Association Between Specificity of Sulfonylureas to Cardiac Mitochondrial K_{ATP} Channels and the Risk of Major Adverse Cardiovascular Events in Type 2 Diabetes

Meng-Ting Wang,[1,2] Ya-Ling Huang,[2] Jyun-Heng Lai,[2] Chien-Hsing Lee,[3] Pin-Chun Wang,[2] Hsueh-Yi Pan,[2] ChenWei Lin,[1] Jun-Ting Liou,[4] and Yu-Juei Hsu[5]

Diabetes Care 2022;45:1276–1287 | https://doi.org/10.2337/dc21-1779

OBJECTIVE

Previous studies have revealed an intraclass difference in major adverse cardiovascular events (MACE) among sulfonylureas. In vitro and ex vivo studies reported several sulfonylureas to exhibit high-affinity blockage of cardiac mitochondrial ATP-sensitive potassium (mitoK$_{ATP}$) channels and could interfere with ischemic preconditioning, the most important mechanism of self-cardiac protection. However, no studies have examined whether these varying binding affinities of sulfonylureas could account for their intraclass difference in MACE. We compared mitoK$_{ATP}$ channel high-affinity versus low-affinity sulfonylureas regarding the MACE risk in real-world settings.

RESEARCH DESIGN AND METHODS

Using the Taiwan nationwide health care claims database, patients with type 2 diabetes initiating sulfonylurea monotherapy between 2007 and 2016 were included in the cohort study. A total of 33,727 new mitoK$_{ATP}$ channel high-affinity (glyburide and glipizide) and low-affinity (gliclazide and glimepiride) sulfonylurea users, respectively, were identified after 1:1 propensity score matching. Cox proportional hazard models were used to estimate adjusted hazard ratios (aHRs) and 95% CI.

RESULTS

MitoK$_{ATP}$ channel high-affinity sulfonylureas were associated with a significantly increased risk of three-point MACE (aHR 1.21 [95% CI 1.03–1.44]), ischemic stroke (aHR 1.23 [95% CI 1.02–1.50]), and cardiovascular death (aHR 2.61 [95% CI 1.31–5.20]), but not with that of myocardial infarction (aHR 1.04 [95% CI 0.75–1.46]). The duration-response analyses revealed the highest MACE risk to be within 90 days of therapy (aHR 4.67 [95% CI 3.61–6.06]).

CONCLUSIONS

Cardiac mitoK$_{ATP}$ channel high-affinity sulfonylureas were associated with an increased MACE risk compared with low-affinity sulfonylureas in a nationwide population with diabetes.

[1]Department of Pharmacy, National Yang Ming Chiao Tung University, Taipei, Taiwan
[2]School of Pharmacy, National Defense Medical Center, Taipei, Taiwan
[3]Division of Endocrinology and Metabolism, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[4]Division of Cardiology, Department of Internal Medicine, China Medical University Hsinchu Hospital, Hsinchu, Taiwan
[5]Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Corresponding authors: Meng-Ting Wang, mtwang@nycu.edu.tw, and Yu-Juei Hsu, yujuei@mail.ndmctsgh.edu.tw

Received 23 August 2021 and accepted 20 February 2022

This article contains supplementary material online at https://doi.org/10.2337/figshare.19209426.

Diabetes continuously poses a significant burden to health worldwide (1). Despite several novel antidiabetic agents, sulfonylureas remain one of the most prescribed medications in the world due to their established glucose-lowering efficacy, low costs, and longtime clinical use (2,3). Notably, sulfonylurea is the second most common monotherapy treatment among patients with type 2 diabetes in current clinical settings across many countries, including Taiwan (4). However, since the past 50 years, concerns were raised regarding the first-generation sulfonylurea tolbutamide-related adverse cardiovascular events (5,6). Studies, including meta-analyses of randomized controlled trials, have shown an increased adverse cardiovascular event risk related to sulfonylureas (7,8) and have documented a differential cardiovascular risk among individual sulfonylureas (9,10). Potential mechanisms, such as pancreas selectivity, which underlies sulfonylurea intraclass differences in cardiovascular risk, have been assessed, but none of them were confirmed (11,12).

Ischemic preconditioning (IPC) is an endogenous cardioprotective mechanism that involves multiple brief ischemic episodes, allowing the heart to adapt itself to become tolerant to a cardiac ischemic injury when a subsequent sustained ischemic event strikes (13). Accumulative evidence showed that IPC could also limit myocardial infarct size and reduce both necrosis and apoptosis of the heart during an acute ischemic event (14). Cardiac mitochondrial ATP-sensitive potassium channels (mitoK$_{ATP}$ channels) are composed of a channel-forming subunit (MITOK) and a regulatory subunit carrying the ATP-binding domain (MITOKSUR), locating across the inner mitochondrial membrane (15). The composition and location of cardiac mitoK$_{ATP}$ channels are different from that of the sarcolemmal K$_{ATP}$ channels. Notably, it is the opening of cardiac mitoK$_{ATP}$ channels that plays a pivotal role in activating multiple cardioprotective kinase pathways in IPC (16). Sulfonylureas have different blockage of mitoK$_{ATP}$ channels in the cardiac muscle (17–20), potentially contributing to differential effects on the heart. Animal models have shown that certain sulfonylureas, such as glyburide and glipizide, exhibit high-affinity blockage of cardiac mitoK$_{ATP}$ channels and could further damage the heart by interfering with IPC (18–20), while others, including gliclazide and glimepiride, have minimal effects on IPC owing to their low affinities to the mitoK$_{ATP}$ channels (17,19). To date, it remains unclear whether sulfonylurea specificity to cardiac mitoK$_{ATP}$ channels is a major contributor to the intraclass adverse cardiovascular risk differences in real-world settings.

We aimed to examine whether cardiac mitoK$_{ATP}$ channel high-affinity sulfonylureas are associated with a higher risk of major cardiovascular events (MACE) than cardiac mitoK$_{ATP}$ channel low-affinity sulfonylureas in a population with diabetes.

RESEARCH DESIGN AND METHODS

Study Design and Data Source

This new user, active comparator, and propensity score (PS)-matched cohort study was conducted using data from the Taiwan Diabetes Mellitus Health Database (DMHD) between 1 January 2006 and 31 December 2017. The DMHD contains the Taiwan National Health Insurance (NHI) claim records for all newly diagnosed patients with diabetes, including details regarding their diagnoses, medical procedures, and prescription refill records. Patients with diabetes were defined as those with at least three diabetes-related outpatient visits, with intervals of $>$4 weeks, in a given year. Additionally, death records were obtained by linking the DMHD with the National Death Registry Database. This study was approved by the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center (1-107-05-196), and the requirement for written informed consent was waived. This study was completed before the lead author became affiliated with the National Yang Ming Chiao Tung University.

Study Population

The study cohort included newly diagnosed patients with type 2 diabetes who initiated sulfonylureas, including gliclazide, glimepiride, glyburide, and glipizide, from 1 January 2007 to 31 December 2016. These sulfonylureas were considered because of the available information on their specificity to cardiac mitoK$_{ATP}$ channels and sufficient number of users; furthermore, they comprised $>$99% of the prescribed sulfonylureas through the study period. Initiators of each individual sulfonylurea were defined as patients at least 20 years of age at cohort entry with the date of the first sulfonylurea prescription marked as the cohort entry date. New sulfonylurea users were not allowed to have any sulfonylurea prescription refill records in the previous year, and they cannot be new users of other antidiabetic drugs in addition to sulfonylureas on cohort entry. Eligible patients were excluded if they experienced the following events in the year preceding cohort entry: *1*) an inpatient visit with a diagnosis of myocardial infarction (MI) or ischemic stroke; *2*) lack of 1-year continuous NHI enrollment; or *3*) pregnancy. The exclusion criteria are detailed in Supplementary eTable 1.

