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ORIGINAL RESEARCH

Effect of SGLT2 Inhibitors on Diabetes Progression in Statin-Treated Patients: A Population-Based Cohort Study

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Background: Statins, though widely used, may accelerate diabetes progression, necessitating interventions to counteract this effect.
Purpose: To compare the effect of sodium-glucose co-transporter 2 inhibitors (SGLT2is) and sulfonylureas or meglitinides on diabetes progression in individuals receiving statins.
Patients and Methods: This retrospective cohort study utilized data from the National Health Insurance Research Database of Taiwan. We included patients with diabetes receiving statins and newly initiated SGLT2is or sulfonylureas/meglitinides between July 1, 2016 and December 31, 2020. Diabetes progression was defined as insulin initiation, increase in antidiabetic medication class, or occurrence of new acute hyperglycemic complications. Propensity score matching was used to adjust baseline characteristics. Cox proportional hazards regression was used to calculate the hazard ratios for diabetes progression between users of SGLT2is and those of sulfonylureas or meglitinides. The statistical significance level was set at 0.05 for all analyses.
Results: SGLT2i users had a significantly lower risk of diabetes progression compared to sulfonylurea/meglitinide users (HR: 0.53, 95% CI: 0.50–0.57, p-value < 0.001). Similar results were found in insulin initiation (HR: 0.48, 95% CI: 0.38–0.61, p-value < 0.001) and increase in antidiabetic medication class (HR: 0.53, 95% CI: 0.50–0.57, p-value < 0.17). However, the risk of new acute glycemic complications did not significantly differ between groups (HR: 2.47, 95% CI: 0.67–9.08, p-value = 0.17).
Conclusion: SGLT2is may be an effective second-line therapy for statin-treated patients by slowing diabetes progression and potentially mitigating statin-induced metabolic disturbances. Further research, including randomized controlled trials or observational studies with comprehensive laboratory data, is needed to confirm these findings and evaluate their broader applicability.
Keywords: SGLT2is, statins, diabetes mellitus, statin-associated diabetes progression

Introduction

Diabetes mellitus (DM) and hypercholesterolemia are important risk factors for atherosclerotic cardiovascular diseases. Statins are recommended as the first-line therapy for controlling low-density lipoprotein cholesterol.[1,2] However, studies have shown statins may worsen patients' glycemic control and are associated with new-onset diabetes.[3–6] A retrospective matched-cohort study in *JAMA Internal Medicine* further pushed this issue forward, indicating that statin initiation was associated with DM progression, even in patients already with DM.[7] The frequent coexistence of hypercholesterolemia and type 2 diabetes mellitus (T2DM) [8] creates a treatment dilemma for diabetic patients requiring statin therapy.

Although the exact mechanism of statin-associated diabetes is unclear, insulin resistance is hypothesized to play a role.[9] This proposed mechanism leads to the question as to whether early use of antidiabetic drugs that improve insulin sensitivity can mitigate T2DM progression in statin-treated patients. Recently, several studies have shown that sodium-

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glucose co-transporter 2 inhibitors (SGLT2is) might improve insulin resistance, though these findings are restricted to case reports or small-scale clinical studies.[10–16] Possible mechanisms have been postulated to explain why SGLT2is can induce insulin sensitivity, including inhibiting glucose toxicity, aiding weight loss, attenuating inflammation, and reducing oxidative stress.[17]

Although evidence suggests a link between statin use and diabetes progression, guidelines continue to recommend statins for primary and secondary prevention for patients with atherosclerotic cardiovascular disease (ASCVD), as their cardiovascular benefits outweigh the associated diabetes risk.[2] Nevertheless, risk-tailored approaches to mitigate the metabolic effect of statins are lacking. There is growing evidence that SGLT2is improves insulin resistance and may potentially defer diabetes progression. In view of this, the objective of this study is to evaluate whether the use of SGLT2is as the second-line therapy, compared to sulfonylureas or meglitinides, can attenuate diabetes progression among patients with diabetes with statin treatment.

Materials and Methods

Study Design

This is a retrospective matched-cohort study with active-comparator and new-user design to minimize unmeasured confounders.[18] The detailed study design is elaborated in the following sections, and the study time frames are briefed in Figure S1. This study was reviewed and approved by the Research Ethics Committee of the National Taiwan University Hospital (Rec. No. 202204113RINC).

Study Population

We used inpatient claims, outpatient claims, and pharmacy claims from the National Health Insurance Research Database (NHIRD) to identify diabetic patients between July 1, 2016 and December 31, 2020. The index date was defined as the date of the first prescription of the study drug (either SGLT2is or sulfonylureas/meglitinides) in outpatient claims.

Patients meeting the following inclusion criteria were included in this study: (1) diagnosed diabetes mellitus before the index date, defined as having an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code of E11 at any position in outpatient claims; (2) received metformin exposure before the index date, defined as having at least one prescription for metformin before the index date in outpatient claims; (3) aged ≥20 years at the index date; and (4) concurrent statin use, defined as having a prescription covering or on the index date.

We excluded patients who initiated SGLT2is and sulfonylurea/meglitinides on the same date and those with unknown sex or age at the index date. Patients receiving antidiabetic agents other than metformin within 180 days before the index date were also excluded. This exclusion criterion was set to ensure that all the study subjects had comparable baseline treatment and disease severity and to restrict the study population to guideline-recommended therapy (ie, metformin as the first-line therapy). We further excluded patients with stain exposure less than 90 days before the index date. Previous studies have shown that statin-associated insulin resistance can be observed around ten weeks after statin initiation,[9] so we hypothesized that patients with at least 90 days of statin exposure have some degree of insulin resistance.

Given that patients may defer their refills, a 28-day grace period was applied to define continuity. Patients who did not get statins refilled for more than 28 days after the end of their previous statin prescription were considered "statin discontinuation." Finally, we excluded patients with a history of dialysis 90 days before or at the index date. Since metformin and SGLT2is are not recommended for patients on dialysis, we excluded these patients to enhance internal validity and to prevent potential selection bias. Dialysis records were defined by having at least one National Health Insurance procedure code for dialysis in outpatient claims. The diagnosis and procedure codes used for patient selection are listed in Table S1.

