



Association of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitor Use With Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus Patients With Stabilized Acute Myocardial Infarction: A Propensity Score Matching Study

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Background: Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM), who are at a greater risk of acute myocardial infarction (AMI) and sudden cardiac death. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce cardiovascular events and mortality in T2DM patients with a risk of cardiovascular disease. This study aimed to investigate the effect of SGLT2 inhibitor use on the adverse cardiovascular and renal outcomes in T2DM patients with AMI.

Methods: A total of 1,268 patients admitted to the Coronary Care Unit due to AMI were retrospectively screened. Patients taking SGLT2 inhibitors before or during the index AMI hospitalization were assigned as group 1. Patients who never received SGLT2 inhibitors were assigned as group 2. Patients in groups 1 and 2 were matched in a 1:2 ratio, and 198 T2DM patients with stabilized AMI were retrospectively enrolled for the final analysis.

Results: With a mean follow-up period of 23.5 ± 15.7 months, 3 (4.5%) patients in group 1 and 22 (16.7%) patients in group 2 experienced rehospitalization for acute coronary syndrome (ACS), while 1 (1.5%) patient in group 1 and 7 (5.3%) patients in group 2 suffered sudden cardiac death. The Kaplan–Meier curves demonstrated that the patients in group 1 had a lower risk of adverse cardiovascular outcomes. According to the multivariate analysis, the baseline estimated glomerular filtration rate (eGFR) ($P = 0.008$, 95% CI: 0.944–0.991) and the use of SGLT2 inhibitors ($P = 0.039$, 95% CI: 0.116–0.947)

were both independent predictors of adverse cardiovascular outcomes. On the other hand, the use of SGLT2 inhibitors was not associated with adverse renal outcomes.

Conclusion: In T2DM patients with stabilized AMI, the use of SGLT2 inhibitors was associated with a lower risk of adverse cardiovascular outcomes. In addition, the baseline renal function was also an independent predictor of adverse cardiovascular outcomes.

Keywords: diabetes, mortality, hospitalization, SGLT2 inhibitor, myocardial infarction

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM) (1–3). Patients with T2DM are at a greater risk of acute myocardial infarction (AMI), heart failure, and sudden cardiac death (4–7). A report by the Global Registry of Acute Coronary Events has demonstrated that in CAD patients presented to hospitals, approximately 1 out of 4 has a history of T2DM, which shows the high co-occurrence rate of T2DM and CAD (8). In addition, previous studies have revealed that T2DM patients and CAD patients have a similar risk for sudden cardiac death and major adverse cardiovascular events (MACE) (9). Therefore, these patients are considered as a single population regarding their risk for sudden cardiac death and MACE (10, 11).

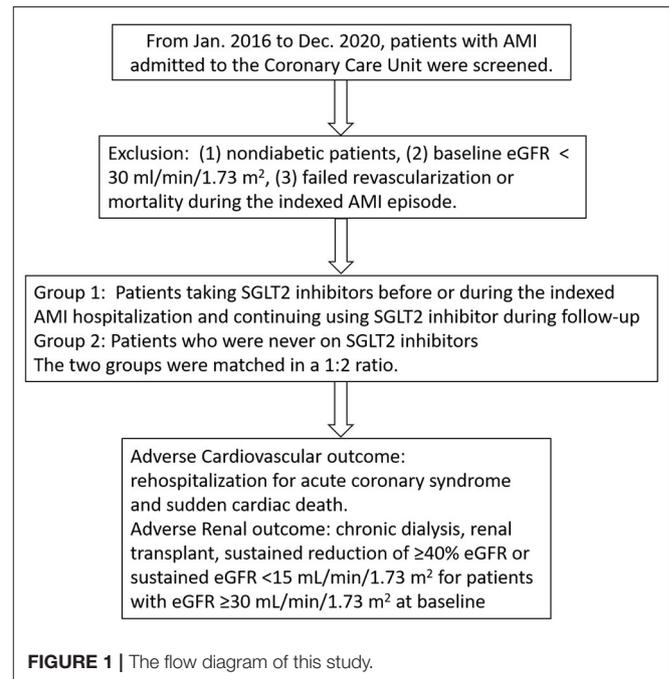
Sodium-glucose cotransporter (SGLT) 2 inhibitors comprise a novel class of oral hypoglycemic agents that has been shown to improve cardiovascular outcomes in patients with T2DM and heart failure (11–14). Recently, four cardiovascular outcome trials (CVOTs) have been conducted to explore the safety and efficacy of SGLT2 inhibitors on cardiovascular outcomes in T2DM patients with a high risk of cardiovascular events (EMPA-REG OUTCOME, DECLARE-TIMI 58, CANVAS, and VERTIS-CV) (15–18). Based on the data of these CVOTs, a meta-analysis concluded that SGLT2 inhibitors reduce the risk for cardiovascular events and mortality, especially in patients with both T2DM and CAD at baseline (19).