Patients were classified into two groups based on the sulfonylurea specificity to cardiac mitoK$_{ATP}$ channels: cardiac mitoK$_{ATP}$ channel-high affinity (glyburide and glipizide) and channel-low affinity (gliclazide and glimepiride) sulfonylurea users. The two groups were followed from the cohort entry date until primary major cardiovascular outcome occurrence (defined below), NHI enrollment discontinuation, sulfonylurea treatment discontinuation or switch, add-on of other antidiabetic drugs, pregnancy, or the end of the study period (31 December 2017), whichever came first. Continuous sulfonylurea use was determined based on prescription refill records with a 30-day grace period. For patients who discontinued sulfonylurea therapy, an additional 30-day period was added to the follow-up period in order to observe a MACE that might shortly occur after sulfonylurea treatment cessation.

The PS, the probability of initiating mitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy, was estimated using multivariable logistic regression models, conditional on all factors listed in Table 1. Each new cardiac mitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy user was matched with a new cardiac mitoK$_{ATP}$ channel low-affinity sulfonylurea monotherapy user based on the cohort entry date (±90 days), duration from the first diabetes diagnosis to cohort entry in deciles, adapted Diabetes Complications Severity Index (aDCSI; 0, 1, 2, and $\geq$3), and closest PS corresponding to the nearest neighboring PS-matching scheme without a replacement and with a caliper width of 0.02 of the estimated PS (21).

Table 1—MitoK$_{ATP}$ channel high-affinity and low-affinity sulfonylurea user characteristics before and after matching among patients with diabetes

Characteristics[a]	Before matching			After matching[b]		
	MitoK$_{ATP}$ channel high-affinity sulfonylureas (*n* = 34,138)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (*n* = 130,527)	Standardized difference[c]	MitoK$_{ATP}$ channel high-affinity sulfonylureas (*n* = 33,727)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (*n* = 33,727)	Standardized difference[c]
Age (years), mean (± SD)	59.2 (± 13.1)	59.2 (± 12.7)	0.001	59.1 (± 13.1)	58.9 (± 13.0)	0.013
Sex (male), *n* (%)	18,419 (54.0)	67,815 (52.0)	0.040	18,170 (53.9)	18,248 (54.1)	0.005
Period from the first diabetes diagnosis to the initial use of medication (years), mean ± (SD)	0.57 (± 1.23)	0.74 (± 1.40)	0.128	0.57 (± 1.22)	0.57 (± 1.22)	<0.001
Entry years, *n* (%)						
2007	3,959 (11.6)	9,496 (7.3)	0.146	3,930 (11.7)	3,910 (11.6)	0.002
2008	6,164 (18.1)	17,152 (13.1)	0.134	6,087 (18.1)	6,082 (18.0)	<0.001
2009	5,653 (16.6)	17,536 (13.4)	0.087	5,604 (16.6)	5,684 (16.9)	0.006
2010	4,313 (12.6)	15,919 (12.2)	0.013	4,268 (12.7)	4,232 (12.6)	0.003
2011	3,482 (10.2)	14,714 (11.3)	0.035	3,437 (10.2)	3,449 (10.2)	0.001
2012	2,914 (8.5)	13,833 (10.6)	0.071	2,871 (8.5)	2,851 (8.5)	0.002
2013	2,610 (7.7)	12,443 (9.5)	0.068	2,566 (7.6)	2,573 (7.6)	0.001
2014	2,030 (6.0)	11,081 (8.5)	0.099	2,000 (5.9)	1,989 (5.9)	0.001
2015	1,676 (4.9)	10,106 (7.7)	0.117	1,649 (4.9)	1,627 (4.8)	0.003
2016	1,337 (3.9)	8,247 (6.3)	0.110	1,315 (3.9)	1,330 (3.9)	0.002
Diabetes severity indicators, *n* (%)						
No. of diabetes drugs						
0	25,233 (73.9)	90,340 (69.2)	0.100	25,021 (74.2)	25,158 (74.6)	0.009
1	7,505 (22.0)	34,586 (26.5)	0.107	7,380 (21.9)	7,211 (21.4)	0.012
≥2	1,400 (4.1)	5,601 (4.3)	0.009	1,326 (3.9)	1,358 (4.0)	0.005
aDCSI						
0	25,301 (74.1)	95,386 (73.1)	0.023	25,234 (74.8)	25,234 (74.8)	<0.001
1	4,785 (14.0)	20,522 (15.7)	0.048	4,725 (14.0)	4,725 (14.0)	<0.001
2	2,915 (8.5)	10,625 (8.1)	0.014	2,772 (8.2)	2,772 (8.2)	<0.001
≥3	1,137 (3.3)	3,994 (3.1)	0.015	996 (3.0)	996 (3.0)	<0.001
Metabolic acidosis	28 (0.1)	94 (0.1)	0.004	27 (0.1)	28 (0.1)	0.001
Measures of health care utilization, *n* (%)						
No. of physician visits						
Diabetes-related						
First tertile	18,875 (55.3)	61,831 (47.4)	0.152	18,646 (55.3)	18,652 (55.3)	<0.001
Second tertile	4,614 (13.5)	19,851 (15.2)	0.049	4,557 (13.5)	4,600 (13.6)	0.004
Third tertile	10,649 (31.2)	48,845 (37.4)	0.134	10,524 (31.2)	10,475 (31.1)	0.003
Nondiabetes-related						
First tertile	12,160 (35.6)	44,615 (34.2)	0.030	12,092 (35.9)	12,485 (37.0)	0.024
Second tertile	10,567 (31.0)	42,434 (32.5)	0.034	10,479 (31.1)	10,283 (30.5)	0.013
Third tertile	11,411 (33.4)	43,478 (33.3)	0.002	11,156 (33.1)	10,959 (32.5)	0.012

