Figure 2 shows the cumulative all-cause mortality incidence curves for the study cohorts and revealed that the value for gliclazide monotherapy was the highest (log-rank test $P < .0001$). Compared with the AHR for patients administered glimepiride, the AHRs for those administered gliclazide and metformin were 1.32 (95% CI 1.06–1.64) and 0.761 (95% CI 0.71–0.81), respectively.

3.2. AMI and stroke

For AMI, metformin monotherapy also demonstrated a lower incidence (AHR = 0.852, 95% CI 0.76–0.95) than glimepiride

Table 2

Incidence of all-cause mortality and hazard ratio, measured using multivariate Cox proportional hazards regression analysis, for each monotherapy.

Drug	N	Event of all-cause mortality	Duration (person- years)	Incidence Rate (Case/1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
Total						
Metformin	160,370	2900	655855.8	4.422	0.606 (0.569–0.646)	0.761 (0.714–0.811)
Glimepiride	33,322	1520	175705.5	8.651	1 (ref.)	1 (ref.)
Gliclazide	1,543	88	7390.5	11.907	1.455 (1.174–1.804)	1.319 (1.063–1.636)
Male						
Metformin	78,492	1575	320540.6	4.914	0.625 (0.574–0.681)	0.725 (0.665–0.79)
Glimepiride	16,900	820	88641.5	9.251	1 (ref.)	1 (ref.)
Gliclazide	849	54	4053.8	13.321	1.517 (1.152–1.998)	1.291 (0.98–1.7)
Female						
Metformin	81,878	1325	335315.3	3.952	0.589 (0.537–0.647)	0.814 (0.74–0.894)
Glimepiride	16,422	700	87063.9	8.040	1 (ref.)	1 (ref.)
Gliclazide	694	34	3336.7	10.190	1.347 (0.955–1.9)	1.402 (0.993–1.979)
20–49						
Metformin	38,041	166	158621.9	1.0465	0.445 (0.349–0.569)	0.516 (0.403–0.66)
Glimepiride	7,414	111	39855.0	2.785	1 (ref.)	1 (ref.)
Gliclazide	274	5	1349.0	3.707	1.402 (0.572–3.434)	1.393 (0.569–3.411)
50–69						
Metformin	97,378	1140	399778.0	2.852	0.65 (0.586–0.721)	0.735 (0.662–0.817)
Glimepiride	19,387	542	103229.7	5.250	1 (ref.)	1 (ref.)
Gliclazide	928	31	4490.5	6.903	1.391 (0.969–1.998)	1.389 (0.967–1.995)
70-						
Metformin	24,951	1594	97456.0	16.356	0.752 (0.691–0.818)	0.824 (0.757–0.897)
Glimepiride	6,521	867	32620.8	26.578	1 (ref.)	1 (ref.)
Gliclazide	341	52	1551.1	33.526	1.341 (1.013–1.773)	1.277 (0.965–1.691)

CI = confidence interval, HR = hazard ratio.

Adjustment with age, sex, location, income, concurrent hypertension, and dyslipidemia.

did as the reference. In the subgroup analysis, female patients (adjusted HR 0.76) and the 50- to 69-year-old age group (AHR = 0.83) on metformin monotherapy showed a significantly lower rate of AMI than those on glimepiride did (Table 3). However, the gliclazide group showed no difference in the incidence of AMI compared to the glimepiride group.

