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Comparison of mortality and cardiovascular event risk associated with various insulin secretagogues: A nationwide real-world analysis

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ABSTRACT

Aims: Several insulin secretagogues are widely used to treat diabetes; however, few outcome-based comparative studies have clarified which one of these should be used when indicated. We investigated mortality and cardiovascular event risk associated with optimal forms of insulin secretagogues.

Methods: In this cohort study using real-world data from the diabetes database of Taiwan's National Health Insurance program, patients with diabetes were enrolled if their initial treatment was glimepiride, gliclazide, glipizide, glyburide, or repaglinide from 1999 to 2013. Each group was propensity score-matched to the glimepiride group before comparison. Primary outcomes were all-cause mortality and the combined cardiovascular event risk of acute myocardial infarction and ischemic stroke. Hazard ratios were calculated by Cox proportional hazard regression models.

Results: There were 66,790, 97,426, 38,806, 92,970, and 11,468 participants in the glimepiride, gliclazide, glipizide, glyburide, and repaglinide groups, respectively. The median follow-up time was 8 years. Glimepiride was associated with the best clinical outcome, showing the lowest mortality and lowest cardiovascular event risk of the five insulin secretagogues. Using patients on glimepiride as the reference group, the adjusted hazard ratios of all-cause mortality and cardiovascular event risk were 1.52 ($p < 0.001$) and 1.22 ($p = 0.005$) for gliclazide, 1.42 ($p < 0.001$) and 1.19 ($p = 0.073$) for glipizide, 1.43 ($p < 0.001$) and 1.32 ($p < 0.001$) for glyburide, and 1.88 ($p < 0.001$) and 1.69 ($p = 0.001$) for repaglinide.

Conclusions: For patients with diabetes taking an insulin secretagogue, glimepiride was associated with the best clinical outcome, showing the lowest mortality and cardiovascular event risk.

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1. Introduction

Current pharmacotherapy guidelines for type 2 diabetes recommend treatment initiation with metformin monotherapy. For patients in which the side effects of metformin are not tolerated or if additional drugs are needed due to unsatisfactory glycaemic control, there is no clear evidence to guide choices among the many available alternatives [1].

Abbreviations: NHIRD, National Health Insurance Research Database; DB, diabetes dataset; aHR, adjusted hazard ratio

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Of the various oral drugs available to treat type 2 diabetes, only gliclazide and metformin are listed in the latest edition of the World Health Organization (WHO) Model List of Essential Medicines [2]. Sulfonylureas (the class to which gliclazide belongs) and meglitinides, are two types of insulin secretagogues that act by binding to different subtypes of the SUR1 receptor complex with different affinity strengths aimed at increasing insulin secretion [3]. Second-generation sulfonylureas including gliclazide, glimepiride, glipizide, and glyburide (glibenclamide) are widely used in clinical practice. Meglitinides are considered less potent compared to sulfonylureas with a faster onset time and shorter duration of action [4]. A study of the 2009 national prescription patterns in Taiwan found that meglitinide, mostly repaglinide, and sulfonylureas accounted for 37% of all the monotherapy agents used and were administered in 92% of patients with diabetes who were receiving dual-agent therapy [5].

A review of the literature showed that the efficacies of repaglinide and the four above-mentioned second-generation sulfonylureas were comparable. A second meglitinide, nateglinide, is less effective compared to the others [4] and used less often in Taiwan [5]. Owing to a lack of clinical outcome-based evidence to guide the choice of these five equally potent insulin secretagogues, expert recommendations are predominantly based on their pharmacokinetic characteristics, except in the case of glyburide, which is not suitable for those aged older than 60 years. Faster onset times and shorter durations of action are considered favourable attributes of insulin secretagogues [6]. Drugs with this property are expected to be more flexible in terms of the timing of use and are associated with fewer hypoglycaemic events. In a 2007 review, there was inadequate evidence on the relative risk of morbidity and mortality among users of different sulfonylureas [7]; however, some subsequent publications reported that each sulfonylurea may have a different risk profile, but with conflicting results [6,8–10]. Meta-analyses comparing the safety of each sulfonylurea were hampered by the heterogeneity of the included studies, often under certain specific conditions, and yielded conflicting results [6]. The available studies often had a relatively small number of cases, inadequate statistical power, and short follow-up duration, and verified patient medications only at the beginning of treatment that were complicated by many concurrent drugs used.

