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Metformin was associated with lower all-cause mortality in type 2 diabetes with acute coronary syndrome: A Nationwide registry with propensity score-matched analysis☆,☆☆

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ABSTRACT

Background: No randomized controlled trials evaluating metformin therapy efficacy in patients with type 2 diabetes mellitus (DM) and acute coronary syndrome (ACS) have been reported. We aimed to examine the mortality benefit of metformin therapy in patients with type 2 DM and ACS, compared with non-metformin anti-diabetes agents users.

Methods: Data were extracted from the prospective nationwide ACS-DM Taiwan Society of Cardiology registry. Propensity score (PS) matching on baseline characteristics and treatment measures was performed for metformin versus non-metformin users. The Cox proportional hazards model was used to compare mortality outcomes among the PS-matched cohort as the primary analysis. The Cox proportional hazards models adjusting for all pre-determined covariates and quintiles of the PS among the overall population were performed as the secondary analyses.

Results: Of 1157 patients with type 2 DM and ACS receiving anti-diabetes agents, 78 patients (6.7%) died over the 2-year follow-up period. After PS matching, 318 metformin users were matched with 318 non-metformin users. Metformin users had a lower all-cause mortality rate (adjusted hazard ratio [aHR] 0.50, 95% confidence interval [CI] 0.26–0.95) in the primary analysis. The survival benefit of metformin therapy was consistent in the secondary analyses (aHR 0.30, 95% CI 0.17–0.54 while adjusting for all pre-determined covariates, and aHR 0.34, 95% CI 0.19–0.59 while adjusting for quintiles of the PS).

Conclusions: Among patients with type 2 DM and ACS, metformin was associated with lower all-cause mortality. However, a detrimental effect of any of the comparators could not be excluded.

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1. Introduction

In recent clinical trials concerning acute coronary syndrome (ACS), one-quarter of the study population have been reported as suffering from diabetes mellitus (DM) [1]. DM patients had a doubling mortality rate compared to non-DM patients in the post-ACS phase [2] and this highlights the importance of secondary prevention in patients with both DM and ACS. Several recent clinical trials involving novel anti-diabetes agents have focused on cardiovascular outcome in this high-risk population. Empagliflozin and liraglutide have been shown to reduce all-cause and cardiovascular mortality in established cardiovascular disease or high-risk atherosclerotic cardiovascular disease (ASCVD) populations. Nevertheless, the proportion of patients with prior myocardial infarction in both trials was only 45% and 30%, respectively [3,4]. Two randomized controlled trials have evaluated the cardiovascular outcome of alogliptin and lixisenatide in type 2 DM patients with recent ACS; however, the mortality endpoint in these clinical trials was disappointing [5,6].

Metformin has been recommended as a first-line medication therapy for type 2 DM for over a decade [7]. Metformin has shown greater benefits on all-cause mortality, DM-related endpoints, and stroke compared with sulfonylurea and insulin in overweight, newly diagnosed DM patients with low cardiovascular risk [8]. The survival benefit of metformin therapy is controversial in populations with stable ASCVD [9,10]. To date, there have been few non-randomized studies evaluating the efficacy of metformin on mortality among ACS patients, [11–13] and most of the previous studies were conducted prior to the modern primary percutaneous coronary intervention (PCI) era. The proportion of patients receiving primary PCI was low (<10%) and the prescription rate regarding guideline-recommended medications during the acute phase of ACS, especially concerning dual anti-platelet therapy (DAPT), has been reported as <20% in those studies [11–13]. As modern treatment strategies have evolved, along with reduced mortality rates in the ACS population, [14,15] new data concerning the beneficial effect of metformin in modern PCI era is required.

To assess the beneficial effect of metformin on mortality in DM patients with ACS, we conducted an analysis using a Taiwanese nationwide registry database.

2. Methods

2.1. Study design and data source

We used data from the Acute Coronary Syndrome-Diabetes Mellitus (ACS-DM) Registry of the Taiwan Society of Cardiology (TSOC), a prospectively collected database, to evaluate the effectiveness of metformin in a real-world ACS cohort within the modern PCI era. The ACS-DM Registry of the TSOC is a prospective, nationwide, multicentered registry initiated by the Scientific Committee of the TSOC. This registry collects data pertaining to patients with DM who also have ST-segment elevation myocardial infarction (STEMI), non-ST segment elevation myocardial infarction (NSTEMI), or unstable angina, from 27 participating centers nationwide in Taiwan. Site selection for the registry was determined by the Scientific Committee of the TSOC to ensure good quality and representation of the ACS-DM population in Taiwan [16]. Patients are treated according to international or local guidelines and evidence-based strategies. The protocol and consent forms used in this study were consistent with the Declaration of Helsinki and relevant regulations. The ethics committees of each participating hospital approved the study, and all enrolled patients provided written informed consent.