Data Sources

This study used data from the NHIRD in Taiwan between July 2016 and December 2020. The NHIRD is a nationwide population-based database which includes beneficiaries' inpatient, outpatient, and pharmacy records together with their demographic features (eg, age, sex), diagnosis, procedures, and treatment records. Patient consent was not required for this study because all data obtained from the NHIRD were de-identified. The raw data of the NHIRD are protected and

not available due to data privacy laws. Access may be obtained upon reasonable request and application to the Health and Welfare Data Science Center, Ministry of Health and Welfare of Taiwan.

Exposure Assessment

The final study sample was divided into two groups: SGLT2i users versus sulfonylurea/meglitinide users, based on the patients' index prescription. SGLT2is included in this study were empagliflozin, dapagliflozin, canagliflozin, and ertugliflozin. These were the four available SGLT2is during the study period. Sulfonylureas and meglitinides included glibenclamide, chlorpropamide, tolbutamide, glibornuride, tolazamide, carbutamide, glipizide, gliquidone, gliclazide, metahexamide, glisoxepide, glimepiride, acetohexamide, nateglinide, and repaglinide. The ATC codes are provided in Table S2.

We merged sulfonylurea and meglitinide into one class and chose it as the active comparator, because these two agents act similarly by stimulating insulin secretion rather than improving insulin resistance. On the contrary, SGLT2is act through insulin-independent pathways and show potential to attenuate insulin resistance. Furthermore, antidiabetic agents other than metformin were equally recommended as add-on therapies in American Diabetes Association (ADA) guidelines before 2018. These reasons made sulfonylureas/meglitinides good active comparators, since they have a similar indication and therapeutic status to SGLT2is and are not related to the proposed mechanism (ie, improving insulin resistance) for outcomes.

Outcome Measures

We defined diabetes progression by (1) insulin initiation, defined as having any prescription for insulin in outpatient claims; (2) initiation of a new class of antidiabetic agents, defined as having two consecutive prescriptions for a new antidiabetic medication class with a gap <28 days in outpatient claims; and (3) new acute hyperglycemic complications, defined as receiving a primary diagnosis for ketoacidosis or nonketotic hyperglycemic hyperosmolar state (NKHHS) in inpatient claims. The codes for outcome measurement are provided in Table S3. These definitions were adapted from Mansi et al with two modifications.[7] First, we used ICD-10 codes instead of ICD-9 codes to define new acute hyperglycemic complications. Because there are no diagnoses for uncontrolled diabetes in ICD-10, we used ketoacidosis and NKHHS instead. Second, we did not apply the definitions that use laboratory data, because no laboratory data were available in the NHIRD.

Follow-Up Assessment

The follow-up period started from the index date and continued until one of the following happened: (1) occurrence of the outcome (diabetes progression), (2) end of the observation period (ie, December 31, 2020), (3) death, (4) switch between the two exposures, and (5) discontinuation of the index study drugs. Switching was defined as having a prescription for sulfonylurea/meglitinide and discontinuing SGLT2is in the SGLT2i group, and vice versa. Discontinuation was defined by a gap >28 days between the two prescriptions.

Baseline Characteristics and Covariates

Baseline characteristics and covariates included in this study were patient demographics, comorbidities, and comedications (Table S4). Demographics included age and sex, defined in the index date. Since guideline recommendations varied from year to year, we also included calendar year to control for potential changes in practice.

Comorbidities were divided into four groups: cardiovascular-disease-related diseases (CVD-related diseases), renal and hepatic diseases, immunocompromised conditions, and history of urogenital mycotic infection. Under the CVD-related diseases, chronic obstruction pulmonary disease (COPD), bronchiectasis, and asthma were also included as a proxy for smoking status. Comorbidities were defined as having at least one inpatient diagnosis or two outpatient diagnoses within 180 days before the index date.

To correct for potential imbalanced diabetes severity between groups, we adopted Glasheen et al's work to calculate the Diabetes Complications Severity Index (DCSI) as a covariate to address this issue.[19] Higher scores indicated worse diabetes complications. The ICD-10-CM codes and the weights for diabetes complications are provided in Table S5.

Comedications included antihypertensives, antithrombotics, non-statin lipid-lowering agents and other medications, which might influence glycemic control, such as systemic steroids, non-steroid immunosuppressants, antidepressants, antipsychotics, antiepileptics, systemic beta 2 agonists, theophylline, and antiretroviral agents. Comedications were defined as having at least one prescription for 28 days or longer for the designated drugs. Previous studies suggested that there might be a dose–response relationship between statins and diabetes progression, so we also included statin intensity as a covariate. The intensity of the statin was defined according to the American Heart Association guidelines[1] (Table S6).

Statistical Analysis

We performed 1:1 nearest-neighbor propensity-score matching (PSM) without replacement to minimize potential confounders and imbalanced risk factors. Propensity scores were calculated using the logit model and a caliper of 0.2-fold. A standard deviation of the logit propensity scores was used for searching neighbors.[20] Absolute standardized mean difference (aSMD) was used, before and after matching, to evaluate if there were imbalanced covariates between the two groups. Covariates with an aSMD less than 0.1 after matching were considered balanced between the two groups.[21]

In the outcome analysis, the Kaplan–Meier analysis was conducted for the crude analysis; the Log rank test was used to test if there were differences between the two survival curves. Cox-proportional hazard models were used in PSM adjusted analysis, and the hazard ratio (HR) with its 95% confidence interval (CI) was calculated.

Statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA). The statistical significance level was set at 0.05.