Continued on p. 1279

Table 1—Continued

Characteristics[a]	Before matching: MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 34,138)	Before matching: MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 130,527)	Before matching: Standardized difference[c]	After matching[b]: MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 33,727)	After matching[b]: MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 33,727)	After matching[b]: Standardized difference[c]
No. of hospital admissions						
Diabetes-related						
0	31,745 (93.0)	123,448 (94.6)	0.070	31,537 (93.5)	31,606 (93.7)	0.008
1	1,889 (5.5)	5,716 (4.4)	0.053	1,756 (5.2)	1,702 (5.1)	0.007
2	504 (1.5)	1,363 (1.0)	0.039	434 (1.3)	419 (1.2)	0.004
Nondiabetes-related						
0	30,445 (89.2)	118,824 (91.0)	0.065	30,242 (89.7)	30,368 (90.0)	0.012
1	2,512 (7.4)	8,535 (6.5)	0.032	2,430 (7.2)	2,382 (7.1)	0.006
2	1,181 (3.5)	3,168 (2.4)	0.061	1,055 (3.1)	977 (2.9)	0.014
Number of ER visits						
Diabetes-related						
0	33,012 (96.7)	126,857 (97.2)	0.029	32,671 (96.9)	32,660 (96.8)	0.002
1	830 (2.4)	2,870 (2.2)	0.015	791 (2.4)	812 (2.4)	0.004
2	296 (0.9)	800 (0.6)	0.030	265 (0.8)	255 (0.8)	0.003
Nondiabetes-related						
0	26,745 (78.3)	104,375 (80.0)	0.041	26,581 (78.8)	26,789 (79.4)	0.015
1	4,273 (12.5)	16,272 (12.5)	0.002	4,188 (12.4)	4,123 (12.2)	0.006
2	3,120 (9.1)	9,880 (7.6)	0.057	2,958 (8.8)	2,815 (8.4)	0.015
Monthly income-based insurance premium, n (%)						
First tertile	8,623 (25.3)	31,840 (24.4)	0.020	8,476 (25.1)	8,452 (25.1)	0.002
Second tertile	14,303 (41.9)	51,759 (39.7)	0.045	14,119 (41.9)	14,194 (42.1)	0.005
Third tertile	11,212 (32.8)	46,928 (36.0)	0.066	11,132 (33.0)	11,081 (32.9)	0.003
Hospital level, n (%)						
Academic medical centers	2,699 (7.9)	9,211 (7.1)	0.032	2,628 (7.8)	2,581 (7.7)	0.005
Metropolitan hospitals	4,286 (12.6)	15,817 (12.1)	0.013	4,221 (12.5)	4,095 (12.1)	0.011
Local community hospitals	3,928 (11.5)	10,839 (8.3)	0.106	3,751 (11.1)	3,752 (11.1)	<0.001
Physician clinics	22,375 (65.5)	92,277 (70.7)	0.115	22,277 (66.1)	22,346 (66.3)	0.004
No medical record	850 (2.5)	2,383 (1.8)	0.115	850 (2.5)	953 (2.8)	0.004
Comorbidities, n (%)						
CV diseases						
Heart failure	1,272 (3.7)	4,954 (3.8)	0.004	1,208 (3.6)	1,182 (3.5)	0.004
Hypertension	16,045 (47.0)	68,861 (52.8)	0.119	15,827 (46.9)	15,407 (45.7)	0.025
Cerebrovascular disease	1,611 (4.7)	5,822 (4.5)	0.033	1,537 (4.6)	1,513 (4.5)	0.005
Ischemic heart disease	3,841 (11.3)	16,075 (12.3)	0.012	3,747 (11.1)	3,801 (11.3)	0.003
Arrhythmia	211 (0.6)	754 (0.6)	0.002	194 (0.6)	203 (0.6)	0.001
Dyslipidemia	9,391 (27.5)	47,594 (36.5)	0.199	9,334 (27.7)	9,212 (27.3)	0.008
Peripheral arterial disease	575 (1.7)	2,455 (1.9)	0.015	555 (1.7)	557 (1.7)	<0.001
Coronary revascularization	95 (0.3)	356 (0.3)	0.004	92 (0.3)	110 (0.3)	0.001

Continued on p. 1280

Table 1—Continued

Characteristics[a]	Before matching			After matching[b]		
	MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 34,138)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 130,527)	Standardized difference[c]	MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 33,727)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 33,727)	Standardized difference[c]
Cardiomyopathy	73 (0.2)	254 (0.2)	0.001	67 (0.2)	69 (0.2)	0.010
Venous thromboembolism	95 (0.3)	339 (0.3)	0.004	88 (0.3)	85 (0.3)	0.002
Pulmonary disease						
Asthma	1,761 (5.2)	7,025 (5.4)	0.010	1,728 (5.1)	1,662 (4.9)	0.009
COPD	2,066 (6.1)	6,966 (5.3)	0.031	1,964 (5.8)	1,887 (5.6)	0.010
Pneumonia	1,491 (4.4)	4,653 (3.6)	0.041	1,376 (4.1)	1,361 (4.0)	0.002
Mental disease						
Depression	1,174 (3.4)	4,388 (3.4)	0.004	1,137 (3.4)	1,083 (3.2)	0.009
Anxiety	3,526 (10.3)	14,540 (11.1)	0.026	3,477 (10.3)	3,420 (10.1)	0.006
Schizophrenia	333 (1.0)	1,081 (0.8)	0.016	326 (1.0)	309 (0.9)	0.005
Neurologic disorders						
Dementia	569 (1.7)	1,741 (1.3)	0.027	532 (1.6)	512 (1.5)	0.005
Epilepsy	146 (0.4)	524 (0.4)	0.004	144 (0.4)	152 (0.5)	0.004
Bone and joint disorders						
Fracture	1,642 (4.8)	5,796 (4.4)	0.018	1,592 (4.7)	1,574 (4.7)	0.003
Osteoporosis	919 (2.7)	3,422 (2.6)	0.004	891 (2.6)	901 (2.7)	0.002
Osteoarthritis	5,244 (15.4)	21,048 (16.1)	0.021	5,159 (15.3)	5,132 (15.2)	0.002
Anemia	1,135 (3.3)	4,227 (3.2)	0.005	1,067 (3.2)	1,053 (3.1)	0.002
Thyroid disease	918 (2.7)	3,758 (2.9)	0.012	908 (2.7)	940 (2.8)	0.006
Chronic liver disease	4,497 (13.2)	18,498 (14.2)	0.029	4,432 (13.1)	4,393 (13.0)	0.003
Chronic renal disease	2,538 (7.4)	9,313 (7.1)	0.012	2,299 (6.8)	2,240 (6.6)	0.007
Obesity or weight gain	799 (2.3)	3,377 (2.6)	0.016	792 (2.4)	781 (2.3)	0.002
Tobacco use	261 (0.8)	1,047 (0.8)	0.004	258 (0.8)	262 (0.8)	0.001
Alcohol-related disorder	246 (0.7)	739 (0.6)	0.019	236 (0.7)	240 (0.7)	0.001
Hyperkalemia	78 (0.2)	182 (0.1)	0.021	56 (0.2)	38 (0.1)	0.014
Hypokalemia	384 (1.1)	1,151 (0.9)	0.024	363 (1.1)	347 (1.0)	0.005
Hypoglycemia	30 (0.1)	63 (0.1)	0.015	22 (0.1)	17 (0.1)	0.006
Autoimmune diseases	942 (2.8)	3,240 (2.5)	0.017	912 (2.7)	891 (2.6)	0.004
Cancer	1,894 (5.6)	5,925 (4.5)	0.046	1,808 (5.4)	1,758 (5.2)	0.007
Comedication, n (%)[b]						
Diabetes medication						
Biguanide	6,975 (20.4)	32,961 (25.3)	0.117	6,896 (20.5)	6,767 (20.1)	0.010
Meglitinides	959 (2.8)	3,734 (2.9)	0.003	902 (2.7)	919 (2.7)	0.003
Thiazolidinediones	220 (0.6)	1,034 (0.8)	0.018	216 (0.6)	230 (0.7)	0.005
α-Glucosidase inhibitors	658 (1.9)	3,282 (2.5)	0.040	646 (1.9)	677 (2.0)	0.007
DPP-4 inhibitors	305 (0.9)	1,735 (1.3)	0.042	292 (0.9)	288 (0.9)	0.001
Insulin						
Short-acting	1,323 (3.9)	3,659 (2.8)	0.060	1,199 (3.6)	1,172 (3.5)	0.004
Intermediate-acting	268 (0.8)	663 (0.5)	0.035	238 (0.7)	214 (0.6)	0.009
Premixed	210 (0.6)	541 (0.4)	0.028	192 (0.6)	196 (0.6)	0.002
Long-acting	92 (0.3)	378 (0.3)	0.004	87 (0.3)	97 (0.3)	0.006