Based on these results, the 2019 European Society of Cardiology Guidelines on Diabetes and Cardiovascular Diseases listed SGLT2 inhibitors as one of the first-line glucose-lowering drugs for the treatment of T2DM patients with a high risk of cardiovascular disease (20). Nevertheless, although previous studies have shown the effect of SGLT2 inhibitors on diabetic patients at a high risk for cardiovascular disease, their effect on T2DM patients with stabilized AMI remains unknown. Therefore, this study was designed to investigate the effect of SGLT2 inhibitors on long-term cardiovascular and renal outcomes in T2DM patients after successful revascularization and stabilization of AMI.

METHODS

Patient Population

The present study was approved by the Institutional Review Board at Taipei Veterans General Hospital, Taipei, Taiwan (IRB no. 2022-01-033CC). The data used in this study were anonymized before analysis. From January 2016 to December



2020, a total of 1,268 patients admitted to the Coronary Care Unit due to AMI were retrospectively screened in this study. The exclusion criteria were as follows: (1) nondiabetic patients, (2) those with a baseline estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m², (3) those who experienced failed revascularization or mortality during the index AMI episode. The patients who had been taking SGLT2 inhibitors before or during the index AMI episode, and continued using SGLT2i during the clinics follow-up, were defined as group 1. The patients who had never used SGLT2 inhibitors were defined as group 2. As shown in **Figure 1**, the study subjects of groups 1 and 2 were matched in terms of age, sex, congestive heart failure (CHF), and chronic kidney disease (CKD) at a 1:2 ratio. The definition of AMI was based on the diagnostic criteria; AMI was diagnosed by a coronary angiogram and confirmed by two expert cardiologists (21). By definition, all of the enrolled patients received successful revascularization and were discharged with stable conditions.

Data Collection

The demographic profiles, comorbidities, laboratory data, and medication profiles of the participants were collected by the review of medical records. After being discharged, all of the

participants were scheduled to have a follow-up visit at the clinic 2 weeks later. The subsequent clinic visits were arranged at 1–3-month intervals, according to the discretion of the attending cardiologist. Data of the follow-up period were obtained by a medical record review and confirmed by a telephone interview. The composite of rehospitalization due to acute coronary syndrome (ACS) or sudden cardiac death was defined as an adverse cardiovascular outcome. Meanwhile, the composite of the initiation of chronic dialysis, renal transplant, eGFR decline of $\geq 40\%$, or eGFR of < 15 mL/min/1.73 m² was defined as an adverse renal outcome. Chronic dialysis was defined as dialysis treatment for more than 90 days (22).

Statistical Methods

All analyses were performed using SPSS statistical software, version 24.0 (SPSS, Inc., Chicago, IL, USA). Continuous variables were reported as the mean and standard deviation. Categorical variables were reported as frequencies and percentages. The chi-squared test was used to analyze categorical variables. Kaplan–Meier survival curves with the log-rank test were used to compare the occurrence of outcomes. The Cox proportional regression model was used to calculate the hazard ratio (HR) for the occurrence of outcomes.