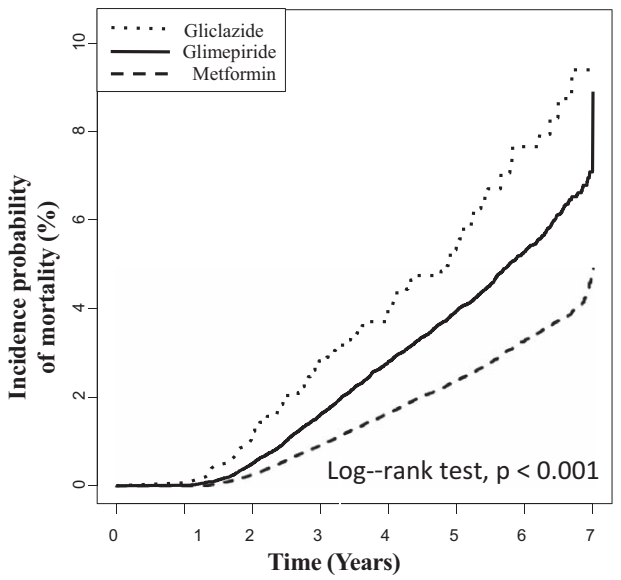

Figure 2. Kaplan–Meier survival curves of metformin, glimepiride, and gliclazide monotherapy for all-cause mortality.

Over a total of 4.3 ± 1.4 years of follow-up, the AHRs of stroke were 0.84 (95% CI 0.77–0.93) and 0.91 (95% CI 0.60–1.39) for the metformin and gliclazide groups, respectively compared with the glimepiride group (Table 4). Furthermore, both men and women exhibited a significantly lower risk of stroke in the metformin group than in other groups. Across the age groups in metformin monotherapy, only the 50- to 69-year-old age group (AHR = 0.83) showed a significantly lower rate of stroke than the glimepiride group did. However, the gliclazide group exhibited no difference in the incidence of stroke compared to the glimepiride group.

4. Discussion

This nationwide cohort study demonstrated that gliclazide monotherapy exhibited increased risk of all-cause mortality and similar risk of AMI or stroke compared with glimepiride monotherapy. However, the subgroup analysis, which used data stratified by sex and age groups, showed no significant differences in all-cause mortality between gliclazide and glimepiride. However, metformin showed a significantly lower risk of all-cause mortality, AMI, and stroke than the glimepiride monotherapy group.

This study is the first study which demonstrated that gliclazide monotherapy may increase the all-cause mortality (AHR = 1.32) compared with glimepiride monotherapy, which is quiet contrary to the previously reported results that gliclazide showed significantly less or similar mortality to that of glimepiride in a first-line therapy. In past and recent study, some SUs therapies have been reported to increase the mortality or cardiovascular risks in type 2 diabetes mellitus compared with other SUs such as

Table 3

Incidence of acute myocardial infarction and hazard ratio, measured using multivariate Cox proportional hazards regression analysis, for each monotherapy.

Drug	N	Event of AMI	Duration (person-years)	Incidence rate (Case/1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
Total						
Metformin	160,370	1166	653939.4	1.783	0.776 (0.694–0.867)	0.852 (0.761–0.953)
Glimepiride	33,322	440	174854.0	2.516	1 (ref.)	1 (ref.)
Gliclazide	1,543	21	7364.8	2.851	1.169 (0.755–1.811)	1.101 (0.711–1.706)
Male						
Metformin	78,492	608	319553.1	1.903	0.935 (0.794–1.102)	0.977 (0.829–1.152)
Glimepiride	16,900	195	88256.4	2.209	1 (ref.)	1 (ref.)
Gliclazide	849	15	4032.6	3.720	1.730 (1.023–2.926)	1.562 (0.923–2.643)
Female						
Metformin	81,878	558	334386.4	1.669	0.651 (0.559–0.758)	0.759 (0.65–0.886)
Glimepiride	16,422	245	86597.6	2.829	1 (ref.)	1 (ref.)
Gliclazide	694	6	3332.2	1.801	0.657 (0.292–1.477)	0.667 (0.297–1.5)
20–49						
Metformin	38,041	143	158383.5	0.903	0.851 (0.609–1.189)	0.914 (0.652–1.279)
Glimepiride	7,414	47	39748.6	1.182	1 (ref.)	1 (ref.)
Gliclazide	274	1	1348.6	0.741	0.649 (0.09–4.703)	0.617 (0.085–4.474)
50–69						
Metformin	97,378	661	398620.4	1.658	0.796 (0.684–0.926)	0.834 (0.716–0.971)
Glimepiride	19,387	235	102745.4	2.287	1 (ref.)	1 (ref.)
Gliclazide	928	11	4473.6	2.459	1.108 (0.605–2.027)	1.09 (0.595–1.996)
70-						
Metformin	24,951	362	96935.5	3.734	0.851 (0.704–1.029)	0.878 (0.725–1.063)
Glimepiride	6,521	158	32360.1	4.883	1 (ref.)	1 (ref.)
Gliclazide	341	9	1542.2	5.836	1.239 (0.633–2.425)	1.236 (0.631–2.423)