Although a large proportion of type 2 diabetes patients are prescribed insulin secretagogues, there is no definite consensus regarding the differences in all-cause mortality and cardiovascular event risk associated with different insulin secretagogues, according to the current limited evidence [6–10]. Therefore, we conducted a nationwide real-world analysis to demonstrate outcome-based head-to-head comparisons between the different insulin secretagogues. The outcomes of interest were all-cause mortality and the combined cardiovascular event risk of acute myocardial infarction and ischemic stroke.

2. Materials and methods

2.1. Data sources

A nationwide real-world cohort study was conducted using Taiwan's National Health Insurance Research Database (NHIRD). The National Health Insurance in Taiwan is a single-payer program that covers 99.6% of the country's population of 23.6 million people. The administrative claims data of this program constitutes the NHIRD [11]. The claims records of 120,000 randomly selected newly diagnosed diabetes patients were added to this diabetes dataset (DB) of the NHIRD each year from 1999 to 2012 (total of 1.68 million diabetes patients). The DB comprises the claims records of these 1.68 million patients from 1997 to 2013 and includes claims pertaining to all outpatient visits for medical, dental, and traditional Chinese medicine services, medications used and the date in which the prescriptions for them were filled, number of days and total amount of medication supplied, hospital admissions, status on the day of discharge, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coded diagnostic and procedure information. This study was conducted in accordance with the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. The ethics committee of Hualien Tzu Chi Hospital approved this study and the need for informed consent was waived.

2.2. Study population and exposures

Patients were included in this study if they were aged 20 years or older, did not have a history of acute myocardial infarction or ischemic stroke, and had started diabetes monotherapy with one of the following drugs: glimepiride, gliclazide, glipizide, glyburide, or repaglinide. Follow-up was initiated on the day the first prescription was filled. Follow-up continued until a primary outcome event occurred, until the time of censoring or the end of 2013, whichever came first. Patients were censored on the day their prescription for diabetes was changed, 90 days after the last prescription was expected to run out, or when a patient died without a cardiovascular event in the case of cardiovascular event risk comparisons. The outcome of each group was compared with that of the glimepiride users. Glimepiride was chosen as the reference drug as it has been the most commonly prescribed insulin monotherapy secretagogue since 2003.

2.3. Outcomes

The outcomes of the study were all-cause mortality and the combined cardiovascular event risk of acute myocardial infarction and ischemic stroke. The NHIRD does not include death certificates; however, death status can be inferred in NHIRD records with 100% sensitivity and high specificity, as validated in several previous publications [12,13]. Death was identified if the final insurance status was withdrawn from the National Health Insurance program and no subsequent

claims were filed. The date of withdrawal was the inferred death date. Acute myocardial infarction (ICD9-CM main code 410) and ischemic thromboembolic stroke (ICD9-CM main code 433 or 434) were identified through inpatient claims records or at the emergency room visit.

2.4. Covariates and comorbidities

Covariates were collected in the 2 years before the index date and included: age, sex, calendar index year (the year of type 2 diabetes diagnosis starting with insulin secretagogue use), indicators of healthcare use (hospitalization within 3 months before diagnosis, hospitalization between 3 and 12 months before the index date, and number of outpatient visits in the year before the index date), and presence of comorbidities defined similar to those reported in the online supplement by Roumie et al. [14].

2.5. Propensity score matching and statistical analysis

Glimepiride was sequentially compared to each of the other four insulin secretagogues. The disparities in the distribution of the attributes between the different groups listed in Table 1 were minimized through the use of propensity score matching. The propensity score associated with the reception of each treatment was estimated using a logistic model including all comorbidities and covariates in Table 1 as reported previously [15]. We performed 1:1 propensity score matching utilizing the user written psmatch2 package for Stata [16]. The options specified for psmatch2 were logit, 1:1 nearest-neighbour matching protocol with a calliper of 0.2 standard deviation without replacement, on common support [17,18].

