Acta Cardiol Sin 2018;34:211–223
Original Article
doi: 10.6515/ACS.201805_34(3).20180207B

Coronary Artery Disease

In-Hospital Implementation of Evidence-Based Medications is Associated with Improved Survival in Diabetic Patients with Acute Coronary Syndrome – Data from TSOC ACS-DM Registry

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Background: Patients with acute coronary syndrome (ACS) and diabetes mellitus (DM) receive less aggressive treatment and have worse outcomes in Taiwan. We sought to explore whether the current practices of prescribing guideline-directed medical therapy (GDMT) for ACS and clinical outcomes have improved over time.

Methods: A total of 1534 consecutive diabetic patients with ACS were enrolled between 2013 and 2015 from 27 hospitals in the nationwide registry initiated by the Taiwan Society of Cardiology (the TSOC ACS-DM Registry). Baseline and clinical demographics, treatment, and clinical outcomes were compared to those of 1000 ACS patients with DM recruited in the Taiwan ACS-full spectrum (ACS-FS) Registry, which was performed between 2008 and 2010.

Results: Compared to the DM patients in the Taiwan ACS-FS Registry, even though reperfusion therapy was carried out in significantly fewer patients, the primary percutaneous coronary intervention (PCI) rate for ST-segment elevation myocardial infarction (STEMI) and the prescription rates of GDMT for ACS including P2Y12 inhibitors, renin-angiotensin blockers, beta-blockers, and statins were significantly higher in those in the TSOC ACS-DM Registry. Moreover, significant reductions in 1-year mortality, recurrent nonfatal MI and stroke were observed compared to those of the DM patients in the Taiwan ACS-FS Registry. Multivariate analysis identified reperfusion therapy in combination with GDMT as a strong predictor of better 1-year outcomes [hazard ratio (95% confidence interval) = 0.54 (0.33-0.89)].

Conclusions: Marked improvements in performing primary PCI for STEMI and prescribing GDMT for ACS were observed over time in Taiwan. This was associated with improved 1-year event-free survival in the diabetic patients with ACS.

Key Words: Acute coronary syndrome • Guideline-directed medical therapy • Oral anti-diabetic drug • Outcome • Type 2 diabetes

Received: September 20, 2017 Accepted: February 7, 2018

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INTRODUCTION

Diabetes mellitus (DM) is associated with increased cardiovascular morbidity and mortality.[1,2] Coronary artery disease (CAD) is the most common cause of cardiovascular morbidity and mortality. Cardiovascular deaths are increased by up to four-fold in diabetic compared to non-diabetic patients.[3] In particular, after acute coronary syndrome (ACS) or acute myocardial infarction with or without ST-segment elevation (STEMI or NSTEMI), patients with DM have been reported to have worse survival rates compared with those without DM.[4-6] Hyperglycemia is an important predictor of long-term outcomes after acute coronary events.[7,8] The management of many risk factors including blood pressure, cholesterol and hemoglobin A1c (HbA1c) has been shown to reduce vascular complications in patients with type 2 DM.[9,10] Therefore, lifestyle changes and aggressive management of hyperglycemia is recommended in current clinical guidelines.[10]

Similar to hypertension control, most diabetic patients receive anti-diabetic therapy indefinitely for glycemic control. By the end of 2015, six groups of oral anti-diabetic drugs (OADs) were approved for clinical use in Taiwan, including biguanides, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones (TZD), and dipeptidyl peptidase-4 inhibitors (DPP-4is). Metformin has been shown to reduce cardiovascular mortality and non-fatal cardiovascular events compared with other anti-diabetic treatments in diabetic patients with cardiovascular disease and myocardial infarction.[11-14] However, no prospective studies with metformin have been performed in patients with type 2 DM after ACS. Some first generation sulfonylureas have been shown to increase the risk of cardiovascular death in patients with type 2 DM,[15] although second generation sulfonylureas have not shown the same adverse effects.[16,17] Therefore, except that first generation sulphonylureas are contraindicated in patients with type 2 DM with ACS, other types of OADs are not contraindicated in this special group of diabetic patients as suggested by the French Society of Cardiology and French Society of Diabetes.[18] In Taiwan, DPP-4is are increasingly being used, and they have become the third most commonly prescribed OAD in type 2 diabetic patients because of fewer adverse events (less hypoglycemia and weight gain).[19] However, the clinical outcomes of using DPP-4is in patients with type 2 DM and ACS are unknown. Pioglitazone has been shown to be beneficial for type 2 diabetic patients with ACS,[20] although some recent studies have reported an increased risk of bladder cancer with pioglitazone.[21,22] Other groups of OADs are less frequently prescribed in Taiwan.

To reach the therapeutic goal, combining therapy with OADs is very common and is widely used in clinical practice. The outcomes of combining sulfonylureas and metformin is controversial.[23,24] The combination of metformin and DPP-4is in patients with type 2 DM and ACS has yet to be reported. Data regarding comparisons of metformin plus pioglitazone and metformin plus DPP-4is in patients with type 2 DM and ACS are also lacking.

Therefore, the aim of the present prospective observational study was to explore the current practices of prescription of evidence-based cardiovascular medications and OADs for glycemic control, and clinical outcomes in this high-risk group of patients in Taiwan.