Subgroup Analyses

SGLT2is have shown benefits in several subgroups of patients, including heart failure, chronic kidney disease (CKD), and ASCVD.[22,23] However, these reported benefits were mostly long-term cardiorenal protective effects rather than glycemic controls. Therefore, we wanted to understand if the benefits of delaying diabetes progression could be seen in these subgroups. Subgroups were defined using the same ICD-10-CM codes as defining covariates (Table S4). ASCVD was defined as ischemic heart disease, cerebrovascular disease, or peripheral vascular disease (Table S7).

Sensitivity Analyses

We performed three sensitivity analyses to test the robustness of our results. First, we excluded ketoacidosis and NKHHS from the definition of diabetes progression, because SGLT2is are associated with an increased risk of ketoacidosis, which might lead to outcome misclassification. Since it can be sometimes difficult to differentiate between NKHHS and ketoacidosis, we excluded NKHHS as well.

Second, we restricted the time horizons to include and to follow patients from 2016 to 2018. Since SGLT2is have been reported to be beneficial to a wide variety of patient populations since 2018, physicians may have added or switched to SGLT2is for patients who were originally on sulfonylureas/meglitinides, even if they had good glucose control. This could bias the result, because we defined add-on as diabetes progression. By restricting the time horizons to when SGLT2is were just reimbursed and not found to be as beneficial to the target organs as they are in the recent years, we mitigated the potential outcome misclassification caused by physicians' preference or practice change over time.

Third, we used the National Taiwan University Hospital-integrated Medical Database (NTUH-iMD) to include laboratory data to address the concern of unmeasured confounders, including baseline diabetes severity and low-density lipoprotein (LDL) control. The NTUH-iMD is an electronic medical record research database established by the National Taiwan University Hospital (NTUH), which includes demographics, inpatient, outpatient, and emergency visit information, as well as laboratory data. Like the NHIRD, patient consent was not required for this study as all data in the NTUH-iMD database were de-identified to ensure patient privacy.

We adopted the inclusion and exclusion criteria of the main analysis to form the study cohort in the NTUH-iMD. Additionally, we excluded patients without the required laboratory data at baseline. Since prescribing data is more complete than dispensing data in the NTUH-iMD, prescribing data, rather than dispensing data, were used in the validation study. The exposure, outcome and follow-up assessments were the same as those in the main analysis except

that, we did not adjust baseline comorbidity and comedication in the validation study because of the small sample size. Instead, we controlled for baseline LDL, hemoglobin A1c (HbA1c), and estimated glomerular filtration rate (eGFR) in regression models. In addition, because of the limited sample size, we did not perform PSM in this sensitivity analysis. Instead, the Cox proportional hazard model was used to control for age, sex, calendar year, LDL, HbA1c, and eGFR.

Finally, because diabetes progression was not defined by HbA1c, we further investigated whether physicians added a new class of antihyperglycemic agents based on diabetes progression rather than the prescribing preference. Physicians might consider adding a different class of antihyperglycemic agents with organ-protective benefits, even if the patient's diabetes is well managed. We conducted an auxiliary analysis to validate this outcome definition using the NTUH-iMD. We identified a subgroup of patients who had HbA1c tests performed both at baseline and prior to the add-on and evaluated the changes in HbA1c levels between these two points. While patients may have had different goals of HbA1c, we considered HbA1c higher than 7.0 as poor glucose control. Two types of patients were considered adding of an additional antidiabetic agent due to diabetes progression: (1) those whose HbA1c levels remained above 7.0 both at baseline and prior to add-on therapy, or (2) those who had baseline HbA1c levels of 7.0 or lower, but experienced an increase to above 7.0 before the add-on.

Results

Study Sample

We first identified 85,867 eligible SGLT2i and sulfonylurea/meglitinide users from the NHIRD between July 1, 2016 and December 31, 2020. There were 69,846 (81.34%) sulfonylurea/meglitinide new users and 16,021 (18.66%) SGLT2i new users. After PSM, 13,840 pairs were matched (Figure 1).

Baseline Characteristics

Compared to sulfonylurea/meglitinide users, SGLT2i users were younger (59.32 years old vs 60.35 years old, aSMD: 0.35), with a higher proportion of males (56.75% vs 48.63%, aSMD: 0.16) and fewer new users in 2016 (4.96% vs 66.95%, aSMD: 1.69) before matching.

In terms of comorbidities, SGLT2i users had a lower proportion of hyperlipidemia (71.10% vs 80.54%, aSMD: 0.22), higher proportions of ischemic heart disease (23.29% vs 12.46%, aSMD: 0.29), cardiac arrhythmia and conduction disorders (5.77% vs 3.52%, aSMD: 0.11), heart failure (3.41% vs 1.53%, aSMD: 0.12), and obesity (2.58% vs 0.41%, aSMD: 0.18). The mean DCSI score was also higher in the SGLT2i group before matching (0.13 vs 0.08, aSMD: 0.12).

In terms of comedications, SGLT2i users had a lower proportion of low-intensity statin (15.93% vs 24.31%, aSMD: 0.21) and higher proportions of antithrombotics (38.11% vs 30.68%, aSMD: 0.16) and non-statin lipid-lowering agents (9.49% vs 5.46%, aSMD: 0.15) before matching. After matching, all baseline covariates were balanced across the two groups (Table 1).