The Kaplan-Meier method was used to estimate the risks of mortality and cardiovascular event development, and a log-rank test was used to compare the differences between the cumulative incidence curves. The adjusted hazard ratio (aHR) of each primary outcome for each secretagogue vs. glimepiride was calculated using a Cox proportional hazards model that was stratified on the matched pair. In the analyses of cardiovascular events, those who died without any cardiovascular events were treated as censored by a competing risk. All p values reported were two-sided and not corrected for multiple testing. There were eight pre-specified comparisons (four insulin secretagogues vs. glimepiride, two primary outcomes each). Using Bonferroni correction for multiple testing, $p < 0.006$ was considered statistically significant. Database management and statistical analysis were performed using Stata (Stata Corp., version 14.0).

2.6. Sensitivity analysis

Although propensity score matching can help balance participant baseline characteristics, some participants may be excluded if they cannot be matched to a suitable case or control; these exclusions may also cause bias. Therefore, to further confirm our study results, we conducted a sensitivity analysis that included all type 2 diabetes patients starting diabetes monotherapy with insulin secretagogues without matching procedures. We constructed multivariate Cox proportional hazards regression models adjusting for all the covariates listed in Table 1 to calculate the aHR of mortality and cardiovascular events.

3. Results

3.1. Study population

In this set of 1.68 million newly diagnosed diabetes patients, there were 66,790, 97,426, 38,806, 92,970, and 11,468 participants in the glimepiride, gliclazide, glipizide, glyburide, and repaglinide groups, respectively. Their basic demographic characteristics and comorbidities as of the index date are shown in Table 1.

3.2. All-cause mortality

Glimepiride use was sequentially compared to the use of each of the four other insulin secretagogues. The set of glimepiride users matched to gliclazide, glipizide, glyburide, and repaglinide users were labelled set 1, set 2, set 3, and set 4, respectively (Table 2). The Kaplan-Meier methods revealed that all the other four insulin secretagogue groups (gliclazide, glipizide, glyburide, and repaglinide) had significantly higher risks of mortality than the glimepiride group (Fig. 1A, B, C, and D, respectively). The number of participants included for the comparison after 1:1 propensity score matching, the incidence rate, the aHR, and corresponding 95% confidence interval (CI) of all-cause mortality for each insulin secretagogue vs. glimepiride are shown in Table 2. Overall, all four insulin secretagogues were associated with significantly increased mortality risks relative to glimepiride. The number of matched users, corresponding aHR (95% CI), and p value are as follows: n = 50,302, aHR = 1.52 (1.33–1.73), $p < 0.001$ for gliclazide; n = 23,835, aHR = 1.42 (1.19–1.70), $p < 0.001$ for glipizide; n = 40,083, aHR = 1.43 (1.24–1.64), $p < 0.001$ for glyburide; and n = 11,247, aHR = 1.88 (1.45–2.43), $p < 0.001$ for repaglinide (Table 2).

3.3. Cardiovascular event risk

In terms of the combined cardiovascular event risk of acute myocardial infarction and ischemic stroke, the comparisons between the insulin secretagogues were similar to those in the case of all-cause mortality except that those who died without any cardiovascular events were treated as censored by a competing risk. Kaplan-Meier analyses revealed that all four insulin secretagogue groups (gliclazide, glipizide, glyburide, and repaglinide) had significantly higher risks of cardiovascular events than the glimepiride group (Fig. 2A, B, C, and D, respectively). The number of matched users, corresponding aHR (95% CI), and p value were as follows: n = 50,302, aHR = 1.22 (1.06–1.40), $p = 0.005$ for gliclazide; n = 23,835, aHR = 1.19 (0.98–1.44), $p = 0.073$ for glipizide; n = 39,830, aHR = 1.32 (1.14–1.53), $p < 0.001$ for glyburide; and n = 11,247, aHR = 1.69 (1.25–2.59), $p = 0.001$ for repaglinide (Table 3). All but glipizide use showed a significantly increased cardiovascular event risk relative to glimepiride; however, glipizide use still showed a trend of higher cardiovascular event risk.