METHODS

Study design

This prospective, nationwide, multi-center, non-interventional, observational study, the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology (TSOC ACS-DM Registry), was initiated by the Scientific Committee of the TSOC. Sites were selected for the registry by the Scientific Committee of TSOC to ensure good quality and representation of the diabetic ACS population. Each participating site was requested to enroll 30-100 consecutive patients who met the study criteria during the 12-month recruitment period of the study. This consecutive recruitment was required to limit subject selection bias. All of the participating hospitals could perform 24/7 primary percutaneous coronary interventions (PCIs) as listed in the Supplement Material.

Data including the patients' baseline characteristics, past medical history, risk factors, clinical diagnosis, medications including OADs at the time of admission and discharge, in-hospital biochemistry, revascularization interventions/procedures, and in-hospital and 1-year outcomes regarding mortality, recurrent nonfatal myocardial infarction (MI) and stroke were collected.

The patients were treated according to international or local guidelines, evidence-based strategies and local approved labeling. The protocol and consent forms were consistent with the Good Clinical Practice, the Declaration of Helsinki, and all relevant regulations. The ethics committee of each participating hospital approved this study, and all of the enrolled patients provided written informed consent.

Patient recruitment

Patients who were 20 years of age or older, those diagnosed with ACS within 30 days of patient enrollment, and those with type 2 DM (either newly or previously diagnosed), and who provided informed consent were eligible to be included in this study. All patients could only be enrolled once in this registry, and later ACS episodes were recorded as adverse events.

Patients with the following conditions were excluded from the study: ACS accompanied by or precipitated by significant co-morbidities e.g. motor vehicle accidents, trauma, severe gastrointestinal bleeding, peri-operative or peri-procedural MI, or participating in an investigational drug study.

Definition of type 2 DM and ACS

The diagnosis of type 2 DM was based on the World Health Organization and American Diabetes Association criteria: i.e., HbA1c level of 6.5% or higher, or fasting venous plasma glucose concentration of 7.0 mmol/L (126 mg/dL) or higher, or 2-hour post-glucose load venous plasma glucose of 11.1 mmol/L (200 mg/dL) or higher, confirmed on two occasions prior to enrollment in the registry.

ACS represents a heterogeneous spectrum of conditions ranging from unstable angina (UA), NSTEMI to STEMI. STEMI was defined as presentation with clinical features consistent with ACS (chest pain or overwhelming shortness of breath > 20 minutes duration at rest) together with persistent ST elevation > 1 mm in two or more contiguous leads or with new or presumed new left bundle branch block pattern on initial electrocardiogram (ECG). NSTEMI was defined as presentation with clinical features consistent with ACS (chest pain or overwhelming shortness of breath ≥ 10 minutes duration at rest) with no evidence of persistent STEMI. These patients were also required to have creatine kinase-MB (CK-MB) or troponin T or I levels greater than the upper limit of normal. If data on CK-MB or troponin T or I were not available, total CK greater than two times the upper limit of normal was acceptable. Unstable angina was defined as a history of chest discomfort or ischemic symptoms for ≥ 10 minutes at rest with persistent or transient ST-segment deviation ≥ 1 mm in one or more ECG leads without elevation of CK-MB or troponin T or I, but with a Thrombolysis in Myocardial Infarction (TIMI) risk score ≥ 3.

Data collection

The demographic data, clinical characteristics, biochemistry data, inpatient therapy, and in-hospital outcomes including mortality, recurrent non-fatal MI, and nonfatal stroke were collected by the study coordinators at the study sites. Medications at admission, during the in-hospital stay, and at discharge were also collected, retrospectively and prospectively. All data were then submitted electronically to a central laboratory for verification.

Statistical analysis

Data were transferred from the database to the Statistical Program for Social Sciences program (version 17.0 for Windows, SPSS Inc., Chicago, IL, USA). Univariate comparisons of demographic parameters between groups were made. Continuous variables are expressed as mean ± standard deviation or median (interquartile range). For comparability between groups, the chi-square test or Fisher's exact test was used for categorical variables, and analysis of variance (ANOVA) was used for continuous variables. In multivariable analyses, the predictors of adverse outcomes at 1 year were identified.

Between October 2008 and January 2010, a total of 3183 eligible patients from 39 medical centers and regional hospitals in Taiwan were enrolled in another large observational, prospective study, the Taiwan ACS Full Spectrum (Taiwan ACS-FS) Registry. The disease management data collected at admission, during the in-hospital stay, and 1-year outcomes of the 1000 diabetic patients (DM subgroup) in the Taiwan ACS-FS Registry were used as historical controls.[6] Reperfusion therapy was defined as receiving PCI or pharmacological reperfusion for thrombolysis during the index admission. Guideline-directed medical therapy (GDMT) was defined as

ACS patients who received P2Y12 inhibitors, renin-angiotensin blockers, beta-blockers, or statins. These parameters were also compared between the two registries and different ACS subgroups in the TSOC ACS-DM Registry.

RESULTS

Demographics and baseline characteristics

A total of 1534 eligible patients were enrolled between 2013 July and 2015 December from 27 medical centers and regional hospitals throughout Taiwan. Table 1 shows the key baseline characteristics of the diabetic patients with ACS in the TSOC ACS-DM and Taiwan ACS-FS registries.

As in the previous Taiwan ACS-FS Registry, the current TSOC ACS-DM Registry had a male preponderance of 71.3%. The mean age of the enrolled patients in the TSOC ACS-DM Registry was similar to that of the diabetic patients in the Taiwan ACS-FS Registry. A significantly lower proportion of the patients in the TSOC ACS-DM Registry had Killip class ≥ III symptoms compared to the Taiwan ACS-FS Registry (16.3% vs. 26.9%, $p < 0.0001$). There were no significant differences in a previous history of hypertension, dyslipidemia, current smoking, CAD, stroke, peripheral artery disease, and heart failure between the two registries.