RESULTS

Baseline Characteristics of the Study Subjects

This retrospective observational study included 198 AMI patients, among whom 66 patients were in group 1, and 132 patients were in group 2. The mean age of the patients was 66.1 ± 12.3 years old in group 1 and 67.7 ± 11.9 years old in group 2. The age, sex, comorbidities, and baseline eGFR were similar between the two groups. Notably, the percentage of patients with ST-elevation myocardial infarction, the thrombolysis in myocardial infarction (TIMI) risk score, and the volume of contrast medium used for revascularization were not significantly different between the two groups (Table 1). The above findings suggest that the two matched groups presented to the hospital with a similar severity of AMI. In group 1, the majority of SGLT2 inhibitor prescription was empagliflozin (78.8%), and 12(18.2%) patients have been using the SGLT2 inhibitors before the index AMI hospitalization, with the mean duration of 12.8 ± 9.2 months.

Risk of Adverse Cardiovascular and Renal Outcomes

With a mean follow-up period of 23.5 ± 15.7 months (data not shown), 3 (4.5%) patients in group 1 and 22 (16.7%) patients in group 2 experienced rehospitalization due to ACS, while 1 (1.5%) patient in group 1 and 7 (5.3%) patients in group 2 experienced sudden cardiac death. Overall, the adverse cardiovascular outcomes occurred more frequently in group 2 (Table 1). To confirm the higher risk of adverse cardiovascular outcomes in group 2, Kaplan–Meier survival curves were constructed. The results demonstrated that the patients in group 1 had a longer adverse cardiovascular outcome-free survival than

TABLE 1 | Baseline characteristics of the study subjects.

	Group 1 (n = 66)	Group 2 (n = 132)	P-value
Age, years	66.1 \pm 12.3	67.7 \pm 11.9	0.382
Male, n (%)	50 (75.8%)	95 (71.9%)	0.612
Dyslipidemia, n (%)	21 (31.8%)	40 (30.3%)	0.871
Diabetes mellitus, n (%)	66 (100.0%)	132 (100.0%)	-
Congestive heart failure, n (%)	5 (7.6%)	6 (4.5%)	0.511
Hypertension, n (%)	44 (66.7%)	97 (73.5%)	0.323
Coronary artery disease, n (%)	66 (100.0%)	132 (100.0%)	-
Chronic kidney disease, n (%)	5 (7.6%)	15 (11.4%)	0.464
Old stroke, n (%)	4 (6.1%)	11 (8.3%)	0.777
Atrial fibrillation, n (%)	7 (10.6%)	10 (7.6%)	0.591
SGLT2 inhibitor			
Empagliflozin, n (%)	52 (78.8%)	0 (0%)	-
Dapagliflozin, n (%)	12 (18.2%)	0 (0%)	-
Canagliflozin, n (%)	2 (3%)	0 (0%)	-
Insulin therapy, n (%)	8 (12.1%)	20 (15.2%)	0.668
Left ventricular ejection fraction, %	52.0 \pm 12.8	52.3 \pm 10.6	0.873
eGFR, mL/min/1.73 m ²	72.1 \pm 22.7	67.7 \pm 18.6	0.172
ST elevation myocardial infarction, n (%)	30 (45.5%)	48 (36.4%)	0.222
TIMI risk score	3.8 \pm 1.8	4.1 \pm 1.5	0.282
Contrast medium during revascularization, mL	204.6 \pm 97.9	217.1 \pm 106.3	0.473
Adverse cardiovascular outcomes, n (%)	4 (6.1%)	29 (22.0%)	0.004
Rehospitalization for ACS, n (%)	3 (4.5%)	22 (16.7%)	-
Sudden cardiac death, n (%)	1 (1.5%)	7 (5.3%)	-
Adverse renal outcomes, n (%)	4 (6.1%)	17 (12.9%)	0.220

ACS, Acute coronary syndrome; eGFR, estimated glomerular filtration rate; SGLT2, sodium glucose cotransporter 2; TIMI, thrombolysis in myocardial infarction.

the patients in group 2 (Figure 2). The above findings suggest that post-AMI patients treated with SGLT2 inhibitors have a lower risk of adverse cardiovascular outcomes than those who are not taking this class of drug.