Continued on p. 1281

Table 1—Continued

Characteristics[a]	Before matching			After matching[b]		
	MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 34,138)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 130,527)	Standardized difference[c]	MitoK$_{ATP}$ channel high-affinity sulfonylureas (n = 33,727)	MitoK$_{ATP}$ channel low-affinity sulfonylureas (n = 33,727)	Standardized difference[c]
CV medication						
ACE inhibitors	2,922 (8.6)	12,474 (9.6)	0.035	2,873 (8.5)	2,773 (8.2)	0.011
Angiotensin receptor blockers	5,475 (16.0)	28,635 (21.9)	0.153	5,412 (16.1)	5,409 (16.0)	<0.001
α-Blockers	1,013 (3.0)	3,729 (2.9)	0.007	983 (2.9)	1,008 (3.0)	0.004
β-Blockers	8,155 (23.9)	33,605 (25.8)	0.043	8,037 (23.8)	7,850 (23.3)	0.013
Calcium channel blockers						
Dihydropyridines	10,323 (30.2)	45,151 (34.6)	0.095	10,192 (30.2)	9,864 (29.3)	0.021
Nondihydropyridines	1,291 (3.8)	4,684 (3.6)	0.010	1,239 (3.7)	1,223 (3.6)	0.003
Diuretics						
Thiazides	8,263 (24.2)	37,413 (28.7)	0.103	8,145 (24.2)	7,976 (23.7)	0.012
Loop	2,526 (7.4)	8,160 (6.3)	0.045	2,357 (7.0)	2,290 (6.8)	0.008
Potassium-sparing agents	1,397 (4.1)	4,703 (3.6)	0.025	1,320 (3.9)	1,233 (3.7)	0.014
Antiplatelets	6,595 (19.3)	25,647 (19.7)	0.008	6,411 (19.0)	6,309 (18.7)	0.008
Anticoagulants	565 (1.7)	1,977 (1.5)	0.011	510 (1.5)	496 (1.5)	0.003
Lipid-lowering agents						
Statins	4,348 (12.7)	23,218 (17.8)	0.143	4,304 (12.8)	4,264 (12.6)	0.004
Others	2,025 (5.9)	8,673 (6.6)	0.029	1,990 (5.9)	1,947 (5.8)	0.005
Nitrates	1,377 (4.0)	4,794 (3.7)	0.019	1,306 (3.9)	1,277 (3.8)	0.004
Antiarrhythmic agents	604 (1.8)	1,970 (1.5)	0.020	561 (1.7)	576 (1.7)	0.003
Digoxin	570 (1.7)	2,128 (1.6)	0.003	549 (1.6)	519 (1.5)	0.007
Erythropoietin	210 (0.6)	264 (0.2)	0.065	64 (0.2)	57 (0.2)	0.005
Potassium channel opener (nicorandil)	336 (1.0)	1,562 (1.2)	0.020	324 (1.0)	341 (1.0)	0.005
Inhibitors of mitochondrial PT pore						
Cyclosporin A	24 (0.1)	72 (0.1)	0.006	20 (0.1)	22 (0.1)	0.002
Adenosine	22 (0.1)	94 (0.1)	0.003	22 (0.1)	21 (0.1)	0.001
Opioids	7,287 (21.4)	27,329 (20.9)	0.010	7,100 (21.1)	7,017 (20.8)	0.006
Anti-inflammatory agents						
NSAIDs	21,285 (62.4)	83,233 (63.8)	0.030	21,017 (62.3)	20,762 (61.6)	0.015
Steroids	7,150 (20.9)	26,166 (20.1)	0.022	6,964 (20.7)	6,725 (19.9)	0.018
PPI	1,866 (5.5)	6,450 (4.9)	0.024	1,758 (5.2)	1,677 (5.0)	0.011
Anticonvulsants	1,698 (5.0)	6,237 (4.8)	0.009	1,614 (4.8)	1,648 (4.9)	0.005
Antidepressants	2,498 (7.3)	9,900 (7.6)	0.010	2,449 (7.3)	2,457 (7.3)	0.001
Antipsychotics	3,117 (9.1)	10,890 (8.3)	0.028	3,003 (8.9)	2,969 (8.8)	0.004

COPD, chronic obstructive pulmonary disease; CV, cardiovascular; ER, emergency room; NSAID, nonsteroidal anti-inflammatory drug; PT, permeability transition; PPI, proton pump inhibitor. [a]All comorbidities, diabetes severity indicators, and aDSCI/metabolic acidosis scores were measured in the year preceding the cohort entry date. [b]Comedications were evaluated 6 months before the cohort entry date. [c]Standardized difference >0.1 represents meaningful differences between the two groups.

Table 2—Comparison of risk of cardiovascular adverse events between mitoK_{ATP} channel high-affinity and low-affinity sulfonylurea monotherapy

	MitoK_{ATP} channel high-affinity sulfonylureas (n = 33,727)			MitoK_{ATP} channel low-affinity sulfonylureas (n = 33,727)				
	No. of events	Total no. of person-years	Incidence rate/100 person-years	No. of events	Total no. of person-years	Incidence rate/100 person-years	HR (95% CI)	aHR (95% CI)[c]
Primary outcomes								
3-point MACE[a]	274	18,959	1.45 (1.28–1.63)	269	24,498	1.10 (0.97–1.24)	1.22 (1.03–1.44)	1.21 (1.03–1.44)
Secondary outcomes								
MI	63	19,023	0.33 (0.26–0.42)	73	24,607	0.30 (0.24–0.37)	1.05 (0.75–1.47)	1.04 (0.75–1.46)
Ischemic stroke	196	18,969	1.03 (0.90–1.19)	189	24,511	0.77 (0.67–0.89)	1.23 (1.01–1.50)	1.23 (1.02–1.50)
Cardiovascular death[b]	25	19,033	0.13 (0.09–0.19)	12	24,618	0.05 (0.03–0.09)	2.62 (1.31–5.22)	2.61 (1.31–5.20)
Arrhythmia	65	19,002	0.34 (0.27–0.44)	65	24,571	0.27 (0.21–0.34)	1.26 (0.90–1.78)	1.26 (0.89–1.78)
All-cause mortality	208	19,029	1.09 (0.95–1.25)	206	24,613	0.84 (0.73–0.96)	1.22 (1.01–1.48)	1.21 (1.00–1.47)
Severe hypoglycemia	293	18,953	1.55 (1.38–1.73)	236	24,538	0.96 (0.85–1.09)	1.45 (1.22–1.72)	1.44 (1.22–1.72)

[a]Three-point MACE include MI, ischemic stroke, and cardiovascular death. [b]Cardiovascular death was defined as death due to MI or ischemic stroke. [c]Adjusted for the deciles of PS.

Outcome Definition

The primary outcome was MACE, defined as MI- or ischemic stroke–related hospitalization or cardiovascular mortality (Supplementary eTable 1). The employed algorithms for identifying MI and ischemic stroke events were found to be highly accurate in the analyzed database, with a reported positive predictive value of 88% and 88.4% for MI and ischemic stroke, respectively (22,23). Secondary outcomes included individual components of the three-point MACE, arrhythmias, hypoglycemia, and all-cause mortality.

Potential Confounders

Multiple characteristic dimensions were considered, including patient demographic and clinical features, such as age, sex, proxy indicators of diabetes severity (e.g., aDCSI), comorbidities (e.g., cardiovascular or pulmonary disease), and comedications (e.g., different types of antidiabetic agents and agents that may activate or inhibit cardiac mitoK_{ATP} channels). All factors were evaluated in the year preceding cohort entry, except for comedications evaluated in the previous 6 months. All confounders are detailed in Supplementary eTable 1.