Significantly fewer patients who had CAD prior to enrollment had previous MI, underwent PCI or coronary artery bypass grafting (CABG) in the TSOC ACS-DM Registry compared to those in the Taiwan ACS-FS Registry (16.9% vs. 28.7%, $p < 0.0001$; 26.3% vs. 51.3%, $p < 0.001$; and 5.5% vs. 10.3%, $p = 0.005$, respectively). Moreover, significantly more diabetic patients in the TSOC ACS-DM Registry had a family history of CAD (30.8% vs. 22.2%, $p < 0.0001$).

Overall, 29.7% of the patients enrolled in the TSOC ACS-DM Registry had a discharge diagnosis of STEMI, which was significantly lower than that reported in the Taiwan ACS-FS Registry (29.7% vs. 43.7%, $p < 0.001$). However, the incidence rates of NSTEMI and UA were

Table 1. Baseline characteristics of the diabetic patients in the TSOC ACS-DM registry and Taiwan ACS-FS Registry

Variables	DM subgroup of the Taiwan ACS-FS Registry (n = 1000)	TSOC ACS-DM Registry (n = 1534)	p valve
Male gender, n (%)	698 (69.8)	1094 (71.3)	0.438
Age, mean (SD)	65.1 (11.9)	64.9 (11.9)	0.891
Killip Class ≥ III, n (%)	208 (26.9)	250 (16.3)	< 0.0001
Hypertension, n (%)	769 (77.2)	1198 (78.1)	0.634
Dyslipidemia, n (%)	508 (51)	758 (49.4)	0.459
Smoking, n (%)	488 (49.5)	792 (51.6)	0.314
Prior CAD, n (%)	343 (34.3)	569 (37.1)	0.165
Prior PCI, n (%)	234 (51.3)	404 (26.3)	< 0.0001
Prior CABG, n (%)	47 (10.3)	85 (5.5)	0.0005
Prior MI, n (%)	131 (28.7)	260 (16.9)	< 0.0001
Prior stroke, n (%)	127 (12.7)	166 (10.8)	0.167
Prior PAD, n (%)	40 (4)	64 (4.2)	0.912
Prior heart failure, n (%)	83 (8.3)	131 (8.5)	0.889
Family history of CAD, n (%)	163 (22.2)	473 (30.8)	< 0.0001
STEMI, n (%)	437 (43.7)	455 (29.7)	< 0.0001
NSTEMI, n (%)	411 (41.1)	750 (48.9)	0.0001
Unstable angina, n (%)	152 (15.2)	329 (21.4)	0.0001
Length of hospital stay (day) (mean ± SD)	10 ± 14	7.9 ± 9.5	NA

CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; Taiwan ACS-FS registry, the Taiwan Acute Coronary Syndrome Full Spectrum Registry; TSOC ACS-DM registry, the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology.
NA, original data not available for analysis.

significantly higher in the TSOC ACS-DM Registry than those in the diabetic population in the Taiwan ACS-FS Registry (41.1% vs. 48.9%, p = 0.0001 and 15.2% vs. 21.4%, p = 0.0001, respectively).

Reperfusion strategy for ACS/AMI and pharmacological treatment at discharge

Comparisons of reperfusion strategies for ACS/acute MI (AMI) and pharmacological treatment at discharge between the Taiwan ACS-FS DM subgroup and the TSOC ACS-DM Registry are shown in Table 2. Reperfusion therapy was performed in 84.7% of the patients in the TSOC ACS-DM Registry, which was significantly lower than that reported in the diabetic patients in the Taiwan ACS-FS Registry DM subgroup (84.7% vs. 87.8%, p = 0.035). This was mainly driven by fewer patients receiving thrombolytic therapy (0.8% vs. 2.4%, p = 0.007) in the TSOC ACS-DM Registry than in the Taiwan ACS-FS Registry.

Medications prescribed at discharge demonstrated that aspirin was prescribed in a similar fashion in both studies. However, the prescription rates of GDMT for ACS including P2Y12 inhibitors (95.5% vs. 92.6%, p = 0.003), renin-angiotensin blockers (65.7% vs. 60.0%, p < 0.001), beta-blockers (64.8% vs. 46.5%, p < 0.001), and statins (77.0% vs. 49.7%, p < 0.001), were significantly higher in the TSOC ACS-DM Registry compared to the DM subgroup of the Taiwan ACS-FS Registry.

Because the prescription data of OADs in the Taiwan ACS-FS Registry DM subgroup were not available, only the prescriptions of OADs in the TSOC ACS-DM Registry are demonstrated in Table 2. At discharge, the most commonly prescribed OADs were metformin (47%), followed by sulphonylureas (34%) and DPP-4is (36%). The other three groups of OADs were prescribed less frequently, with meglitinides in 8%, alpha-glucosidase inhibitors in 8%, and thiazolidinediones in 2%. Of note, combination therapy with OADs was common and widely

Table 2. Comparison of reperfusion strategy for ACS/AMI and pharmacological treatment at discharge between the DM subgroup of the Taiwan ACS-FS Registry and the TSOC ACS-DM Registry