AMI = acute myocardial infarction, CI = confidence interval, HR = hazard ratio.
Adjustment with age, sex, location, income, concurrent hypertension, and dyslipidemia.

Table 4

Incidence of stroke and hazard ratio, measured using multivariate Cox proportional hazards regression analysis, for each monotherapy.

Drug	N	Event of stroke	Duration (person-years)	Incidence rate (case/1000 person-years)	Crude HR (95% CI)	Adjusted HR (95% CI)
Total						
Metformin	160,370	1413	653677.8	2.162	0.72 (0.652–0.794)	0.843 (0.763–0.932)
Glimepiride	33,322	572	174603.2	3.276	1 (ref.)	1 (ref.)
Gliclazide	1,543	23	7366.6	3.122	0.98 (0.646–1.487)	0.914 (0.602–1.388)
Male						
Metformin	78,492	695	319495.9	2.175	0.777 (0.674–0.896)	0.865 (0.749–0.998)
Glimepiride	16,900	270	88113.2	3.064	1 (ref.)	1 (ref.)
Gliclazide	849	9	4047.2	2.224	0.747 (0.384–1.451)	0.639 (0.329–1.242)
Female						
Metformin	81,878	718	334181.9	2.149	0.669 (0.584–0.767)	0.825 (0.718–0.947)
Glimepiride	16,422	302	86490.0	3.492	1 (ref.)	1 (ref.)
Gliclazide	694	14	3319.4	4.218	1.242 (0.727–2.122)	1.285 (0.752–2.197)
20–49						
Metformin	38,041	99	158426.7	0.625	1.165 (0.741–1.83)	1.244 (0.79–1.961)
Glimepiride	7,414	24	39813.5	0.603	1 (ref.)	1 (ref.)
Gliclazide	274	0	1349.0	0	0 (0)	0 (0)
50–69						
Metformin	97,378	696	398637.3	1.746	0.709 (0.616–0.817)	0.778 (0.675–0.898)
Glimepiride	19,387	278	102645.2	2.708	1 (ref.)	1 (ref.)
Gliclazide	928	11	4479.4	2.456	0.934 (0.511–1.707)	0.934 (0.511–1.706)
70-						
Metformin	24,951	618	96613.8	6.397	0.845 (0.73–0.977)	0.884 (0.764–1.024)
Glimepiride	6,521	270	32144.5	8.400	1 (ref.)	1 (ref.)
Gliclazide	341	12	1538.3	7.801	0.959 (0.538–1.71)	0.952 (0.534–1.7)

CI = confidence interval, HR = hazard ratio.
Adjustment with age, sex, location, income, concurrent hypertension, and dyslipidemia.

gliclazide.[10,13] Schramm et al[10] demonstrated that both gliclazide monotherapy in patients without (n = 5,926) and with (n = 517) previous AMI was associated with lower risk of all-cause mortality and cardiovascular outcomes than that with other SUs including glimepiride, and was not statistically different from metformin monotherapy in a nationwide study.