Additional Analyses

Multiple predefined sensitivity analyses were performed. First, to avoid bias from sulfonylurea therapy discontinuation due to the occurrence of the examined outcomes, we adopted a 1-year intent-to-treat analysis. Second, a 14-day and a 60-day grace period was used to redefine continuous sulfonylurea use, respectively. Third, to minimize medication adherence–related confounding, both sulfonylurea groups were restricted to patients with high medication adherence, defined as medication possession ratios $\geq$0.8 (24). Fourth, we used inverse probability of censoring weights that considered covariates measured at monthly intervals during follow-up in order to address differential censoring owing to differential switching between the two groups, as detailed in the Supplementary eApproach. Fifth, to avoid depletion-of-susceptible bias (25), the two groups were followed for a maximum period of 30 days. Sixth, all-cause mortality was considered as a competing event to the examined outcomes (excluding the death outcome). Seventh, a PS-based inverse probability of treatment weighting approach was adopted to avoid sample size reductions (26). Eighth, we broadened the definition for cardiovascular death, which included all cardiovascular mortality events. Ninth, unmeasured confounding was addressed with the implementation of the rule-out approach (27) and high-dimensional PS-matched analyses (28). To further address the lack of information regarding hemoglobin A_{1c} levels in the DMHD, PS calibration was performed with additional information from electronic health care records of the Tri-Service General Hospital, a tertiary medical center (29). The approaches to addressing unmeasured confounding Supplementary eApproach. Finally, we also conducted subgroup analyses that restricted the two comparison groups to pancreas high-affinity sulfonylurea (i.e., glipizide vs. gliclazide) and pancreas low-affinity sulfonylurea (i.e., glyburide vs. glimepiride) users, as well as compared glyburide only with gliclazide/glimepiride. Furthermore, to assess whether the observed MACE risk was mediated through hypoglycemia, hypoglycemic events during follow-up were additionally adjusted for.

Statistical Analysis

A standardized difference with a magnitude $>$0.1 was used to determine imbalances in the examined characteristics (30). The Kaplan-Meier method was used to estimate the cumulative incidence of MACE, arrhythmias, hypoglycemia, and all-cause mortality. Cox proportional hazard models were used to estimate hazard ratios (HRs) for each outcome between the two groups. The proportionality assumption for performing Cox regression analysis was examined through Schoenfeld residuals, in which all of the analyses met the assumption. We further assessed different daily dosage and duration of mitoK_{ATP} channels high-affinity sulfonylurea monotherapy. To further mitigate residual confounding, all analyses were adjusted for PS deciles after the matching procedure. Data cleaning and statistical analyses were performed using SAS software version 9.4 (College Station, TX).

RESULTS

A total of 164,665 patients with diabetes aged $\geq$20 years who received

Table 3—Comparison of MACE[a] risk with different mito$_{KATP}$ channel high-affinity sulfonylurea doses and durations compared with any use of mitoK$_{ATP}$ channel low-affinity sulfonylureas

	No. of events	Total no. of person-years	Incidence rate/100 person-years	HR (95% CI)	aHR (95% CI)[b]
MitoK$_{ATP}$ channel-low affinity sulfonylureas	269	24,498	1.10 (0.97–1.24)	Reference	Reference
Cumulative duration of mitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy					
MitoK$_{ATP}$ channel high-affinity sulfonylureas (days)					
1–90 days	153	1,906	8.03 (6.85–9.41)	4.72 (3.64–6.11)	4.67 (3.61–6.06)
91–180 days	26	1,780	1.46 (0.99–2.14)	1.19 (0.78–1.81)	1.17 (0.77–1.79)
181–365 days	42	2,671	1.57 (1.16–2.13)	1.29 (0.92–1.82)	1.27 (0.91–1.79)
>365 days	53	12,602	0.42 (0.32–0.55)	0.41 (0.31–0.56)	0.41 (0.31–0.56)
Average daily dose of mitoK$_{ATP}$ channel high-affinity sulfonylurea					
MitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy					
<0.5 DDD	158	11,464	1.38 (1.18–1.61)	1.15 (0.94–1.40)	1.16 (0.96–1.42)
0.5–1 DDD	91	6,339	1.44 (1.17–1.76)	1.23 (0.97–1.56)	1.21 (0.95–1.53)
>1 DDD	25	1,157	2.16 (1.46–3.20)	1.76 (1.17–2.65)	1.65 (1.09–2.49)

DDD, defined daily dose. [a]Three-point MACEs include MI, ischemic stroke, and cardiovascular death. [b]Adjusted for the deciles of PS.

sulfonylurea monotherapy were identified as the eligible study cohort (mean age 59.2 years; 52.4% male) after the exclusion criteria were applied (Supplementary eFig. 1). Among these patients, 34,138 and 130,257 were initiators of mitoK$_{ATP}$ channel high-affinity and channel low-affinity sulfonylurea monotherapy, respectively. The number of glipizide and glyburide users among the mitoK$_{ATP}$ channel-high affinity group was 12,714 (37.7%) and 21,013 (62.3%), respectively, while gliclazide and glimepiride accounted for 11,443 (33.9%) and 22,284 (66.1%) of the mitoK$_{ATP}$ channel low-affinity sulfonylureas users, respectively. After 1:1 matching, 33,727 patients were included in each group. The mean treatment duration ranged from 6.8 to 8.9 months, with both groups truncated to a similar extent for various reasons (Supplementary eTable 2). The cumulative incidence rates of the primary and secondary outcomes are displayed in Supplementary eFigs. 2 and 3.

Before matching, most examined characteristics were similar between the two groups (Table 1). However, the mitoK$_{ATP}$ channel high-affinity sulfonylurea group had larger proportions of patients diagnosed with hypertension and dyslipidemia and receiving biguanide and angiotensin receptor blockers than the mitoK$_{ATP}$ channel low-affinity sulfonylurea group. After matching, all factors were well balanced between the two groups.

The MACE incidence rate/100 person-years was 1.45 (95% CI 1.28–1.63) in mitoK$_{ATP}$ channel high-affinity sulfonylurea initiators and 1.10 (95% CI 0.97–1.24) in mitoK$_{ATP}$ channel low-affinity sulfonylurea initiators (Table 2). MitoK$_{ATP}$ channel high-affinity sulfonylurea use was associated with a 1.21-fold (95% CI 1.03–1.44) increased MACE risk compared with mitoK$_{ATP}$ channel low-affinity sulfonylurea use. In the analyses of individual components of MACE, mitoK$_{ATP}$ channel high-affinity sulfonylureas versus mitoK$_{ATP}$ channel low-affinity sulfonylureas were associated with a 2.61-fold (95% CI 1.31–5.20) increased cardiovascular death risk and 1.23-fold (95% CI 1.02–1.50) increased ischemic stroke risk, while the estimate for MI was not statistically significant. The adjusted HR (aHR) was 1.21 (95% CI 1.00–1.47) for all-cause mortality and 1.44 (95% CI 1.22–1.72) for severe hypoglycemia. Table 3 indicates that the mitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy duration was inversely related to an increased risk of three-point MACE, with the highest risk observed within 90 days of therapy (aHR 4.67 [95% CI 3.61–6.06]), and mitoK$_{ATP}$ channel high-affinity sulfonylureas used at a higher daily dose (more than one defined daily dose) were associated with a 1.65-fold (95% CI 1.09–2.49) increased MACE risk.

The calculated number needed to harm revealed that a total of 286 patients would need to receive cardiac mitoK$_{ATP}$ channel high-affinity sulfonylureas instead of mitoK$_{ATP}$ channel low-affinity sulfonylureas in order to cause an additional MACE (Supplementary eTable 3).