Variables	DM subgroup of the Taiwan ACS-FS Registry (n = 1000)	TSOC ACS-DM Registry (n = 1534)	p value
Reperfusion therapy, n (%)	878 (87.8)	1300 (84.7)	0.035
Thrombolysis, n (%)	15 (2.4)	13 (0.8)	0.007
PCI, n (%)	819 (82.2)	1221 (79.6)	0.113
CABG, n (%)	44 (4.4)	66 (4.3)	0.986
GDMT at discharge, n (%)			
Acetylsalicylic acid, n (%)	890 (89.0)	1380 (89.8)	0.479
P2Y12 inhibitors, n (%)	926 (92.6)	1465 (95.5)	0.003
Renin-angiotensin blockers, n (%)	600 (60.0)	1021 (65.7)	< 0.001
Beta-blockers, n (%)	465 (46.5)	1000 (64.8)	< 0.001
Statins, n (%)	497 (49.7)	1182 (77.0)	< 0.001
Oral anti-diabetic drugs at discharge			
Sulphonylureas (SU), n (%)	-	517 (34)	-
Meglitinides, n (%)	-	115 (8)	-
Metformin, n (%)	-	722 (47)	-
DPP-4i, n (%)	-	547 (36)	-
AGI, n (%)	-	119 (8)	-
Thiazolidinediones, n (%)	-	32 (2)	-
SU + Metformin, n (%)	-	318 (21)	-
DPP-4i + Metformin, n (%)	-	287 (19)	-
SU + Metformin + DPP-4i, n (%)	-	140 (9)	-
No. of OAD use > 3, n (%)	-	220 (14)	-

ACS/AMI, acute coronary syndrome or acute myocardial infarction; AGI, alpha-glucosidase inhibitors; CABG, coronary artery bypass grafting; DPP-4i, dipeptidyl peptidase-4 inhibitors; GDMT, guideline directed medical therapy; OAD, oral anti-diabetic drug; PCI, percutaneous coronary intervention; SU, sulphonylureas; Taiwan ACS-FS registry, the Taiwan Acute Coronary Syndrome Full Spectrum Registry; TSOC ACS-DM registry, the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology.

used in clinical practice. A combination of sulfonylureas and metformin was prescribed in 21% of the patients, a combination of DPP-4is and metformin was prescribed in 19% of patients, and a combination of sulphonylureas, metformin, and DPP-4is was prescribed in 9% of patients. In 14% of patients, a combination of ≥ 3 OADs was needed for better control of blood sugar.

Reperfusion strategy and medications at discharge for STEMI/NSTEMI/UA patients in the TSOC ACS-DM Registry (Table 3)

Among the 1534 study patients, 895 (58.3%) were recruited from medical centers and 639 (41.7%) from regional hospitals. As shown in Table 3, more patients with ACS and DM from medical centers were diagnosed with STEMI (medical center vs. non-medical center = 34% vs. 23.6%, p < 0.0001). However, there were no significant differences in terms of primary PCI rates for the STEMI patients and median door-to-balloon time between the medical centers and regional hospitals (data not shown).

Reperfusion therapy was carried out in 98.5% of the STEMI patients in the TSOC ACS-DM Registry, most commonly primary PCI (95.8%). Fibrinolysis was administered in only 1.8% of the patients. In the NSTEMI and UA patients, an early invasive strategy was applied in 73.1% and 72.0%, respectively. Moreover, significantly more NSTEMI patients underwent CABG compared to those with STEMI and UA (6.9% vs. 0.9% vs. 3%, respectively, p < 0.0001).

As to the medications prescribed for the STEMI/NSTEMI/UA patients in the TSOC ACS-DM Registry, antiplatelet medications were used much less frequently among the UA patients. In addition, all of the other GDMT including renin-angiotensin blockers, beta-blockers, and statins, were prescribed more often in the pa-

Table 3. Comparison of reperfusion strategies and medications at discharge among STEMI/NSTEMI/UA patients in the TSOC ACS-DM Registry

Variables	All (n = 1534)	STEMI (n = 455)	NSTEMI (n = 750)	UA (n = 329)	p value
Hospital category					
Medical center, n (%)	895(58.3)	304 (34.0)	411 (45.9)	180 (20.1)	< 0.0001
Non-medical center, n (%)	639 (41.7)	151 (23.6)	339 (53.1)	149 (23.3)	< 0.0001
Reperfusion strategy, n (%)	1300 (84.7)	448 (98.5)	602 (80.3)	250 (76.0)	< 0.0001
PCI, n (%)	1221 (79.6)	436 (95.8)	548 (73.1)	237 (72.0)	< 0.0001
Thrombolysis, n (%)	13 (0.8)	8 (1.8)	2 (0.3)	3 (0.9)	0.023
CABG, n (%)	66 (4.3)	4 (0.9)	52 (6.9)	10 (3.0)	< 0.0001
GDMT at discharge					
Acetylsalicylic acid, n (%)	1380 (89.8)	437 (96.0)	664 (88.5)	279 (84.8)	< 0.001
P2Y12 inhibitors, n (%)	1465 (95.5)	446 (98.0)	688 (91.7)	288 (87.5)	< 0.001
DAPT, n (%)	1293 (84.3)	428 (91.4)	622 (82.9)	243 (73.9)	< 0.001
Renin-angiotensin blockers, n (%)	1021 (65.7)	350 (78.9)	492 (65.6)	179 (54.4)	< 0.001
Beta-blockers, n (%)	1000 (64.8)	331 (72.7)	478 (63.7)	191 (58.1)	< 0.001
Statins, n (%)	1182 (77.0)	386 (84.8)	562 (74.9)	234 (71.1)	< 0.001
Anti-diabetic drugs at discharge					
Insulin, n (%)	434 (28.3)	131 (28.8)	230 (30.7)	73 (22.2)	0.02
Sulphonylureas, n (%)	517 (33.7)	153 (33.6)	251 (33.5)	113 (34.3)	0.96
Meglitinides, n (%)	115 (7.5)	29 (6.4)	57 (7.6)	29 (8.8)	0.44
Metformin, n (%)	722 (47.1)	263 (57.8)	303 (40.4)	156 (47.4)	< 0.0001
DPP-4i, n (%)	547 (35.7)	160 (35.2)	267 (35.6)	120 (36.5)	0.93
AGI, n (%)	26 (7.8)	26 (5.7)	65 (8.7)	28 (8.5)	0.15
Thiazolidinediones, n (%)	32 (2.1)	10 (2.2)	14 (1.9)	8 (2.4)	0.82