SGLT2 Inhibitor Use and Diabetes Progression

Main Analysis

Table 2 presents the results of the main analysis. Before matching, the median follow-up duration of the SGLT2i group and sulfonylurea/meglitinide group were 273 days and 450 days, respectively. After matching, the median follow-up duration of the SGLT2i group and sulfonylurea/meglitinide group were 286 days and 219 days, respectively. We found that SGLT2i users had a significantly lower hazard of diabetes progression compared to sulfonylurea/meglitinide users both before (HR: 0.55, 95% CI: 0.52–0.57, p-value < 0.001) and after matching (HR; 0.53, 95% CI: 0.50–0.57, p-value < 0.001). The Kaplan–Meier analysis also showed a significant difference (p-value < 0.0001) between the two survival curves (Figure 2). In terms of the individual component of the outcome, SGLT2i users had lower hazards of insulin initiation both before (HR: 0.47, 95% CI: 0.39–0.56, p-value < 0.001) and after matching (HR: 0.48, 95% CI: 0.38–0.61, p-value < 0.001); SGLT2i users also had lower hazards of increase in antidiabetic medication class both before (HR: 0.55, 95% CI: 0.52–0.58, p-value < 0.001) and after matching (HR: 0.53, 95% CI: 0.50–0.57, p-value < 0.001). However,

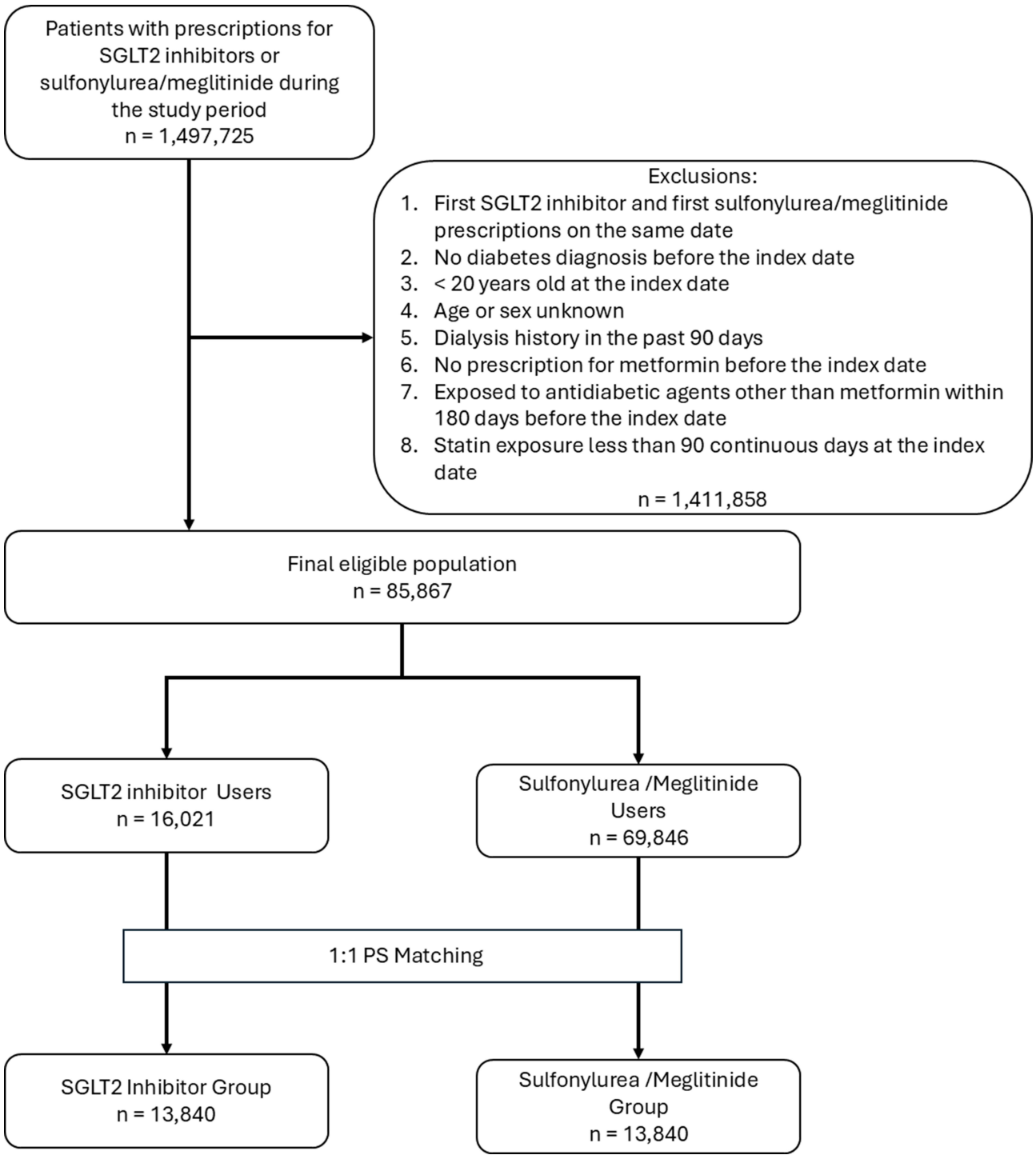


Figure 1 Sample selection flow chart.

no significant differences were found in terms of the hazards of new acute glycemic complications both before (HR: 0.99, 95% CI: 0.47–2.09, p-value = 0.97) and after matching (HR: 2.47, 95% CI: 0.67–9.08, p-value = 0.17).

Subgroup Analysis

In the subgroup analysis, we identified 1,614 patients with heart failure (33.89% of which were SGLT2i users), 84,253 patients without heart failure (18.37% of which were SGLT2i users), 4,149 patients with CKD (22.92% of which were

Table 1 Baseline Characteristics of SGLT2 Inhibitor and Sulfonylurea/Meglitinide Users