Regarding the adverse renal outcomes, there were 4 (6.1%) events in group 1 and 17 (12.9%) events in group 2; however, the difference was not significantly different between the two groups (Table 1). Similarly, the Kaplan–Meier survival curves showed that the adverse renal outcome-free survival was not significantly different between the two groups (Figure 3). The above findings suggest that SGLT2 inhibitors do not change the risk of adverse renal outcomes in post-AMI patients.

Predictors of Rehospitalization for ACS and Sudden Cardiac Death

Compared with the patients without adverse cardiovascular outcomes, those who experienced adverse cardiovascular outcomes were older (72.3 ± 14.6 years old vs. 68.8 ± 11.5 years old, $P = 0.045$) and had a lower baseline eGFR (58.0 ± 20.8 vs. 69.3 ± 20.3 , $P = 0.004$). Notably, the percentage of patients using SGLT2 inhibitors was significantly lower in the group of patients

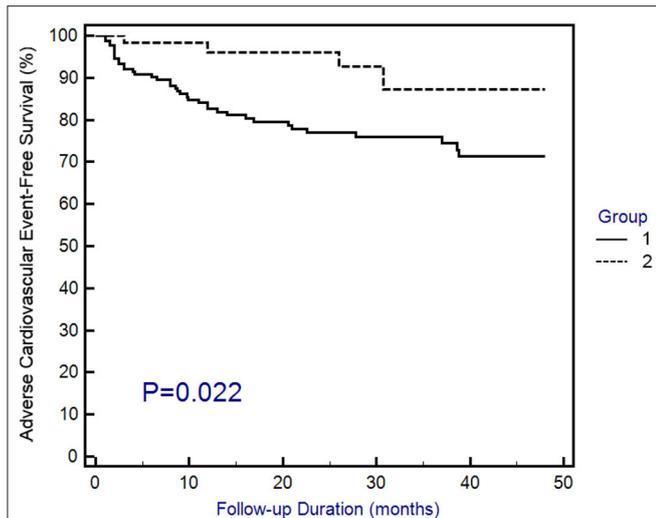


FIGURE 2 | Kaplan–Meier curves of adverse cardiovascular outcomes. Adverse cardiovascular outcomes were defined as the composite of rehospitalization due to acute coronary syndrome or sudden cardiac death. Statistical analysis was performed using the log-rank test.