AGI, alpha-glucosidase inhibitors; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; DPP-4i, dipeptidyl peptidase-4 inhibitors; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; Taiwan ACS-FS registry, the Taiwan Acute Coronary Syndrome Full Spectrum Registry; TSOC ACS-DM registry, the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology; UA, unstable angina.

tients with STEMI. The trend in prescription frequency of these drugs was the same as that for the antiplatelet agents, i.e. STEMI > NSTEMI > UA.

Regarding the anti-diabetic drugs prescribed at discharge, insulin usage was much lower among the UA patients (STEMI vs. NSTEMI vs. UA = 28.8% vs. 30.7% vs. 22.2%, respectively, p = 0.02). In general, all of the OADs were prescribed to a similar extent among the different categories of patients with ACS and DM. The only exception was metformin, and its usage was much higher among the STEMI patients (STEMI vs. NSTEMI vs. UA = 57.8% vs. 40.4% vs. 47.4%, respectively, p < 0.0001).

Clinical outcomes (Table 4)

The in-hospital and 1-year mortality rates were 0.9% and 6.3%, respectively in the TSOC ACS-DM Registry. The incidence rates of recurrent nonfatal MI and stroke during hospitalization and at 1 year were 0.3% and 0.4%, and 0.3% and 0.3%, respectively. Major TIMI bleeding was reported in 3.0% of the patients. Other significant in-hospital complications such as new-onset acute renal failure, cardiogenic shock, ventricular arrhythmia, and atrial fibrillation were noted in 1.8%, 2.2%, 2.1%, and 1.6% of the patients, respectively. The incidence rates of those adverse outcomes were similar among the STEMI, NSTEMI, and UA patients. The only exception was 1-year mortality rate, which was significantly higher in the NSTEMI patients than in the STEMI and UA patients (STEMI vs. NSTEMI vs. UA = 4.0% vs. 8.9% vs. 3.4%, respectively, p < 0.0001).

Because only 1-year outcome data of the DM patients in the Taiwan ACS-FS Registry were available, we then compared them with those of the current TSOC ACS-DM Registry. The results demonstrated that the rates of mortality, recurrent nonfatal MI, and stroke in the TSOC ACS-DM Registry were significantly lower than those in the Taiwan ACS-FS DM subgroup (6.3% vs. 10.1%, p < 0.001; 0.3% vs. 5.2%, p < 0.001; and 0.3% vs. 2.3%, p < 0.001, respectively).

By using a composite outcome of death, recurrent MI and stroke over 1 year as the primary endpoint, multivariate predictors for adverse outcomes were [hazard ratio (95% confidence interval (CI))]: age > 70 years [2.21 (95% CI 1.21 to 3.45)], prior atrial fibrillation [2.26 (95% CI 1.17 to 4.39)], previous stroke [2.63 (95% CI 1.60 to 4.30)], and the presence of in-hospital new-onset acute renal failure [2.55 (95% CI 1.05 to 6.19)], TIMI major bleeding [3.46 (95% CI 1.77 to 6.74)], and cardio-

Table 4. In-hospital and 1-year clinical outcomes in the DM subgroup of ACS-FS Registry and TSOC ACS-DM Registry

Clinical outcomes, n (%)	DM subgroup of the Taiwan ACS-FS Registry	TSOC ACS-DM Registry			
	All (n = 1000)	All (n = 1534)	STEMI (n = 455)	NSTEMI (n = 750)	UA (n = 329)
In-hospital outcomes					
Death	-	14 (0.9)	1 (0.2)	11 (1.5)	2 (0.6)
Recurrent non-fatal MI	-	5 (0.3)	3 (0.7)	1 (0.1)	1 (0.3)
Recurrent non-fatal stroke	-	6 (0.4)	1 (0.2)	2 (0.3)	3 (0.9)
In-hospital complications					
TIMI major bleeding	-	46 (3.0)	6 (1.3)	36 (4.8)	4 (1.2)
Cardiogenic shock	-	28 (1.8)	11 (2.4)	16 (2.1)	1 (0.3)
Ventricular arrhythmia	-	33 (2.2)	18 (4.0)	13 (1.7)	2 (0.6)
Newly onset atrial fibrillation	-	32 (2.1)	6 (1.3)	23 (3.1)	3 (0.9)
Acute kidney injury	-	25 (1.6)	3 (0.7)	18 (2.4)	4 (1.2)
Cumulative 1-year outcomes					
Death	101 (10.1)	96 (6.3)*	18 (4.0)	67 (8.9)#	11 (3.4)
Recurrent non-fatal MI	52 (5.2)	4 (0.3)*	2 (0.4)	1 (0.1)	1 (0.3)
Recurrent non-fatal stroke	23 (2.3)	5 (0.3)*	1 (0.2)	1 (0.1)	3 (0.9)

MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; Taiwan ACS-FS registry, the Taiwan Acute Coronary Syndrome Full Spectrum Registry; TIMI, thrombolysis in myocardial infarction; TSOC ACS-DM registry, the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology.
* Significantly different between DM subgroup in ACS-FS and ACS-DM groups, p < 0.001. # Significantly different among different ACS/AMI categories in the TSOC ACS-DM registry, p < 0.0001.

genic shock [7.75 (95% CI 3.02 to 19.93)]. On the other hand, the use of reperfusion in combination with GDMT and a baseline left ventricular ejection fraction of ≥ 40% at presentation were predictors of better primary outcomes at 1 year in multivariate analysis, with hazard ratios of 0.54 (95% CI 0.33 to 0.89) and 0.47 (95% CI 0.30 to 0.75), respectively (Figure 1).

DISCUSSION

Main findings of the present study

To improve the prognosis of diabetic patients with ACS, it is important to understand the effect of present state-of-the-art treatment for this condition, and to determine the effect of newer treatment modalities. Therefore, the current study examined the characteristics, medications, and clinical outcomes of 1534 diabetic patients across the spectrum of ACS between 2013 July and 2015 December, using data of 1000 diabetic patients collected in the Taiwan ACS-FS Registry conducted from October 2008 to January 2010 as historical controls.

We found that: 1) Overall, fewer patients enrolled in the TSOC ACS-DM Registry had a discharge diagnosis of STEMI, and more patients were diagnosed with NSTEMI and UA than those in the Taiwan ACS-FS Registry DM subgroup. 2) Even though reperfusion therapy was carried out in significantly fewer patients, the primary PCI rate for STEMI and the prescription rates of GDMT for ACS including dual anti-platelet therapy in the STEMI patients, renin-angiotensin blockers, beta-blockers, and statins were significantly higher in the TSOC ACS-DM Registry compared to those in the DM subgroup of the Taiwan ACS-FS Registry. 3) In general, all OADs were prescribed similarly among the different categories of the patients with ACS and DM. However, the prescription rates of metformin in the STEMI patients were higher at discharge. 4) Significant reductions in mortality, recurrent nonfatal MI, and stroke were observed in the current registry compared to the historical registry, which was performed 5 years earlier.

Treatment of ACS in diabetic patients

In contrast to the DM subgroup in the Taiwan ACS-FS study, fewer patients enrolled in the TSOC ACS-DM Registry had a discharge diagnosis of STEMI, and more patients were diagnosed with NSTEMI and UA. One possible explanation for this contradiction is that, over time in our study population, cardiac biomarkers, particularly cardiac troponin I, were used more frequently in Taiwan. Actually, the number of patients admitted for NSTEMI increased dramatically after 2003 in Taiwan, with a relative increase of 300% between 1997 and 2011.[25] Our findings are consistent with this trend.

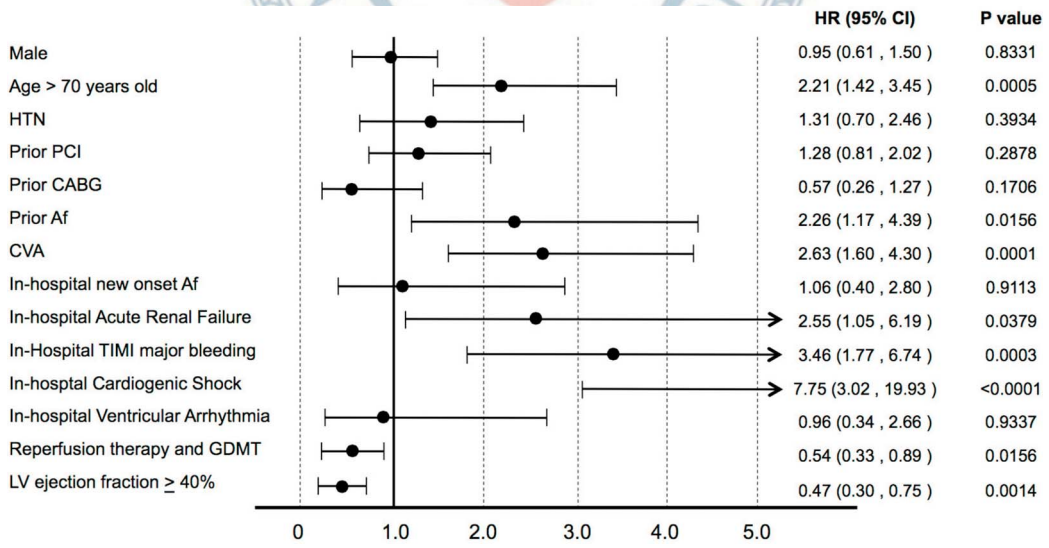

Figure 1. *Results of the multivariable analysis for 1-year major adverse outcomes (a composite outcome of death, recurrent nonfatal myocardial infarction and stroke) in the TSOC ACS-DM Registry. Af, atrial fibrillation; CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; GDMT, guideline directed medical therapy; HTN, hypertension; PCI, percutaneous coronary intervention; LV ejection fraction, left ventricular ejection fraction; TIMI, thrombolysis in myocardial infarction.*