Table 1 – Baseline characteristics of the patients by the insulin secretagogue administered.

Variables	Glimepiride (n = 66,790)	Gliclazide (n = 97,426)	Glipizide (n = 38,806)	Glyburide (n = 92,970)	Repaglinide (n = 11,468)
Age, mean (SD)	57.1 (11.7)	56.8 (11.7)	57.5 (12.0)	56.7 (11.9)	58.8 (12.4)
OPD visits, mean (SD)	21.8 (17.3)	22.9 (18.4)	22.9 (18.5)	22.7 (18.4)	23.3 (18.5)
Sex (%)					
Male	54.1	52.7	53.2	54.2	54.3
Female	45.9	47.3	46.8	45.8	45.7
Hospitalization (%)					
Within 3 months	3.3	3.1	4.2	3.8	5.7
3–12 months	6.5	6.5	7.4	6.9	9.3
Comorbidities (%)					
Malignancy	0.8	0.5	1.0	0.7	2.2
Liver/respiratory failure	1.1	1.3	1.7	1.5	1.9
Congestive heart failure	0.6	0.5	0.7	0.5	1.2
Cardiovascular disease	17.1	12.9	11.4	10.9	18.6
Serious mental illness	0.3	0.2	0.2	0.2	0.6
COPD or asthma	0.7	0.7	1.0	0.8	1.4
Cardiac valve disease	0.3	0.3	0.4	0.3	0.6
Chronic renal failure	0.1	0.1	0.3	0.1	1.0
Arrhythmia	13.3	10.5	9.9	9.0	14.5
Parkinson disease	0.7	0.5	0.5	0.4	1.2
Medications (%)					
Antihypertensives	60.5	50.5	47.6	45.7	59.8
Lipid-lowering agents	26.6	18.6	16.3	15.2	25.9
Inotropes	13.2	10.5	9.9	9.0	14.5
Anticoagulants	6.1	3.7	3.8	3.2	7.3
Nitrates	12.0	8.9	9.1	8.1	14.1
Aspirin	27.4	19.5	17.5	16.3	28.1
Index year (%)					
1999	0	10.0	15.3	16.4	0
2000	0.4	10.2	15.4	15.3	0.2
2001	3.9	10.3	13.2	13.5	7.1
2002	6.2	10.2	11.4	11.2	9.8
2003	7.4	10.8	9.3	9.4	10.8
2004	7.3	10.3	8.0	8.2	9.1
2005	9.2	8.8	6.4	6.6	8.3
2006	10.9	7.8	5.8	5.5	8.5
2007	11.2	6.3	4.5	4.4	7.7
2008	10.2	4.8	3.2	3.2	8.0
2009	9.5	3.8	2.6	2.4	7.2
2010	8.5	2.7	1.9	1.7	7.6
2011	7.8	2.1	1.6	1.2	7.4
2012	6.4	1.5	1.1	0.9	6.5
2013	1.2	0.3	0.2	0.2	1.8

Abbreviations: SD, standard deviation; OPD, outpatient department; COPD, chronic obstructive pulmonary disease.

3.4. *Results of sensitivity analysis*

The sensitivity analysis, conducted using all eligible type 2 diabetes patients without propensity score matching, also revealed a similar pattern in the results. This analysis revealed that patients who were prescribed all four insulin secretagogues (gliclazide, glipizide, glyburide, and repaglinide) had significantly higher risks of both mortality and cardiovascular events than those prescribed glimepiride, similar to the results observed in the main analyses after propensity score matching. The statistical values observed in the sensitivity analysis are shown in Table S1 (in Supplementary Materials).