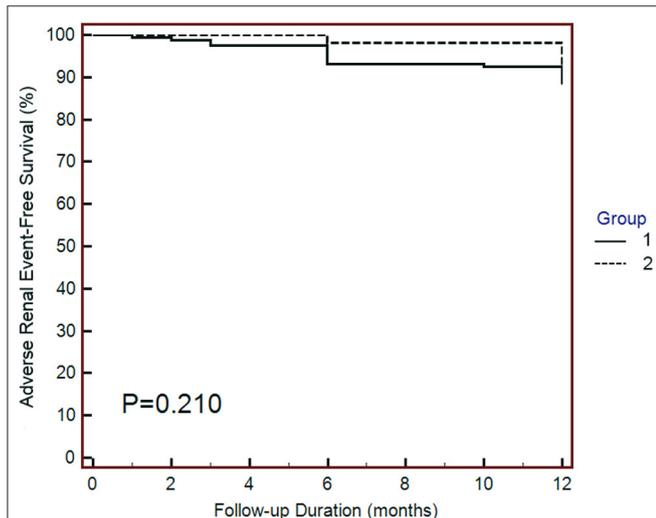


FIGURE 3 | Kaplan–Meier curves of adverse renal outcomes. Adverse renal outcomes were defined as chronic dialysis, renal transplant, sustained reduction of $\geq 40\%$ eGFR, or sustained eGFR < 15 mL/min/1.73 m² for patients with eGFR ≥ 30 mL/min/1.73 m² at baseline. The adverse renal outcomes were similar between the two groups. Statistical analysis was performed using the log-rank test.

with an adverse cardiovascular event (12.1 vs. 37.6%, $P = 0.004$, **Table 2**).

To build the multivariate regression model, the candidate predictors were evaluated for their association with adverse cardiovascular outcomes using univariate Cox proportional regression analysis. The predictors with P -values of < 0.05 were included in the multivariate Cox proportional regression model. Accordingly, age, baseline eGFR, and the use of SGLT2 inhibitors were included in the multivariate regression model.

TABLE 2 | Comparison between patients with vs. without adverse cardiovascular events.

	Patients with an adverse CV event (n = 33)	Patients without an adverse CV event (n = 165)	P-value
Age (years)	72.3 ± 14.6	66.8 ± 11.5	0.045
Male (n, %)	22 (66.7%)	132 (80%)	0.402
Dyslipidemia	11 (33.3%)	55 (33.3%)	0.838
Diabetes mellitus (n, %)	33 (100.0%)	165 (100.0%)	-
CHF (n, %)	4 (12.1%)	8 (4.8%)	0.097
Hypertension (n, %)	27 (81.8%)	127 (77.0%)	0.208
CAD (n, %)	33 (100.0%)	165 (100.0%)	-
CKD (n, %)	7 (21.2%)	20 (12.1%)	0.150
Old stroke (n, %)	1 (3%)	16 (9.7%)	0.482
Atrial fibrillation (n, %)	3 (9.1%)	16 (9.7%)	1.000
LVEF (%)	51.3 ± 9.8	52.1 ± 11.6	0.725
eGFR (mL/min/1.73 m ²)	58.0 ± 20.8	69.3 ± 20.3	0.004
STEMI (%)	11 (33.3%)	70 (42.4%)	0.565
TIMI risk score (mean)	4.3 ± 1.4	4.0 ± 1.6	0.274
SGLT2 inhibitor	4 (12.1%)	62 (37.6%)	0.004

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose cotransporter 2; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

TABLE 3 | Univariate and multivariate analyses of adverse cardiovascular outcomes.

	Cox Univariate Analysis		Cox Multivariate Analysis	
	P-value	95% CI	P-value	95% CI
Age (years)	0.008	1.010–1.038	0.272	0.985–1.055
Male (n, %)	0.454	0.368–1.564	-	-
Dyslipidemia	0.745	0.547–2.327	-	-
Diabetes mellitus (n, %)	-	-	-	-
CHF (n, %)	0.145	0.764–6.195	-	-
Hypertension (n, %)	0.141	0.803–4.711	-	-
CAD (n, %)	-	-	-	-
CKD (n, %)	0.140	0.814–4.323	-	-
Old stroke (n, %)	0.250	0.042–2.277	-	-
Atrial fibrillation (n, %)	0.924	0.323–3.472	-	-
LVEF (%)	0.549	0.958–1.023	-	-
eGFR (mL/min/1.73 m ²)	0.003	0.953–0.990	0.008	0.944–0.991
STEMI (%)	0.272	0.210–1.551	-	-
TIMI risk score (mean)	0.278	0.915–1.363	-	-
SGLT2 inhibitor use	0.030	0.110–0.895	0.039	0.116–0.947

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SGLT2, sodium-glucose cotransporter 2; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

The results demonstrated that only the baseline eGFR ($P = 0.008$, 95% CI: 0.944–0.991) and the use of SGLT2 inhibitors ($P = 0.039$, 95% CI: 0.116–0.947) remained significantly

associated with the risk of adverse cardiovascular outcomes (Table 3).