It is thus even more important to implement known evidence-based treatment in patients with diabetes, because clinical data have shown the same (or even larger) relative and absolute risk reductions with treatment in ACS patients with DM compared to patients without DM.[9,10,26,29] The two mainstays of acute ACS therapy for diabetic patients are aggressive platelet inhibition and an early invasive strategy.[9,10,26,29] All patients, including diabetic and non-diabetic patients, qualify for primary PCI as the therapy of choice for STEMI. The benefits of an early invasive approach, including coronary angiography and, if needed, revascularization, in the setting of NSTEMI or UA are more pronounced in diabetic than in non-diabetic patients. Although in general, the proportions of patients who underwent PCI and CABG in the present study were similar to those in the Taiwan ACS-FS Registry conducted 5 years previously, the primary PCI rate for STEMI was significantly higher in the present study than that in the DM subgroup of Taiwan ACS-FS Registry (95.8% vs. 82.2%, $p < 0.001$).[6]

Moreover, as diabetes induces alterations in the coagulation cascade, with a shift towards a more prothrombogenic state,[27] and alterations in platelet function by increasing platelet aggregation and adhesion,[28] antiplatelet agents could be expected to be more effective in diabetic patients. Aspirin and more potent platelet inhibitors such as P2Y12 could therefore be expected to exert a greater effect in diabetic patients and are suggested in this setting. Additional important secondary preventive measures include high-dose statin therapy, renin-angiotensin blockers, and adequate glucose metabolism control. Taking the increased frequency of risk factors and atherosclerotic diseases into account, a very large proportion of patients with diabetes should be given these medications during the hospital stay.[9,10,26,29]

However, even in randomized trials, these GDMTs are under-utilized. 'Real world' results, as in the Taiwan ACS-FS Registry and others,[6,9,10,26,29] are substantially worse. Fortunately, in the present study, we found that the prescription rates of these evidence-based medications, especially dual antiplatelet therapy (DAPT) in the STEMI patients, renin-angiotensin blockers, beta-blockers, and statins, were significantly higher during the past 5 years (Table 2). The adherence to GDMT was best in the patients with STEMI, followed by the patients with NSTEMI and UA (Table 3).

Antidiabetic treatment for ACS patient with DM

Another important secondary preventive measure for ACS patients with DM is adequate glucose metabolism control. Hyperglycemia is common in ACS patients, even in those who do not have a diagnosis of diabetes, and it has been shown to be a risk factor for the future development of diabetes.[7,8] The National Institute for Health and Clinical Excellence published clinical guidelines for the management of hyperglycemia in patients with ACS.[30] It is therefore recommended that hyperglycemia should be avoided for the first 48 hours following an acute event.

The method for glycemic control is patient dependent, however a dose-adjusted insulin infusion should be considered with regular blood glucose monitoring and avoidance of hypoglycemia.[30] Although earlier studies have suggested that insulin treatment for DM may have a deleterious effect on ACS outcomes, especially in patients with STEMI, including increased in-hospital mortality,[31-33] other studies have demonstrated that insulin-glucose infusion followed by a multi-dose insulin regimen can improve the long-term prognosis of diabetic patients with AMI.[34] This may be because patients with different levels of metabolically derangements and risk factors are recruited in different studies. In general, patients with type 1 DM and poorly controlled DM may need to intensify insulin treatment. Some patients with type 2 DM may also require insulin following ACS to achieve glycemic control.[30] In the present study, 28.3% of the patients needed insulin injections, most of whom had AMI, suggesting that the study population consisted of high-risk diabetic patients.

It is recommended that patients known to have diabetes review their OAD medications during admission for ACS.[10,26,30] For those receiving metformin, there is concern regarding the potential risk of lactic acidosis when given at times of tissue hypoxia, however there is no conclusive evidence to suggest that metformin should not be used following MI.[30] Moreover, metformin has been proven to reduce cardiovascular mortality and non-fatal cardiovascular events compared with other anti-diabetic treatments in diabetic patients with cardiovascular diseases and MI.[11-14] If metformin is the sole agent, it is also important to consider the glycemic impact of removal during the peri-procedural period when a contrast load in combination with metformin may potentially lead to renal impairment and lactic acidosis.[30]

In the present study, metformin was prescribed in 47.1% of the ACS patients with DM, and especially in those with STEMI. This suggests that Taiwanese physicians believe that metformin is cardio-protective and can be safely used in most ACS patients, and that the risk of renal impairment and lactic acidosis is not a major concern.

Other medications used in type 2 DM may also require adjustment. Even though first generation sulphonylureas or glibenclamide are contraindicated in patients with type 2 DM with ACS,[15] and even though the association between second-generation sulphonylureas and post-MI mortality is controversial,[16-18] their prescription rates were still high, albeit reduced in our Taiwanese cohort. Thiazolidinediones, and especially pioglitazone, may reduce rates of recurrent MI,[20] however they may also precipitate cardiac failure and increase the risk of bladder cancer,[21,22] so they are rarely prescribed by Taiwanese physicians.

Since the launch of DPP-4is in Taiwan in 2011, they have been increasingly used in type 2 DM patients because of fewer adverse events. Although the clinical outcomes with the use of DPP-4is and the combination of metformin and DPP-4is in patients with type 2 DM and ACS are unknown, a striking finding in the present study was that the prescription rates of DPP-4is and the use of a combination of DPP-4is and metformin for patients with ACS and DM reached 36% and 19%, respectively.

In practice, many diabetic patients will receive combination therapy with multiple OADs to reach the therapeutic goal.[30] Even though the outcomes of a combination of sulfonylureas and metformin are controversial,[23,24] the most commonly use two-drug combination of OADs in the diabetic ACS patients was still a sulphonylurea and metformin in the current registry. For those who needed $\geq$ 3 OADs for glycemic control, the most commonly used combination was a sulphonylurea, metformin, and a DPP-4i. Analysis is ongoing to explore the current practices of prescriptions of OADs for long-term glycemic control and clinical outcomes in this high-risk group of patients in Taiwan using the TSOC ACS-DM database.