n (%)	Before Matching			After Matching		
	SGLT2i Users (N = 16,021)	Sulfonylurea/ Meglitinide Users (N = 69,846)	Absolute SMD	SGLT2i Users (N = 13,840)	Sulfonylurea/ Meglitinide Users (N = 13,840)	Absolute SMD
Demographics						
Age, mean (SD), y	59.32 (11.64)	63.35 (11.89)	**0.35**	60.10 (11.39)	60.03 (11.36)	0.01
Sex, male	9,092 (56.75)	33,967 (48.63)	**0.16**	7,535 (54.44)	7,462 (53.92)	0.01
Calendar year						
2016	794 (4.96)	46,763 (66.95)	**1.69**	794 (5.74)	782 (5.65)	<0.01
2017	1,923 (12.00)	7,017 (10.05)	0.06	1,890 (13.66)	1,890 (13.66)	0.00
2018	2,926 (18.26)	6,162 (8.82)	**0.28**	2,798 (20.22)	2,808 (20.29)	<0.01
2019	4,667 (29.13)	5,119 (7.33)	**0.59**	3,950 (28.54)	4,025 (29.08)	0.01
2020	5,711 (35.65)	4,785 (6.85)	**0.75**	4,408 (31.85)	4,335 (31.32)	0.01
Comorbidities						
COPD and bronchiectasis	549 (3.43)	2,346 (3.36)	<0.01	469 (3.39)	465 (3.36)	<0.01
Asthma	632 (3.94)	2,491 (3.57)	0.02	556 (4.02)	587 (4.24)	0.01
Hypertension	10,217 (63.77)	46,381 (66.40)	0.06	9,026 (65.22)	9,095 (65.72)	0.01
Hyperlipidemia	11,391 (71.10)	56,251 (80.54)	**0.22**	10,267 (74.18)	10,322 (74.58)	0.01
Ischemic heart disease	8,706 (23.29)	8,706 (12.46)	**0.29**	2,631 (19.01)	2,540 (18.35)	0.02
Valvular heart disease	367 (2.29)	929 (1.33)	0.07	285 (2.06)	275 (1.99)	0.01
Cardiac arrhythmia and conduction disorders	924 (5.77)	2,461 (3.52)	**0.11**	705 (5.09)	678 (4.90)	0.01
Heart failure	547 (3.41)	1,067 (1.53)	**0.12**	360 (2.60)	360 (2.60)	0.00
Cerebrovascular disease	726 (4.53)	3,758 (5.38)	0.04	689 (4.98)	708 (5.12)	0.01
Peripheral vascular disease	71 (0.44)	288 (0.41)	<0.01	59 (0.43)	52 (0.38)	0.01
Venous thromboembolism	47 (0.29)	130 (0.19)	0.02	41 (0.30)	40 (0.29)	<0.01
Obesity	414 (2.58)	288 (0.41)	**0.18**	174 (1.26)	129 (0.93)	0.03
DCSI score, mean (SD)	0.13 (0.49)	0.08 (0.40)	**0.12**	0.11 (0.44)	0.10 (0.44)	0.01
Chronic kidney disease	951 (5.94)	3,198 (4.58)	0.06	777 (5.61)	781 (5.64)	<0.01
Severe liver disease	15 (0.09)	43 (0.06)	0.01	13 (0.09)	11 (0.08)	<0.01
Cancer or neoplasm	738 (4.61)	3,195 (4.57)	<0.01	657 (4.75)	657 (4.75)	0
Chronic immune conditions*	195 (1.22)	942 (1.35)	0.01	176 (1.27)	179 (1.29)	<0.01
History of Urogenital Mycotic Infection	81 (0.51)	371 (0.53)	<0.01	69 (0.50)	67 (0.48)	<0.01
Comedications						
Statins						
Low-intensity	2,552 (15.93)	16,980 (24.31)	**0.21**	2,294 (16.58)	2,329 (16.83)	0.01
Medium-intensity	1,2889 (80.45)	51,807 (74.17)	**0.15**	11,179 (80.77)	11,167 (80.69)	<0.01
High-intensity	580 (3.62)	1,059 (1.52)	**0.13**	367 (2.65)	344 (2.49)	0.01
Antihypertensives	10,933 (68.24)	45,562 (65.23)	0.06	9,264 (66.94)	9,225 (66.65)	0.01
Antithrombotics	6,105 (38.11)	21,429 (30.68)	**0.16**	4,852 (35.06)	4,741 (34.26)	0.02
Non-Statin Lipid-Lowering Agents	1,521 (9.49)	3,814 (5.46)	**0.15**	1,211 (8.75)	1,218 (8.80)	<0.01
Systemic Steroids	233 (1.45)	972 (1.39)	0.01	215 (1.55)	216 (1.56)	<0.01
Non-Steroid Immunosuppressants	88 (0.55)	319 (0.46)	0.01	75 (0.54)	69 (0.50)	<0.01
Antidepressants	1,014 (6.33)	4,337 (6.21)	<0.01	914 (6.60)	886 (6.40)	0.01

(*Continued*)

https://doi.org/10.2147/CLEP.S505242

Table 1 (Continued).

n (%)	Before Matching			After Matching		
	SGLT2i Users (N = 16,021)	Sulfonylurea/ Meglitinide Users (N = 69,846)	Absolute SMD	SGLT2i Users (N = 13,840)	Sulfonylurea/ Meglitinide Users (N = 13,840)	Absolute SMD
Antipsychotics	419 (2.62)	1,916 (2.74)	<0.01	371 (2.68)	353 (2.55)	0.01
Antiepileptics	835 (5.21)	3,296 (4.72)	0.02	730 (5.27)	728 (5.26)	<0.01
Systemic beta 2 agonists	143 (0.89)	847 (1.21)	0.03	130 (0.94)	134 (0.97)	<0.01
Theophylline	261 (1.63)	1,214 (1.74)	0.01	231 (1.67)	238 (1.72)	<0.01
Antiretroviral agents†	75 (0.47)	295 (0.42)	0.01	63 (0.46)	54 (0.39)	0.01

Notes: Boldface indicates absolute SMD > 0.1 †Including Human Immunodeficiency Virus (HIV) infections and chronic autoimmune diseases †Includes Protease Inhibitor (PI), Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI).
Abbreviations: SGLT2: Sodium-Glucose Co-Transporter 2; COPD: Chronic Obstructive Pulmonary Disease; DCSI: Diabetes Complications Severity Index; SMD: Standardized Mean Difference; SD: Standard Deviation.