4. Discussion

This nationwide cohort study using real-world data revealed that glimepiride was associated with the best clinical outcomes, showing the lowest risks of all-cause mortality and cardiovascular events, of the five insulin secretagogues commonly used in Taiwan. This study included a large sample size, long-term follow-up period (median follow-up time of 8 years), and comprehensive head-to-head comparisons (including five different insulin secretagogues). Due to the high prevalence and incidence of type 2 diabetes, the associated cardiovascular disease risk and mortality, as well as the high proportion of patients receiving insulin secretagogue

Table 2 – Risk of all-cause mortality in each insulin secretagogue vs. glimepiride set comparison after propensity score matching.

	N	Events	Person-year	Incidence rate*	aHR† (95% CI)	p value
Set 1						
Gliclazide	50,302	619	347,159	1.78	1.52 (1.33–1.73)	<0.001
Glimepiride	50,302	409	356,742	1.15	1 (ref.)	
Set 2						
Glipizide	23,835	323	194,526	1.66	1.42 (1.19–1.70)	<0.001
Glimepiride	23,835	229	196,010	1.17	1 (ref.)	
Set 3						
Glyburide	40,083	515	296,783	1.74	1.43 (1.24–1.64)	<0.001
Glimepiride	40,083	348	303,080	1.15	1 (ref.)	
Set 4						
Repaglinide	11,247	201	73,782	2.72	1.88 (1.45–2.43)	<0.001
Glimepiride	11,247	119	75,840	1.57	1 (ref.)	

Glimepiride users were assigned to the reference group for each comparison set of insulin secretagogues Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; N, number.

* Per 1000 person-years

† The aHR was calculated using a Cox proportional hazards regression model that was stratified on the matched pair after propensity score matching.