In-hospital and 1-year clinical outcomes in the patients with ACS and DM

In contrast to the lower prevalence of several risk factors such as hypertension, hypercholesterolemia and smoking, the prevalence of type 2 DM has increased in recent years, presumably primarily due to a progressively unhealthy lifestyle. Besides the increased risk of developing atherosclerotic disease, including MI, diabetic patients with MI also have a significantly increased risk of mortality. Mortality and re-infarction rates are substantially increased in diabetic patients following ACS, including MI. This has been demonstrated in several studies, including the subpopulation of diabetic patients in the Taiwan ACS-FS Registry.[6,31,33] Moreover, the ACS patients with diabetes had significantly worse outcomes regarding all-cause death and the combined endpoint of death, re-MI and stroke, compared to the patients without DM.[4-6,31,33] Patients with DM are also given less aggressive treatment, which may be a factor in the worse outcomes.[6,9,10,26,29] In the previous Taiwan ACS-FS Registry, over the course of 1 year of follow-up, the DM patients had higher probabilities of all-cause death (DM vs. non-DM patients = 10.1% vs. 6.06%, $p < 0.05$).[6] In the current study, a significant reduction in in-hospital mortality was observed compared to that of the whole population of the Taiwan ACS-FS Registry. Moreover, the rates of mortality, recurrent nonfatal MI, and stroke were significantly lower in the current TSOC ACS-DM Registry compared to those reported in the DM subgroup of the Taiwan ACS-FS Registry. Furthermore, the use of reperfusion in combination with GDMT was identified as a strong multivariate predictor of better primary outcomes at 1-year, with a hazard ratio of 0.54 (95% CI 0.33 to 0.89).

As mentioned, the increasing detection of less severe infarctions with troponin testing would logically contribute to the decline in short-term mortality rates in NSTEMI patients. Thus, the observed reductions in in-hospital and 1-year mortality rates in our study could, at least partly, be attributable to trends in the recognition of AMI and decreased severity on presentation.[25] Nevertheless, considering that the primary PCI rate for STEMI in our study was significantly higher than that of the DM subgroup of the Taiwan ACS-FS Registry, that the adherence to GDMT was best in the patients with STEMI, and that reperfusion in combination with GDMT was a predictor of better clinical outcomes, our findings also strengthen the importance of intensive post-infarction treatment for diabetic patients.[35-37]

Limitations

This study was a post-hoc analysis based on data

from the TSOC ACS-DM Registry. Several parameters including glucose levels, HbA1c data and glycemic control strategies were not available due to the original study design. Hence, we could not evaluate the relationship between the severity and duration of diabetes and ACS outcomes. In addition, some patients suffering from transient hyperglycemia due to acute coronary events may also have been enrolled in this study. Moreover, the present study reported only short-term outcomes, and it could be useful to follow up the patients for a longer time to obtain more informative data. Finally, the study was conducted from 2013 to 2015, before the launch of sodium-glucose cotransporter-2 inhibitors in Taiwan in 2016. This specific group of OADs have recently shown efficacy in reducing cardiovascular-disease events in patients with type 2 DM,[38,39] and this has increased their prescription in the year since their introduction to Taiwan to patients with type 2 DM and cardiovascular disease. Over the next few years, we will follow the prescription patterns of treating physicians and the clinical outcomes in patients with ACS and DM.

CONCLUSIONS

Because of the proatherosclerotic, proinflammatory, and prothrombotic states associated with diabetes, diabetic patients with ACS are at high risk of subsequent cardiovascular events. However, they also have a greater benefit from evidence-based therapy than patients without diabetes. Our data demonstrated that the in-hospital initiation of evidence-based treatment for diabetic patients with ACS in Taiwan has improved over time, and this is associated with better short-term clinical outcomes.

CONFLICT OF INTEREST

All of the authors declare no conflicts of interest.

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SUPPLEMENTARY MATERIAL (LIST OF HOSPITALS IN ALPHABETICAL ORDER)

Cathay General Hospital, Taipei, Taiwan; Chang Gung

Memorial Hospital, Linkou, Taiwan; Cheng Hsin General Hospital, Taipei, Taiwan; Chimei Medical Center, Tainan, Taiwan; China Medical University Hospital, Taichung, Taiwan; Chung-Shan Medical University Hospital, Taichung, Taiwan; E-Da Hospital, Kaohsiung, Taiwan; Far Eastern memorial Hospital, New Taipei City, Taiwan; Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan; Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan; Kuang Tien General Hospital, Taiwan; Lo-Tung Poh-Ai Hospital, Taiwan; MacKay Memorial Hospital, Taipei, Taiwan; National Cheng Kung University, College of Medicine, Taiwan; National Taiwan University Hospital, Yunlin Branch, Taiwan; National Taiwan University Hospital, Hsinchu Branch, Taiwan; National Taiwan University Hospital, Taipei, Taiwan; National Yang-Ming University Hospital, Taiwan; PingTung Christian Hospital, Taiwan; Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; Shuang Ho Hospital, Taiwan; Taichung Veterans General Hospital, Taichung, Taiwan; Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei City, Taiwan; Taipei Veterans General Hospital, Taipei, Taiwan; Tri-Service General Hospital, Taipei, Taiwan; Wanfang Hospital, Taipei, Taiwan.