The main findings were robust to most of the sensitivity analyses, such as adoption of high-dimensional PS-matched analysis (Fig. 1). Employment of the intention-to-treatment analysis, however, led to attenuated risk. The rule-out analysis indicated that an unmeasured confounder was unlikely to fully explain our main findings (Supplementary Fig. 4). Subgroup analyses revealed that sulfonylurea pancreas high-affinity did not act as an effect modifier of our examined associations, despite the limited sample sizes.

CONCLUSIONS

In this nationwide cohort study of patients with diabetes, cardiac mitoK$_{ATP}$ channel high-affinity sulfonylurea initiation was associated with a 21% increased risk in the three-point MACE compared with cardiac mitoK$_{ATP}$ channel low-affinity sulfonylurea initiation. The association was primarily driven by nonfatal ischemic stroke and cardiovascular death, with a downward trend over time in the cumulative duration analysis of mitoK$_{ATP}$ channel high-affinity sulfonylurea monotherapy. The increased MACE outcome risk persisted in most of the sensitivity analyses. Overall, the data suggest that the specificity of sulfonylureas to cardiac

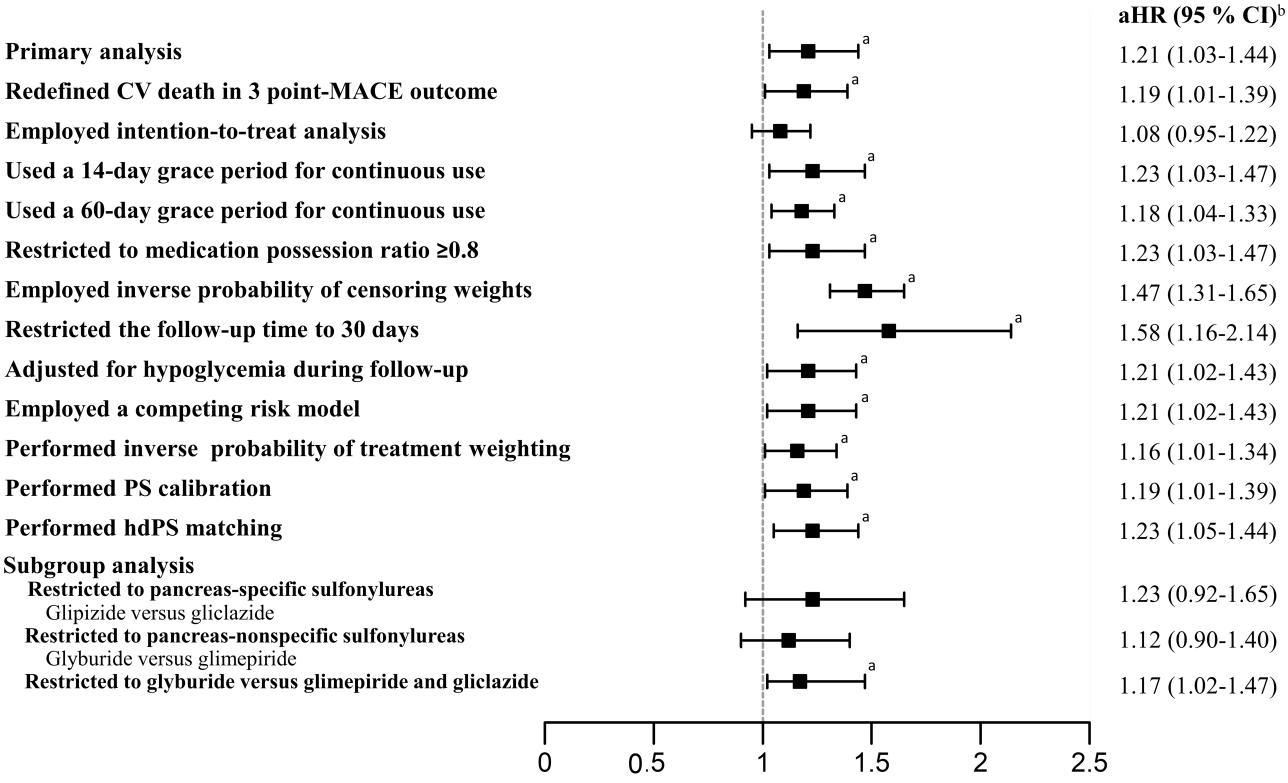

Figure 1—Sensitivity analysis of associated MACE between mitoK_{ATP} channel high-affinity sulfonylureas and mitoK_{ATP} channel low-affinity sulfonylureas. CV, cardiovascular; hdPS, high-dimension PS. [a]$P < 0.05$. [b]Adjusting for the estimated PSs in deciles.

mitochondrial potassium channels is a major determinant of the sulfonylurea intraclass difference in the cardiovascular risk among patients with diabetes.

Our findings on the different risks of MACE between sulfonylureas due to their specificity to cardiac mitochondrial potassium channels are supported by previous preclinical data. IPC plays the most pivotal role in myocardial protection (16) and is triggered by ischemia and reperfusion of the heart; subsequently, it activates downstream intracellular signaling pathways and opens inner membrane mitoK_{ATP} channels that produce mediators of cardioprotection (31). These processes in turn could reduce infarction size, restore cardiac function, and prevent myocardial injuries (14). In vitro and animal studies revealed an infarct size increase with glyburide or glipizide use through blocking the cardiac mitoK_{ATP} channels, as opposed to revealing no effect on infarct size with the use of gliclazide, glimepiride, or tolbutamide, which have low affinities to mitoK_{ATP} channels (17–20). This study translates the preclinical data of sulfonylureas' low and high affinity to cardiac mitoK_{ATP} channels into a major factor accounting for an intraclass difference in cardiovascular risk among patients with diabetes.

MitoK_{ATP} channel low-affinity sulfonylureas gliclazide and glimepiride compared with standard glucose control therapy and dipeptidyl peptidase-4 (DPP-4) inhibitors, respectively, caused no excess in the risk of adverse cardiovascular events in two large randomized controlled trials (32,33). The Action in Diabetes and Vascular Disease Preterax and Diamicron Modified Release Controlled-Evaluation (ADVANCE) trial indicated that glucose control intensification using gliclazide modified release had no significant effect on major macrovascular events compared with standard glucose control involving other antidiabetic medications (33). The Cardiovascular Outcome Study of Linagliptin vs. Glimepiride in Type 2 Diabetes (CAROLINA) also revealed no difference in time to occurrence of three-point MACE between the use of linagliptin, a DPP-4 inhibitor, and glimepiride in patients with diabetes at high cardiovascular risk (HR 0.98 [95.47% CI 0.84–1.14]) (32).

Our duration-response analysis revealed that the risk of MACE varied by duration of mitoK_{ATP} channel high-affinity sulfonylurea, with a higher risk within the first 90 days of treatment initiation. Animal studies have found that IPC causes reduced infarct size (34) and augments postischemic cardiac function within a day (35), indicating the impact of IPC on heart should not be latent. Additionally, IPC has been reported to cause two phases of protection, the "first window" and the "second window of protection," protecting the heart for about 2 h and 1–3 days, respectively, after initiation (36). Although the findings from animal studies cannot be directly extrapolated to humans, the existing experimental evidence can still be derived indirectly as the time course observed from these studies collaborate with the duration findings.