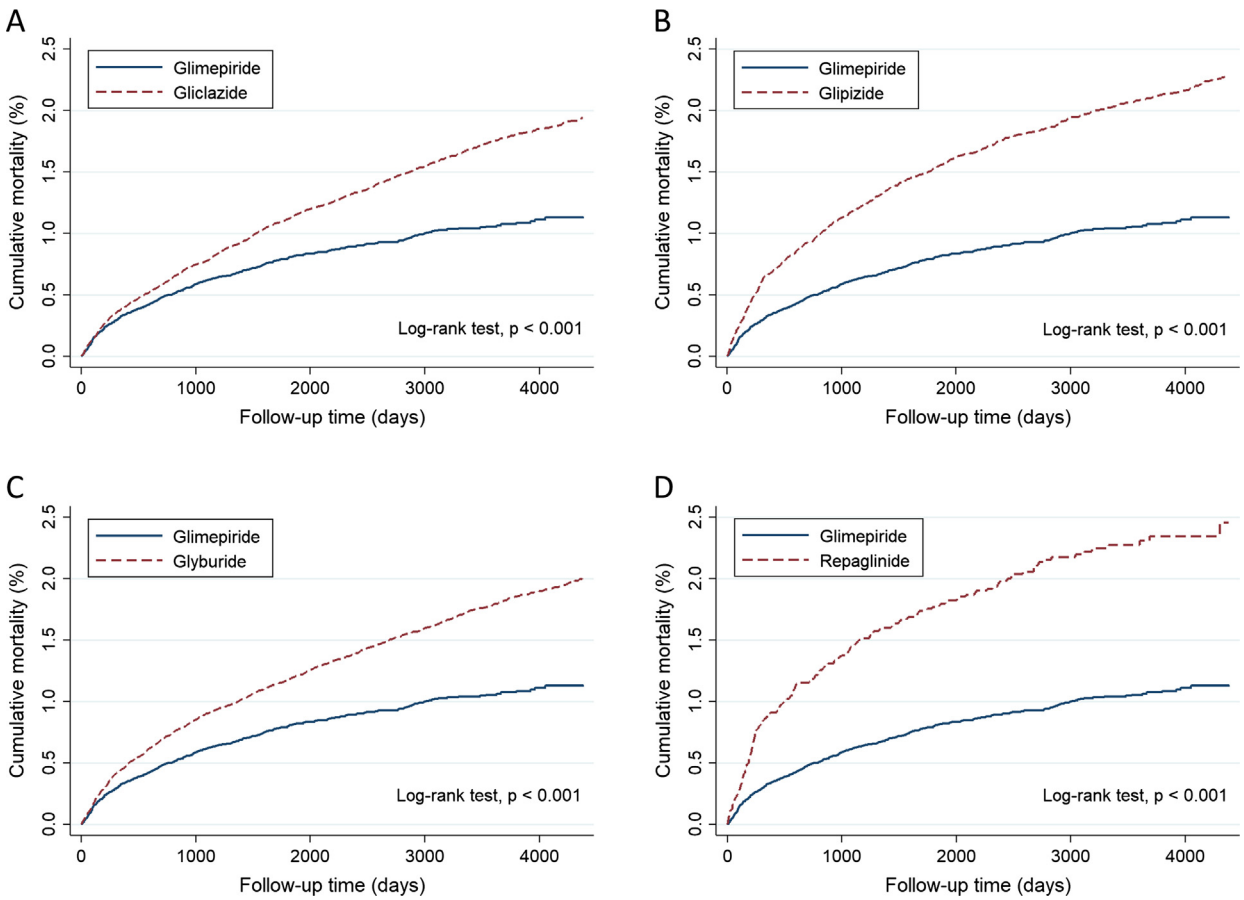

Fig. 1 – Kaplan–Meier curves comparing the cumulative mortality rates between the different insulin secretagogues: (A) gliclazide vs. glimepiride; (B) glipizide vs. glimepiride; (C) glyburide vs. glimepiride; (D) repaglinide vs. glimepiride.

treatment worldwide, the clinical and public health implications of our present study are potentially large.

Although some publications have reported that each sulfonylurea may have a different risk profile, on performing comparisons of the risk profiles associated with the different secretagogues, there is still inadequate evidence on the relative risk of morbidity and mortality among the users of different sulfonylureas, and the results are conflicting [6–10]. A