DISCUSSION

The main findings of this study were as follows: (1) In patients with T2DM and stabilized AMI, the use of SGLT2 inhibitors was associated with a lower risk of adverse cardiovascular outcomes. (2) Among diabetic patients with stabilized AMI, SGLT2 inhibitor use and a lower baseline renal function were both independent predictors of adverse cardiovascular outcomes. (3) The use of SGLT2 inhibitors was not significantly associated with adverse renal outcomes. These findings suggest that the use of SGLT2 inhibitors protects diabetic patients from AMI by reducing adverse cardiovascular events but does not change the risk of adverse renal outcomes in post-AMI patients.

Previous studies have demonstrated that in the early stage of AMI, SGLT2 inhibitor use reduces the myocardial infarct size through activation of signal transducer and activator of transcription 3 and downregulation of inflammatory responses in the infarcted myocardium (23). In addition, in diabetic mice, SGLT2 inhibitors reduce oxidative stress by decreasing the production of reactive oxygen species and the activity of nicotinamide-adenine dinucleotide phosphate (24, 25). Furthermore, SGLT2 inhibitors also have been shown to reduce oxidative stress through increasing endothelial nitric oxide synthase and nitric oxide formation in porcine endothelial cells (26).

Regarding atherosclerosis progression, previous studies have demonstrated that SGLT2 inhibitors suppress the transmigration of monocytes into the intraintral space (24, 25, 27). Moreover, SGLT2 inhibitors also reduce the number of atheroma plaques as well as the size and the surface area of atherosclerotic lesions in animal models of diabetes and atherosclerosis (24, 25, 28–30). Additionally, SGLT2 inhibitors have been shown to stabilize atherosclerotic plaques by reducing the number of macrophages and the cholesterol crystal content in the atherosclerotic plaques (24, 29). The abovementioned studies suggest that SGLT2 inhibitors may treat the infarcted myocardium by restoring endothelial function, decreasing oxidative stress, reducing inflammation, and inhibiting the evolution of monocytes to macrophages to foam cells. Furthermore, SGLT2 inhibitors may prevent the progression of coronary atherosclerosis by reducing the plaque burden, changing the plaque composition, and increasing the plaque stability.

Effects of SGLT2 Inhibitors on Post-infarcted Adverse Cardiac Remodeling

Following AMI, heart failure with adverse remodeling of left ventricle characterized by chamber dilatation and impaired cardiac function is the common outcome (31). In one recently published meta-analysis, including a total of 13 randomized controlled trials that evaluated the effects of SGLT2 inhibitors

on cardiac remodeling in patients with T2DM and/or HF, SGLT2 inhibitors improved left ventricular (LV) ejection fraction, LV mass, LV mass index, LV end-systolic volume, LV end-systolic volume index, and E-wave deceleration time significantly (32). There were plausible effects of SGLT2 inhibitors on adverse cardiac remodeling. First, myocardial ischemia could impair cardiomyocyte autophagy, which has been shown an essential mechanism that protects against adverse cardiac remodeling (33). Recent experimental studies have indicated that SGLT2 inhibitors might exert cardioprotective effects by stimulating autophagy (34). Second, cardiac mitochondrial dysfunction during ischaemia and reperfusion injury is a critical determinant of post-infarcted cardiac cell death, and is associated with future adverse cardiac remodeling (35). There have been several studies demonstrated that cardiac mitochondrial function could be improved by SGLT2 inhibitors (36–38). Taken together, reversed cardiac remodeling may be a mechanism responsible for the favorable clinical effects of SGLT2 inhibitor on patients with heart failure (39).