Recently, in an analysis of 18 studies, Simpson et al[15] showed that gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular mortality compared with glibenclamide. More recently, Dalem et al[13] demonstrated that there were no differences in risk of a first AMI or all-cause mortality between current gliclazide monotherapy users with current nongliclazide SUs monotherapy users (glimepiride, glibenclamide, glipizide, and tolbutamide) in 121,869 eligible patients. In the same study, there was no difference in all-cause mortality between gliclazide and metformin users but metformin users showed lower risk of AMI than gliclazide users did. However, in that study,[13] they defined current gliclazide users as those who were exposed in the last 1 to 90 days, which differed from the definition used in most studies where monotherapy users defined as those who were continuously exposed for at least 1 year to individual agents.

However, in our subgroup analysis, the significant difference in mortality between gliclazide and glimepiride disappeared because we guess that the reason is the relatively small numbers of participants in the sex or age groups to make a statistical significance. This discrepancy in the mortality and cardiovascular risk of gliclazide versus other SUs including glimepiride may be attributable to differences in study designs, study populations, inclusion criteria, duration of follow-up, operating definition of cardiovascular disease, and adjustment of confounding variables for which statistical adjustments were made. Thus, Over the many decades, the different outcomes between individual cohort studies and between meta-analyses continue to make it difficult to draw a firm conclusion, although considerable evidence suggests that SU therapy may be associated with an increased risk of mortality and cardiovascular events than other antidiabetic agents—mostly compared with metformin therapy.

Recently, some antidiabetic agents such as the sodium/glucose cotransporter 2 inhibitors (empagliflozin and canagliflozin) and the glucagon-like peptide-1 receptor agonists (liraglutide and semaglutide) demonstrated a significant benefit in preventing major adverse cardiovascular events.[16] These findings suggest that these agents should be the first choice of antidiabetic agents in patient with previous cardiovascular disease.

Our study showed that there was significantly lower risk of all-cause mortality, AMI, and stroke in the metformin monotherapy group than in the gliclazide and glimepiride groups. The beneficial metformin effects of our largest population-based study are in line with many previous studies.[5,17–19] In a cohort study,[6] monotherapy with SUs was associated with increased risk of all-cause mortality compared with other antidiabetic agents, raising safety concerns of SUs. One of the most popularly proposed mechanisms to explain the higher risk of adverse cardiovascular effects of SUs is hypoglycemia. Overall and severe hypoglycemic events are associated with increased risks of cardiovascular events.[20,21] Therefore, further research into the risks and safety of SUs over other antidiabetic agents or individual SUs is warranted in large representative population-based studies over longer periods. In addition, such research needs to emphasize that various SUs have different clinical outcomes such as mortality and cardiovascular risks.

A major strength of the present study is that the nationwide representative cohort study covered most of the general Korean population, which minimized the selection bias.

These results provide additional information for the ongoing debate regarding the safety profile of individual SUs in mortality and cardiovascular risk and evidence of the superiority of metformin as a first-line therapy compared with SUs.

5. Limitations

In this study, there were some limitations that are worth mentioning. This is not a randomized trial so there might be a bias in choosing the agent of monotherapy according to age, cost, renal function, or risk of hypoglycemia, and renal or liver function. We could not gain access to information on important well-known risk factors such as body mass index, smoking status, physical activity, hemoglobin A1C, and plasma lipid levels. The gliclazide monotherapy group might have been underpowered because there were fewer participants (0.8%) in the all-cause mortality assessment, AMI, and stroke compared with other monotherapy groups. Finally, for each monotherapy group, we could not perform a propensity score-matched cohort analysis because of the extremely low numbers of subjects in the gliclazide group compared to those in the metformin and glimepiride monotherapy groups.

6. Conclusions

In summary, the results of our population-based cohort study suggested that gliclazide may increase the risk of all-cause mortality and has similar risk of AMI and stroke to those of gliclazide monotherapy in Koreans. Metformin monotherapy also showed significant clinical benefits in reducing the risk of all-cause mortality, AMI, and stroke compared with glimepiride and gliclazide.

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