Table 2 Hazards of Outcomes Between SGLT2 Inhibitor Users and Sulfonylurea/Meglitinide Users Before and After Propensity Score Matching

Outcomes, n (%)	Before Matching				After Matching			
	SGLT2i Users (N = 16,021)	Sulfonylurea/ Meglitinide Users (N = 69,846)	HR (95% CI)	p-value	SGLT2i Users (N = 13,840)	Sulfonylurea/ Meglitinide Users (N = 13,840)	HR (95% CI)	p-value
Diabetes progression	1,818 (11.35)	24,503 (35.08)	0.55 (0.52, 0.57)	<0.001	1,628 (11.76)	2,558 (18.48)	0.53 (0.50, 0.57)	<0.001
Insulin initiation	118 (0.74)	1,675 (2.40)	0.47 (0.39, 0.56)	<0.001	97 (0.70)	177 (1.28)	0.48 (0.38, 0.61)	<0.001
Increase in antidiabetic medication class	1,692 (10.56)	22,776 (32.61)	0.55 (0.52, 0.58)	<0.001	1,523 (11.00)	2,378 (17.18)	0.53 (0.50, 0.57)	<0.001
New acute glycemic complications	8 (0.05)	52 (0.07)	0.99 (0.47, 2.09)	0.97	8 (0.06)	3 (0.02)	2.47 (0.67, 9.08)	0.17

Abbreviations: SGLT2: Sodium-Glucose Co-Transporter 2; HR: Hazard Ratio; CI: Confidence Interval.

SGLT2i users), 81,718 patients without CKD (18.44% of which were SGLT2i users), 16,510 patients with ASCVD (26.23% of which were SGLT2i users), and 69,357 patients without ASCVD (16.86% of which were SGLT2i users). Consistent with the results of the main analysis, the Kaplan–Meier analysis showed that SGLT2i users had a significantly lower rate of diabetes progression compared to sulfonylurea/meglitinide users (Figuress S2–S7), and lower hazards of diabetes progression were also observed across all six subgroups, both before and after matching (Figure 3).

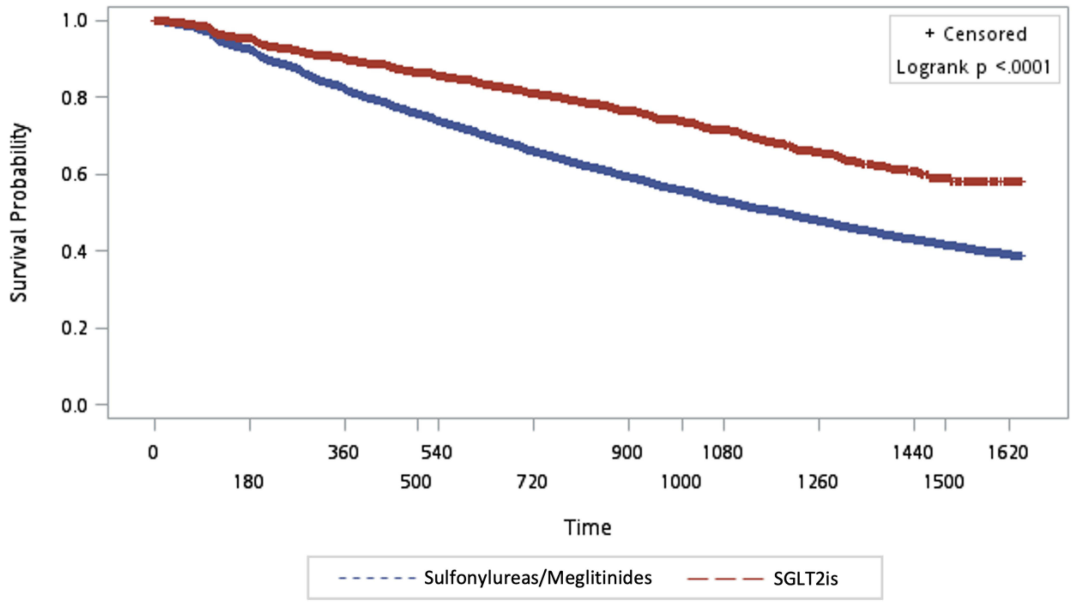
Sensitivity Analysis

Excluding Ketoacidosis and NKHHS from the Outcome Definition

In the first sensitivity analysis (Table S8), we excluded new acute glycemic complications (ketoacidosis and NKHHS) from the outcome definition. The result showed that SGLT2i users had a lower hazard of diabetes progression compared to their sulfonylurea/meglitinide counterparts both before matching (HR: 0.54, 95% CI: 0.52–0.57, p-value < 0.001) and after matching (HR: 0.53, 95% CI: 0.50–0.56, p-value < 0.001). Similar results were found regarding the individual component of outcomes. Lower risk of insulin initiation and increase in antidiabetic medication class were found in SGLT2i users compared to sulfonylurea/meglitinide users. The Kaplan–Meier analysis showed consistent results with the main analysis (Figure S8).