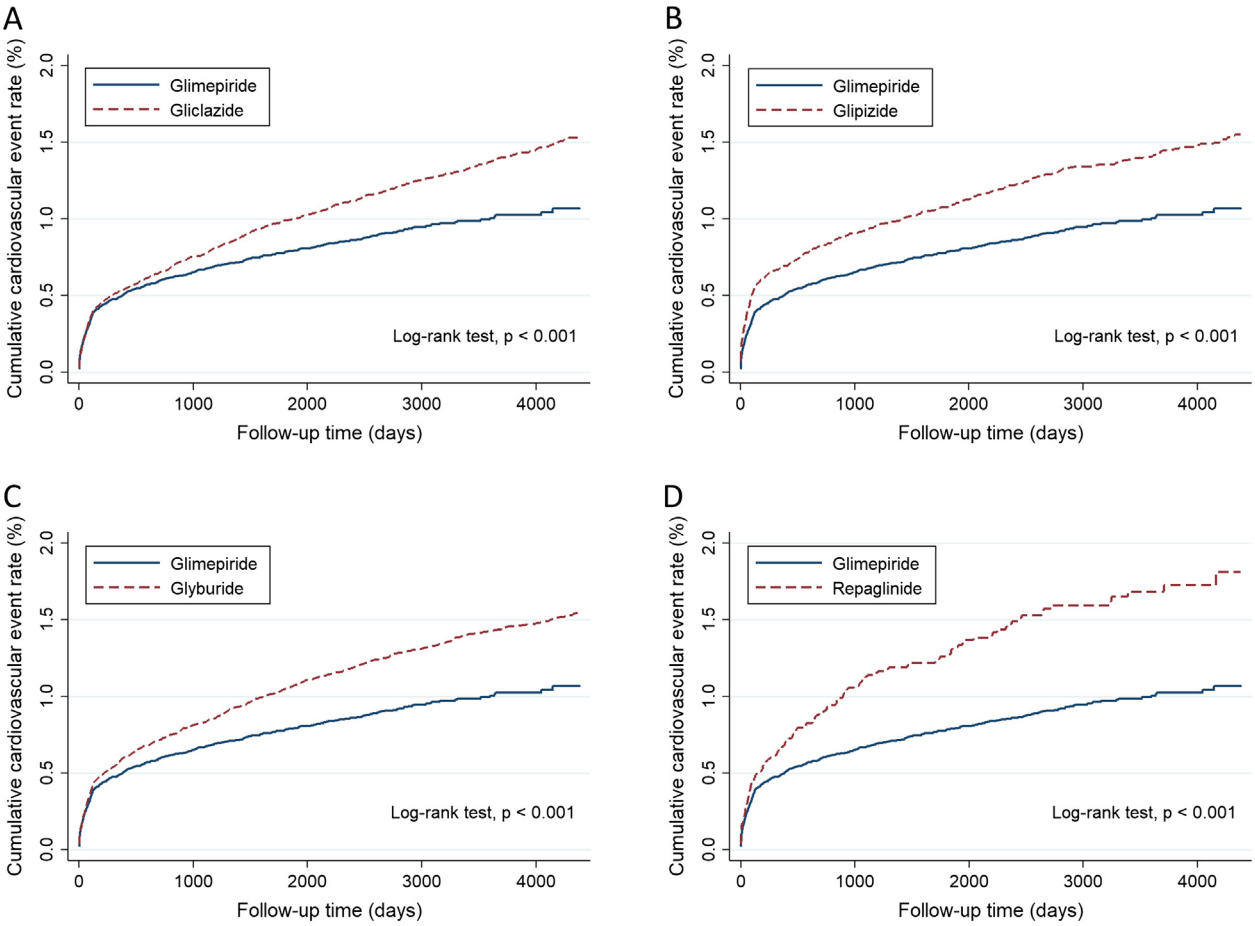

Fig. 2 – Kaplan–Meier curves comparing the cumulative incidences of cardiovascular events between the different insulin secretagogues: (A) gliclazide vs. glimepiride; (B) glipizide vs. glimepiride; (C) glyburide vs. glimepiride; (D) repaglinide vs. glimepiride.

Table 3 – Risk of cardiovascular event in each insulin secretagogue vs. glimepiride set comparison after propensity score matching.

	N	Events	Person-year	Incidence rate*	aHR† (95% CI)	p value
Set 1						
Gliclazide	50,302	505	324,983	1.55	1.22 (1.06–1.40)	0.005
Glimepiride	50,302	410	334,018	1.23	1 (ref.)	
Set 2						
Glipizide	23,835	256	179,993	1.42	1.19 (0.98–1.44)	0.073
Glimepiride	23,835	218	181,388	1.20	1 (ref.)	
Set 3						
Glyburide	39,830	434	276,249	1.57	1.32 (1.14–1.53)	<0.001
Glimepiride	39,830	326	282,546	1.15	1 (ref.)	
Set 4						
Repaglinide	11,247	143	69,267	2.06	1.69 (1.25–2.59)	0.001
Glimepiride	11,247	90	70,968	1.27	1 (ref.)	

Glimepiride users were assigned to the reference group for each comparison set of insulin secretagogues.
Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; N, number.
* Per 1000 person-years.
† The aHR was calculated using Cox proportional hazards regression model that was stratified on the matched pair after propensity score matching.