Pancreas selectivity of sulfonylureas has also been speculated to be a determinant of associated adverse cardiovascular events (37). Several sulfonylureas, such as glyburide and glimepiride, with no specificity to β-cells in the pancreas were hypothesized to lead to a higher adverse cardiovascular disease incidence than pancreas-specific sulfonylureas due to their suspected binding to receptors

on cardiomyocytes and smooth muscle cells (37). However, a well-designed cohort study found that pancreas-nonspecific sulfonylureas (glyburide and glimepiride) were not associated with an increased adverse cardiovascular event risk when compared with pancreas-specific sulfonylureas (gliclazide, glipizide, and tolbutamide) (12). Another cohort study in patients initiating metformin monotherapy observed that adding or switching to pancreas-nonspecific sulfonylureas resulted in a similar adverse cardiovascular event risk to that in patients who stayed on metformin monotherapy (11). Additionally, our subgroup analyses revealed that pancreas specificity of sulfonylureas was not an effect modifier of the examined associations, despite the limited sample sizes. Collectively, these data do not support the view that sulfonylurea pancreas selectivity is the main factor responsible for the associated MACE.

Our observed incidence rates of cardiovascular death are much lower than the three abovementioned relevant studies, including the CAROLINA trial. For example, the incidence rate/100 person-years of cardiovascular death were 0.13 and 0.05 for mitoK$_{ATP}$ channel high-affinity and low-affinity sulfonylureas, respectively, both of which were much lower than the incidence rates in the other studies, ranging from 0.9 to 2.2/100 person-years. This discrepancy in cardiovascular mortality rates may be due to the fact that the sulfonylurea users in our study were younger, had shorter duration of diabetes, and possessed fewer comorbidities compared with the patients in other studies. For instance, the mean duration of diabetes among our patients was $<$1 year as opposed to the mean duration of 6 years in the CAROLINA study. Additionally, only $\sim$11% of our study cohort had a history of coronary artery disease, which is two to three times less than that of the patients included in the aforementioned studies. These attributes of our study subjects' characteristics may indicate that the sulfonylurea users were at a lower risk of MACE, among whom the impact of inhibition of cardiac mitoK$_{ATP}$ channels on the cardiovascular outcomes may be less profound.

The observed risk in the current study was driven by ischemic stroke and cardiovascular mortality rather than MI. IPC has been found not only to exert its cardioprotection function before an extended ischemia insult, but also to function early in perfusion following a sustained severe or potentially lethal ischemia, which reduces reperfusion injury (38). Accordingly, inhibition of IPC may be expected to increase the incidence of MI and/or cause worse outcomes after MI. Yet, owing to the aforementioned characteristics of our included patients and not all fatal MI requiring prior hospitalization, inhibition of IPC would not cause much difference in the incidence rate of MI, but instead would have a profound impact on ischemia reperfusion following a sustained severe or potential lethal MI, leading to worsened outcomes. This may explain the observed twofold increase in cardiovascular mortality. Similarly, the inhibition of IPC was proposed to underlie an excess increase in cardiovascular mortality from the use of tolbutamide, a K$_{ATP}$ channel inhibitor, compared with diet treatment in the University Group Diabetes Program, an early randomized trial (39). Furthermore, IPC has also been found to have a neuroprotective effect involving the activation of mitoK$_{ATP}$ channels. Based on past studies, mitoK$_{ATP}$ channel activation is reported to play an important role in the development of tolerance to forebrain and cerebral ischemia, with evidence showing the neuroprotective effect abolished by mitoK$_{ATP}$ channel blockers. Given these findings, it may also explain the observed increased risk in ischemic stroke.

Although hypoglycemic episodes have been reported to substantially increase the cardiovascular disease risk (40), our observed associations are probably not mediated by hypoglycemia, as this factor was balanced at baseline between the two groups, and only nine patients experienced hypoglycemia before the occurrence of a MACE outcome during follow-up. Further adjustment of hypoglycemic events during follow-up led to results similar to the main findings.

Furthermore, the observed risk was attenuated with the adoption of the intention-to-treat analysis. After checking the percentage of patients who switched between the two types of sulfonylureas in the main analysis, we found a higher percentage of patients switching from mitoK$_{ATP}$ channel high-affinity sulfonylurea to mitoK$_{ATP}$ channel low-affinity sulfonylureas (15.5%) compared with vice versa (4.2%). This higher percentage of switching from the former may explain why the risk observed was attenuated and nonsignificant when performing the intention-to-treat analysis.

Our overall findings support the notion that sulfonylurea specificity to cardiac mitoK$_{ATP}$ channels is associated with an increased MACE risk, which in turn explains the intraclass difference in the MACE risk among different sulfonylureas. Considering our findings on cardiovascular outcomes (especially cardiovascular death) and hypoglycemic events, we strongly recommend using sulfonylureas with low affinities to cardiac mitoK$_{ATP}$ channels, such as gliclazide and glimepiride, for diabetes management where sulfonylurea therapy is preferred. Conversely, health care professionals need to be vigilant in monitoring patients being treated with mitoK$_{ATP}$ channel high-affinity sulfonylureas for any signs of adverse cardiovascular events.

Our study has several strengths. First, to our knowledge, this is the first observational study to evaluate the important pharmacological properties of sulfonylureas with regard to their different specificities to cardiac mitochondrial channels and their association with the risk of MACE. Second, we implemented few exclusion criteria to analyze a nationwide health care claim database of patients with diabetes, thereby assuring high generalizability of our findings. Third, we performed multiple strategies to minimize confounding and bias, such as adopting a new user design with an active comparator analysis, performing PS matching and inverse weighting analyses, and measuring incident cardiovascular outcomes. Fourth, misclassification in the identified MI and ischemic stroke events is expected to be low because the accuracy of the algorithms used for cardiovascular event identification was reported to be high (22,23).

The current study has several limitations. First, although all of the measured factors were balanced after PS matching, unmeasured confounders, such as body weight and smoking, could still be potential threats to our reported findings. While the rule-out analyses based on the primary results (aHR 1.21) suggest that an unmeasured confounder could not fully contribute to our primary finding, the room for potential unmeasured confounding is still possible, especially taking

into account on its possible effect on the lower bound of the 95% CI of the aHR of our results. Second, in order to increase the comparability between the two groups, we analyzed patients newly diagnosed with diabetes who were receiving sulfonylurea monotherapy. Consequently, we may have included patients who did not have a long-standing history of diabetes and, therefore, had a lower tendency to develop MACE. In these patients, IPC was suspected to be less likely to function, and the risk of MACE resulting from the use of sulfonylureas that inhibit cardiac mitoK_{ATP} channels could thus be less profound. Future studies are warranted to evaluate the cardiovascular safety of using mitoK_{ATP} channel high-affinity sulfonylureas in dual or triple therapy. Third, random errors could have occurred in the secondary and subgroup analyses due to the small number of cardiovascular events. Fourth, while we measured obesity from the analyzed database, it seems that a substantial portion of patients with obesity could not be identified using the disease code, indicating the presence of misclassification for obesity status. Fifth, although similar results were obtained after restricting patients with a medication possession ratio $\geq$0.8, we were unable to directly measure patient treatment compliance to sulfonylurea monotherapy. However, it is believed that there was no difference between the two groups in terms of treatment compliance, potentially moving the estimated HRs toward the null value. Finally, our study was aimed at examining the comparative cardiovascular event-related safety between mitoK_{ATP} channel high-affinity and low-affinity sulfonylureas, but this does not mean that the corresponding results can be interpreted to imply that mitoK_{ATP} channel low-affinity sulfonylureas carry no cardiovascular risk. Further researches are urgently required to compare mitoK_{ATP} channel low-affinity sulfonylureas with other types of antidiabetic agents, such as DPP-4 inhibitors, regarding the risk of adverse cardiovascular events in order to determine the comparative safety profile of this type of sulfonylureas.