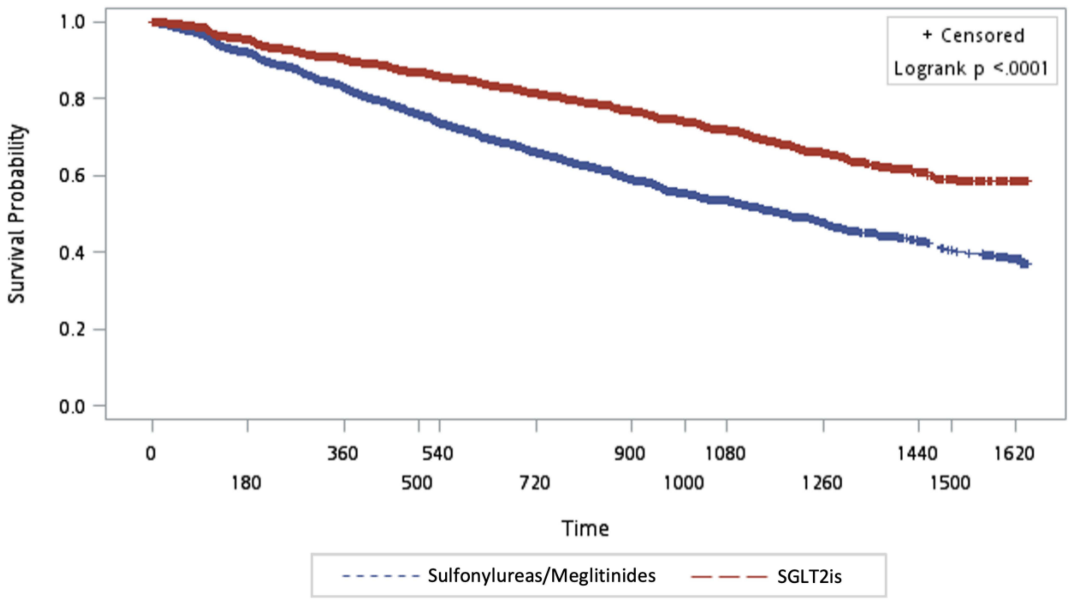
Restricting Time Horizons

In the second sensitivity analysis, we restricted the study population to those initiating SGLT2i or sulfonylurea/ meglitinide between July 1, 2016 and December 31, 2018. We identified 65,585 eligible SGLT2i and sulfonylurea/



Sulfonylureas/Meglitinides	69846	52613	39783	30961	24359	19375	15333	12162	9635	4081
SGLT2is	16021	10132	6558	4164	2617	1577	916	492	202	27

SGLT2is: Sodium-Glucose Co-Transporter 2 Inhibitors

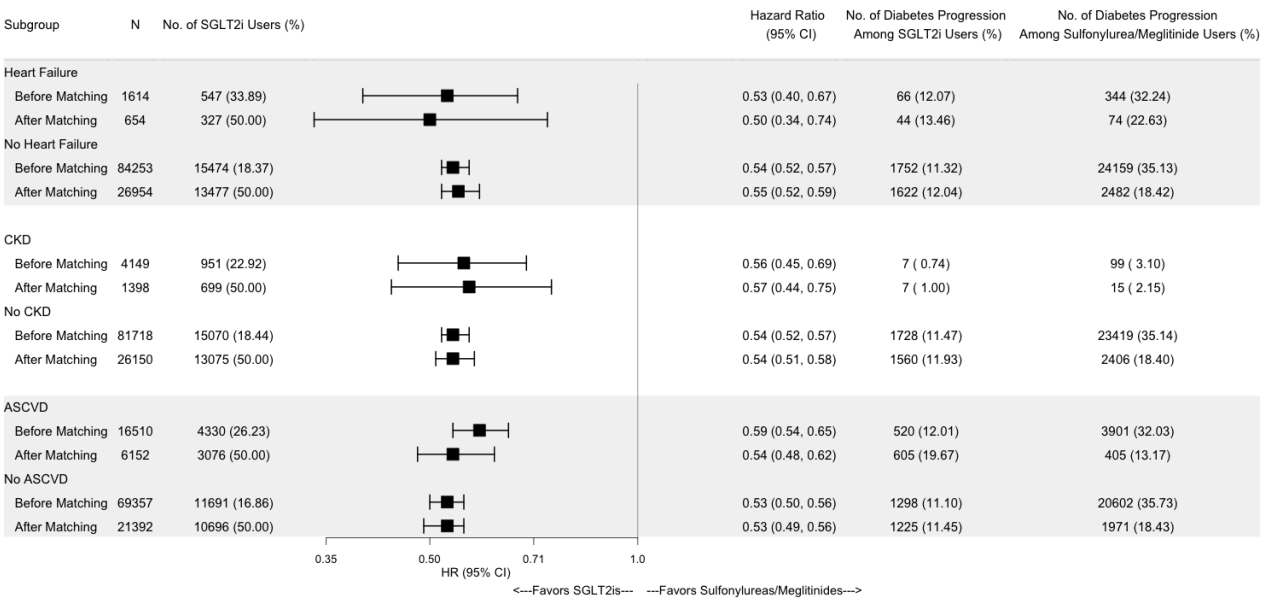


Sulfonylureas/Meglitinides	13840	7984	4813	3006	1719	1068	605	356	162	61
SGLT2is	13840	8939	5985	3895	2524	1538	904	488	201	27

SGLT2is: Sodium-Glucose Co-Transporter 2 Inhibitors

Figure 2 Kaplan–Meier curve of diabetes progression (up: before matching; down: after matching).

https://doi.org/10.2147/CLEP.S505242



SGLT2i: Sodium-Glucose Co-Transporter 2 Inhibitors; CKD: Chronic Kidney Disease; ASCVD: Atherosclerotic Cardiovascular Disease; HR: Hazard Ratio; CI: Confidence Interval

Figure 3 Results of subgroup analysis on diabetes progression between SGLT2i and sulfonylurea/meglitinide users.

meglitinide users. There were 59,942 (91.40%) sulfonylurea/meglitinide new users and 5,643 (8.60%) SGLT2i new users. After PSM, 5,480 pairs were matched (Table S9).

The hazard ratio of outcomes in the second sensitivity analysis was similar to that in the main analysis, but lower numerical values and a wider 95% confidence were found after matching (Table S10). SGLT2i users had a significantly lower hazard of diabetes progression compared to sulfonylurea/meglitinide users both before (HR: 0.54, 95% CI: 0.49–0.59, p-value < 0.001) and after matching (HR; 0.47, 95% CI: 0.42–0.53, p-value < 0.001). In terms of the individual component of outcomes, SGLT2i users had lower hazards of insulin initiation and increases in antidiabetic medication class both before and after matching. However, the hazard ratio of new acute glycemic complications was not significant both before and after matching, which was consistent with the findings from the main analysis. The Kaplan–Meier analysis also showed a significantly lower rate of diabetes progression between the two survival curves both before and after matching (Figure S9).

Validation Using the NTUH-iMD

In the third sensitivity analysis, we identified 2,127 eligible patients in the NTUH-iMD between July 1, 2016 and December 31, 2020. However, 695 patients lacked at least one measurement for either baseline LDL, baseline eGFR, or baseline HbA1c. Therefore, these patients were excluded from the analysis. Finally, there were 1,432 patients eligible for the analysis. A total of 1,019 (71.16%) patients were sulfonylurea/meglitinide new users and 413 (28.84%) patients were SGLT2i new users (Figure S10).