Results of Previous Studies of SGLT2 Inhibitors to Treat Coronary Artery Disease

The meta-analysis of the four major CVOTs mentioned above showed a 12% reduction of the risk for MACE in the group taking SGLT2 inhibitors (HR, 0.88; 95%CI: 0.82–0.94) (40). In particular, there was a 17% reduction in sudden cardiac deaths and a 12% reduction in myocardial infarctions. In this meta-analysis, the authors also analyzed the effects of SGLT2 inhibitors in those with vs. without cardiovascular disease at baseline. The results showed that the risk reduction of myocardial infarction in the secondary prevention cohort was more significant than that in the primary prevention cohort (HR: 0.86; 95% CI: 0.80–0.93 for secondary prevention; and HR: 0.94; 95% CI: 0.82–1.07 for primary prevention). The other two meta-analysis studies also revealed risk reductions of 18% and 21%, respectively, for cardiovascular mortality in the SGLT2 inhibitor-treated group (41, 42). In accordance with these previous studies, our results showed that the patients taking SGLT2 inhibitors had fewer adverse cardiovascular outcomes, including rehospitalization for ACS and sudden cardiac death. Since the study population consisted of patients with stabilized AMI, our results demonstrate the protective effect of SGLT2 inhibitors on the secondary prevention of AMI, which is in line with a previous report (40).

Results of Previous Studies of SGLT2 Inhibitors to Treat Chronic Kidney Disease

The meta-analysis of four CVOTs, including 38,723 participants with T2DM, demonstrated a risk reduction of 35% for end-stage renal disease in patients taking SGLT2 inhibitors (43). Nonetheless, another meta-analysis showed that while treatment with SGLT2 inhibitors reduced the risk of major renal outcomes by 46% in patients with macroalbuminuria and atherosclerotic cardiovascular disease, it had no significant effect on renal outcomes in the subgroup with eGFR <60 mL/min/1.73 m²

(HR: 0.74, 95% CI: 0.51–1.06) (44). In the current study, we did not observe a significant benefit of SGLT2 inhibitors on renal outcomes in diabetic patients with AMI. This finding could be explained by the small number of cases analyzed or the limited observation period.

In the past two decades, although the mortality due to AMI has improved (45, 46), the long-term cardiovascular mortality and post-AMI heart failure remain significant issues (45, 47). Thus, cardiac protection with early reperfusion to reduce the size of the myocardial infarct and the incidence of post-AMI cardiovascular adverse events are important topics to be studied. To the best of our knowledge, this is the first study showing that SGLT2 inhibitor use reduces the risk of adverse cardiovascular outcomes in T2DM patients with stabilized AMI.

This study has several limitations that must be addressed. First, due to the long period of enrollment, heterogeneity in treatment/stenting strategies may exist and confound the analysis. A second limitation is the single-center design and the relatively small number of included patients. A third limitation is that the physician skills regarding coronary revascularization were not controlled, which may also confound the analysis. Fourth, although a propensity score-adjusted analysis was employed to minimize the selection bias, remaining bias may still affect the analysis. Fifth, the retrospective nature of this study and the low number of events in each group limited further important subgroup analyses, such as an analysis based on the presence of absence of heart failure.

In conclusion, the findings of the present study might suggest that in T2DM patients with stabilized AMI, the use of SGLT2 inhibitors is associated with a lower risk of adverse cardiovascular outcomes, including rehospitalization for ACS and sudden cardiac death. Our study also demonstrates at least partly that the use of SGLT2 inhibitors could provide cardioprotection to T2DM patients with AMI. However, studies with a larger sample size are needed to verify these findings.

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DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, Taipei Veterans General Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

T-YC and C-TLu analyzed the data and drafted the manuscript. H-LH and R-HC collected and analyzed the data. C-CC and C-TLiu drew the tables and figures. P-HH and S-JL designed the study and revised the manuscript. All authors contributed to the article and approved the submitted version.

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