previous retrospective cohort study in the united states performed overall mortality comparisons in type 2 diabetes patients receiving glipizide, glyburide, or glimepiride monotherapy [8]. That study did not identify significant differences in the mortality risk between the three individual sulfonylureas. Although the authors of that study stated that glimepiride may be the preferred sulfonylurea due to the associated trend of lower mortality risk in the subgroup with underlying cardiovascular disease, statistical significance was not found [8]. Another study that compared the mortality risks among type 2 diabetes patients being treated with glibenclamide, gliclazide, or glimepiride found that glibenclamide treatment for type 2 diabetes was associated with a greater risk of all-cause mortality than gliclazide or glimepiride treatment [9]. The different approaches to methods and designs among the studies might lead to a discrepancy of results [19]. A previous meta-analysis conducted by Gangji et al. indicated that glyburide was not associated with an increased risk of cardiovascular events and mortality compared to some other secretagogues [7]. However, this meta-analysis only included limited studies that compared cardiovascular events and mortality associated with glibenclamide to other sulfonylurea derivatives (but not those containing gliclazide) [7]. On the other hand, another recent meta-analysis revealed that gliclazide and glimepiride were associated with a lower risk of all-cause and cardiovascular-related mortality than glibenclamide [6]. However, those meta-analyses were often hampered by the heterogeneity of the included studies under certain specific conditions and yielded conflicting results [6]. Other available studies often had inadequate statistical power [20] and a short follow-up period [21], included medication verification only at the beginning [8], or showed complications associated with the concurrent use of many drugs [22]. Most of those comparisons were based on hypoglycaemia risk, glycaemic control, or blood tests. Nonetheless, glyburide was removed from the WHO essential medicines list in 2013 due to safety concerns pertaining to its use in elderly patients and those with a history of cardiovascular events [2,23].

Although it is useful to conduct randomized controlled trials (RCTs) of head-to-head comparisons between drugs, it is rarely feasible to conduct them due to the associated high cost. The sample size required for an RCT to detect the difference between two approved insulin secretagogues with sufficient statistical power is expected to be much larger than that required for a typical RCT focusing on new drug approval due to the much smaller expected difference. The availability of many large population-based databases in recent years has provided the opportunity for researchers to address this and other similar questions using an observational study design. A rigorously designed observational study may be as accurate as an RCT and its performance may entail much lower costs [24]. The conclusions of such observational studies may be the best available evidence to guide clinical practice in the absence of RCTs. The NHIRD is the claims database of the National Health Insurance Program of Taiwan [11] and has been mined by over 3000 research articles in PubMed. Our large-scale study, using real-world data, provided sufficient statistical power to answer such important clinical questions and provide clinicians reliable evidence on the comparisons of mortality and the cardiovascular event risk among insulin secretagogues.

This study has some limitations that should be acknowledged. The lack of randomization as well as key physiological variables such as body mass index, glycated haemoglobin (HbA1c), and blood lipid profile in the NHIRD is a major limitation of this study. Although well-designed observational studies are considered to be as accurate as RCTs [24] and allow for causal conclusions to be drawn under certain conditions [25], RCTs remain the universally accepted study design for the definite confirmation of the causal relationship between treatment and outcome. Despite this limitation, our study still provides among the best available evidence to guide clinical practice. Another major limitation is that we could not directly confirm the accuracy of the study outcomes by approaching the patients directly because the National Health Research Institute encrypted all personal identifiers before releasing the database. However, the accuracy of the diagnostic codes for both ischemic stroke and acute myocardial infarction has been validated previously and high accuracy was found [26–28]. The method of identifying mortality in the NHIRD records has also been proven with high accuracy [12,13]. Thus, the validity of the outcomes observed in this study could be considered satisfactory.

In conclusion, this real-world nationwide cohort study showed that, in incident adult patients with diabetes using only an insulin secretagogue, glimepiride was associated with the best clinical outcomes, including the lowest all-cause mortality and cardiovascular event risk. Until definitive RCT results are available in this context, it would be prudent to consider using glimepiride when an insulin secretagogue is needed.

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2. The National Health Insurance claims data of a representative cohort of 2 million enrollees linked to the registry of death was provided by the Health and Welfare Statistics Application Center, Ministry of Health and Welfare, Taiwan.

Author contributions

Jih-I Yeh designed the study, analysed and interpreted the data, and wrote this manuscript. Huei-Kai Huang interpreted the data and wrote this manuscript. Jih-I Yeh had full access to all of the data in the study and takes responsibility for the contents of the article.

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Conflicts of interest

The authors declare that no conflicts of interest exist.

Ethical approval

The ethics committee of Hualien Tzu Chi Hospital approved this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.diabres.2019.04.032.

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