Table S11 presents the baseline characteristics of the NTUH-iMD sample. HbA1c is balanced between the two groups. Compared to sulfonylurea/meglitinide users, SGLT2i users were younger (62.27 vs 66.37 years old), had a higher proportion of males (67.80% vs 52.60%), were less likely to be included in 2016 (11.38% vs 78.12%), had slightly lower baseline level of LDL (86.15 mg/dL vs 88.76 mg/dL) and higher baseline level of eGFR (86.31 mL/min/1.73 m² vs 83.27 mL/min/1.73 m²).

In the outcome analysis, consistent results were found for diabetes progression (crude HR: 0.40, 95% CI: 0.30–0.55, p-value < 0.001; adjusted HR (aHR): 0.58, 95% CI: 0.40–0.84, p-value = 0.004) and increase in antidiabetic medication (crude HR: 0.39, 95% CI: 0.28–0.54, p-value < 0.001; aHR: 0.55, 95% CI: 0.37–0.80, p-value = 0.002). However, no

statistically significant result was found for insulin initiation (crude HR: 0.46, 95% CI: 0.14–1.57, p-value = 0.22; aHR: 1.29, 95% CI: 0.32–5.20, p-value = 0.72). We were unable to perform the analysis for the outcome of acute glycemic complications because of the low event number (Table S12).

Finally, in validating the outcomes of diabetes progression, our findings indicated that 62% of the SGLT2i and sulfonylurea/meglitinide users had an HbA1c level exceeding 7.0 prior to the add-on (Table S13).

Discussion

Our results showed that compared to sulfonylureas/meglitinides, use of SGLT2is was associated with a lower hazard of diabetes progression. Specifically, patients receiving SGLT2is may initiate their next line antidiabetic therapy, including insulin, later than those who received sulfonylureas/meglitinides as their second-line antidiabetic treatment. Given the concern of statin-associated insulin resistance, SGLT2is may be an optimal second-line choice for patients with diabetes who received statin treatment.

To the best of our knowledge, this is the first study comparing the efficacy of SGLT2is versus sulfonylureas/meglitinides on diabetes progression. Evidence suggests SGLT2is outperform sulfonylureas in glycemic control. Early clinical trials focused on the general diabetic population and found that dapagliflozin and empagliflozin were non-inferior to sulfonylureas as add-ons to metformin in HbA1c reduction.[24,25] Follow-up studies even showed that empagliflozin was associated with a greater HbA1c reduction compared to sulfonylureas.[26] However, the real-world effectiveness of SGLT2is versus sulfonylureas on glycemic control is limited.

In this study, we observed a higher proportion of patients taking medium- and high-intensity statins in the SGLT2i group. As the dose–response relationship between stain intensity and risk of DM development has been reported,[5,7] the high proportion of high-intensity statin use in SGLT2i users suggest a higher likelihood of diabetes progression compared to sulfonylurea/meglitinide users. This could lead to an underestimation of the protective effect of SGLT2is. Nevertheless, we still found significantly lower hazards of diabetes progression with SGLT2i use.

The ADA guidelines recommend SGLT2is for patients with ASCVD, heart failure, or CKD due to their known benefits. Our subgroup analyses consistently showed that SGLT2is were associated with a slower progression of diabetes across various patient populations, including those without traditional indications for SGLT2is, such as heart failure, chronic kidney disease, or atherosclerotic cardiovascular disease. This finding reinforces the robustness of the primary results, and highlights that SGLT2is, may offer benefits beyond glycemic control, potentially addressing statin-induced metabolic disturbances, even in patients without compelling indications for SGLT2 therapy.

The sensitivity analyses further supported the reliability of our findings. Consistent results, despite excluding ketoacidosis and NKHHS or limiting the study timeframe, suggest that SGLT2 inhibitors' protective effects are not influenced by outcome definitions or timeline variations. These analyses strengthen the conclusion that SGLT2is may be a preferred second-line therapy for statin-treated diabetes patients.

Together, these findings suggest that earlier introduction of SGLT2is may help delay diabetes progression in statin-treated patients. A prior observational study suggested that the protective effect of SGLT2is against all-cause mortality could be extended to patients with diabetes without cardiovascular disease and eGFR greater than 60 mL/min/1.73 m^2.[27] Collectively, these results suggest that the benefits of SGLT2is may extend beyond the subgroups specified in the guidelines, offering advantages beyond cardiorenal protection.

This study has some limitations. Firstly, claimes data allow us to see medication refills but not the patients' actual medication taking behavior. Second, due to the retrospective nature, some unmeasured confounders might exist. It could be argued that confounding by disease severity could be an issue, but we incorporated the DCSI (from the NHIRD), HbA1c (from the NTUH-iMD), and LDL levels (from the NTUH-iMD) into our study, and the results were robust. Third, due to the reimbursement restriction and guideline recommendation, we only included patients with diabetes with metformin as the first-line therapy. Future studies could explore the effectiveness and cost-benefit of SGLT2is on diabetes progression as the first-line therapy or in patients using statins without a diabetes diagnosis. Finally, our analyses used a large nationwide database, ensuring that our results are broadly applicable to the Taiwanese population. While further research is needed to see if these findings apply to other populations, particularly Western populations, current evidence does not suggest racial differences in diabetes treatment response or progression, so our findings should

be generally relevant. Additionally, future randomized controlled trialsare necessary to confirm these observations in a controlled setting.

Conclusion

Our findings suggest that SGLT2is may be a preferred second-line therapy for statin-treated patients by mitigating diabetes progression and potentially addressing statin-induced metabolic disturbances. While these results provide real-world evidence supporting their clinical benefits, further validation through randomized controlled trials or observational studies with comprehensive laboratory data is warranted to confirm these findings and assess their generalizability across diverse populations.

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Disclosure

The authors report no conflicts of interest in this work.

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