In conclusion, our study revealed an increased risk of MACE associated with the use of mitoK_{ATP} channel high-affinity sulfonylureas compared with that of mitoK_{ATP} channel low-affinity sulfonylureas. The observed risk was driven by ischemic stroke and cardiovascular death and was particularly elevated within 90 days of initiating mitoK_{ATP} channel high-affinity sulfonylureas. These data support cardiac mitoK_{ATP} channel inhibition acting as a major contributor to the intraclass difference in the adverse cardiovascular risk among sulfonylureas.

Acknowledgments. The authors thank the Health and Welfare Data Source Center, Ministry of Health and Welfare, Taiwan, for providing the Taiwan DMHD to be analyzed. Additionally, part of the data used in this research were from the Tri-Service General Hospital (TSGH) Integrated Database Center (IRDC). The authors also thank the IRDC, TSGH, for allowing access to the electronic medical records there. The interpretations of conclusions of the findings in the current study do not represent those of Health and Welfare Data Source Center, Ministry of Health and Welfare, Taiwan. Any interpretation or conclusions described in this article do not represent the views of the IRDC, TSGH.

Funding. This study was supported by the Ministry of Science and Technology (MOST), Taiwan (grant MOST 108-2320-B-016-010-MY2).

MOST had no role in design and conduct of the study, collection, management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. All authors conceptualized and designed the current study. M.-T.W. acquired the database. M.-T.W. and Y.-L.H. analyzed the data. All authors interpreted the data. M.-T.W., Y.-L.H., J.-H.L., and H.-Y.P. drafted the manuscript. All authors made critical revisions and approved the submitted manuscript. M.-T.W. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edition, 2019. Accessed 8 November 2021. Available from https://www.diabetesatlas.org
2. Dennis JM, Henley WE, McGovern AP, et al.; MASTERMIND consortium. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: a retrospective analysis of primary care data, 2010-2017. Diabetes Obes Metab 2019;21:1576–1584
3. Montvida O, Shaw J, Atherton JJ, Stringer F, Paul SK. Long-term trends in antidiabetes drug usage in the U.S.: real-world evidence in patients newly diagnosed with type 2 diabetes. Diabetes Care 2018;41:69–78
4. Chu WM, Ho HE, Huang KH, et al. The prescribing trend of oral antidiabetic agents for type 2 diabetes in Taiwan: an 8-year population-based study. Medicine (Baltimore) 2017;96:e8257
5. Khunti K, Chatterjee S, Gerstein HC, Zoungas S, Davies MJ. Do sulphonylureas still have a place in clinical practice? Lancet Diabetes Endocrinol 2018;6:821–832
6. Webb DR, Davies MJ, Jarvis J, Seidu S, Khunti K. The right place for sulphonylureas today. Diabetes Res Clin Pract 2019;157:107836
7. Monami M, Genovese S, Mannucci E. Cardiovascular safety of sulfonylureas: a meta-analysis of randomized clinical trials. Diabetes Obes Metab 2013;15:938–953
8. Phung OJ, Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. Diabet Med 2013;30:1160–1171
9. Pantalone KM, Kattan MW, Yu C, et al. The risk of overall mortality in patients with type 2 diabetes receiving glipizide, glyburide, or glimepiride monotherapy: a retrospective analysis. Diabetes Care 2010;33:1224–1229
10. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. Lancet Diabetes Endocrinol 2015;3:43–51
11. Douros A, Dell'Aniello S, Yu OHY, Filion KB, Azoulay L, Suissa S. Sulfonylureas as second line drugs in type 2 diabetes and the risk of cardiovascular and hypoglycaemic events: population based cohort study. BMJ 2018;362:k2693
12. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. Diabetes Care 2017;40:1506–1513
13. Nakano A, Cohen MV, Downey JM. Ischemic preconditioning: from basic mechanisms to clinical applications. Pharmacol Ther 2000;86:263–275
14. Iliodromitis EK, Lazou A, Kremastinos DT. Ischemic preconditioning: protection against myocardial necrosis and apoptosis. Vasc Health Risk Manag 2007;3:629–637
15. Paggio A, Checchetto V, Campo A, et al. Identification of an ATP-sensitive potassium channel in mitochondria. Nature 2019;572:609–613
16. Sato T, Sasaki N, Seharaseyon J, O'Rourke B, Marbán E. Selective pharmacological agents implicate mitochondrial but not sarcolemmal K(ATP) channels in ischemic cardioprotection. Circulation 2000;101:2418–2423
17. Argaud L, Garrier O, Loufouat J, et al. Second-generation sulfonylureas preserve inhibition of mitochondrial permeability transition by the mitochondrial K+(ATP) opener nicorandil in experimental myocardial infarction. Shock 2009;32:247–252
18. O'Rourke B. Evidence for mitochondrial K+ channels and their role in cardioprotection. Circ Res 2004;94:420–432
19. Sato T, Nishida H, Miyazaki M, Nakaya H. Effects of sulfonylureas on mitochondrial ATP-sensitive K+ channels in cardiac myocytes: implications for sulfonylurea controversy. Diabetes Metab Res Rev 2006;22:341–347
20. Szewczyk A, Wójcik G, Lobanov NA, Nałecz MJ. The mitochondrial sulfonylurea receptor: identification and characterization. Biochem Biophys Res Commun 1997;230:611–615
21. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J 2009;51:171–184

22. Cheng CL, Lee CH, Chen PS, Li YH, Lin SJ, Yang YH. Validation of acute myocardial infarction cases in the national health insurance research database in Taiwan. J Epidemiol 2014;24:500–507
23. Hsieh CY, Chen CH, Li CY, Lai ML. Validating the diagnosis of acute ischemic stroke in a National Health Insurance claims database. J Formos Med Assoc 2015;114:254–259
24. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. Ann Pharmacother 2006;40:1280–1288
25. Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. Pharmacoepidemiol Drug Saf 2020;29:1101–1110
26. Rosenbaum PR. Model-based direct adjustment. J Am Stat Assoc 1987;82:387–394
27. Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. Pharmacoepidemiol Drug Saf 2006;15:291–303
28. Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology 2009;20:512–522
29. Stürmer T, Schneeweiss S, Avorn J, Glynn RJ. Adjusting effect estimates for unmeasured confounding with validation data using propensity score calibration. Am J Epidemiol 2005;162:279–289
30. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simul Comput 2009;38:1228–1234
31. Murphy E, Steenbergen C. Mechanisms underlying acute protection from cardiac ischemia-reperfusion injury. Physiol Rev 2008; 88:581–609
32. Rosenstock J, Kahn SE, Johansen OE, et al.; CAROLINA Investigators. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155–1166
33. Zoungas S. ADVANCE in context: the benefits, risks and feasibility of providing intensive glycaemic control based on gliclazide modified release. Diabetes Obes Metab 2020;22(Suppl. 2):5–11
34. Li YW, Whittaker P, Kloner RA. The transient nature of the effect of ischemic preconditioning on myocardial infarct size and ventricular arrhythmia. Am Heart J 1992;123:346–353
35. Banerjee A, Locke-Winter C, Rogers KB, et al. Preconditioning against myocardial dysfunction after ischemia and reperfusion by an alpha 1-adrenergic mechanism. Circ Res 1993;73: 656–670
36. Rahmi Garcia RM, Rezende PC, Hueb W. Impact of hypoglycemic agents on myocardial ischemic preconditioning. World J Diabetes 2014;5:258–266
37. Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. Diabetes Obes Metab 2012;14:130–138
38. Downey JM, Davis AM, Cohen MV. Signaling pathways in ischemic preconditioning. Heart Fail Rev 2007;12:181–188
39. Schwartz TB, Meinert CL. The UGDP controversy: thirty-four years of contentious ambiguity laid to rest. Perspect Biol Med 2004;47:564–574
40. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. Diabetes Care 2015; 38:316–322