2.2. Data collection

Patients' demographic data, clinical characteristics, biochemistry data, in-patient therapies, coronary lesion morphology, transthoracic echocardiography results, and in-hospital outcomes (including mortality, recurrent non-fatal myocardial infarction, and non-fatal stroke) were collected by trained study coordinators at the study sites. After hospital discharge, information from the first clinical follow-up visit, as well as from the 6-month, 1-year, and 2-year visits, were acquired through telephone contact or through review of the medical records. Information concerning patient medication were also collected at admission, during hospital stay, at discharge, and during regular follow-up, retrospectively and prospectively. All data were then submitted electronically to a central laboratory for verification. To establish a complete lipid profile, we used the Friedewald formula to estimate low-density lipoprotein cholesterol (LDL-C) levels if they had not been directly measured. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 calculated using the modification of diet in renal disease (MDRD) formula.

2.3. Study population

This study was based on 1535 patients who had been diagnosed with ACS and type 2 DM according to current international guidelines, and who had been enrolled in the ACS-DM TOSC registry between November 1, 2013, and September 30, 2016. Patients aged 20 years or older and diagnosed with ACS were enrolled. The registry enrolled patients only once; i.e., at the first ACS event, while subsequent ACS episodes were recorded as adverse events. Patients were followed until January 18, 2017. We excluded patients with malignancy (n = 47), advanced CKD (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease (ESRD) who had received regular hemodialysis or peritoneal dialysis (n = 128), since these patients were contraindicated to use metformin. Furthermore, 15 patients who were underweight (body mass index [BMI] <18.5 kg/m^2) were excluded to avoid potential cachexia and occult malignancy. In addition, 163 patients who did not have prescriptions for anti-diabetes medications were excluded. Lastly, 25 patients with unavailable data concerning survival status were also excluded. Ultimately, the final dataset included 1157 patients. (Supplementary Fig. 1).

2.4. Exposure and outcome variables

The exposures of interest were defined as metformin users (with either monotherapy or combination therapy) and non-metformin anti-diabetes agents users. Medication information was obtained from the prescriptions upon discharge following the index admission. The primary outcome was the cumulative incidence of all-cause mortality within the study period. The vital status was acquired through telephone contact or review of the medical records. The beginning of the follow-up period was defined as the date of index admission, while the end of follow-up was the date of death or the end of the study, whichever occurred first. The predetermined confounding factors included age, sex, BMI, duration of DM, glycated hemoglobin (HbA1c), LDL-C, hypertension, smoking status, previous heart failure, CKD, atrial fibrillation, stroke, peripheral vascular disease, ACS subtype (STEMI/NSTEMI/unstable angina), left ventricular ejection fraction (LVEF) <40%, intra-aortic balloon pump or inotropic agents used, left main coronary artery disease, multi-vessel disease, PCI therapy, coronary artery bypass grafting (CABG), and discharge medications (such as angiotensin-converting-enzyme inhibitor [ACEI]/angiotensin II receptor blocker [ARB], beta-blocker, dual antiplatelet therapy, statin therapy, and insulin).

2.5. Statistical analysis

Categorical variables are expressed as percentages and continuous variables are expressed as mean values with standard deviations. The differences in the categorical variables between the metformin users and the non-metformin users among the overall population were examined using the chi-squared test, while differences in continuous variables were tested using the *t*-test.

A propensity score (PS) was derived using logistic regression to model the probability of receipt of metformin or not as a function of all the potential confounders listed in Table 1. Based on the PS, metformin users were matched to non-metformin users (using the greedy matching algorithm) at a 1:1 ratio to create a PS-matched population. The balance in baseline characteristics between the metformin and non-metformin groups among the PS-matched population was assessed using the Mantel-Haenszel test for categorical variables and the paired *t*-test for continuous variables. The incidence rates of all-cause mortality are presented as cases per 1000 person-years among the overall population and the PS-matched population, respectively. In the primary analysis, the Cox proportional hazards model was used to compare the risk of mortality outcome between the metformin group and the non-metformin group among the PS-matched cohort. To examine the robustness of our results, we used the traditional Cox proportional hazards model with adjustment of all the pre-determined covariates, and adjustment of the quintiles of the PS (PS-stratification analysis) among the overall population, as the secondary analyses. In addition, three sensitivity analyses were conducted. The first sensitivity analysis excluded patients taking a single oral anti-diabetes agent to improve comparability between the study groups. To ensure the treatment effect of metformin on the long-term outcome, mortality during index hospitalization and incident metformin users with metformin initiated during index hospitalization were excluded in the second and third sensitivity analysis, respectively.

To explore the homogeneity of relative risk of mortality outcomes between both groups among patients with different baseline characteristics and co-morbid status, 10 subgroup analyses stratified according to age (<65 years/≥65 years), sex, BMI (<25 kg/m^2/≥25 kg/m^2), DM duration (<10 years/≥10 years), glycated hemoglobin (<7%/≥7%), receiving insulin therapy or not, CKD (eGFR <60 mL/min/1.73 m^2/≥60 mL/min/1.73 m^2), ACS subtype (unstable angina and NSTEMI/STEMI), LVEF (<40%/≥40%), and receiving beta blocker therapy or not were conducted, with PS-matched analysis performed within each subgroup analysis separately. Interaction between metformin therapy and stratifying factors was assessed through the addition of an interaction term into the proportional hazards model among the overall population, and tested using a likelihood ratio test.

Table 1
Baseline characteristics, revascularization strategy and medications at discharge of overall population and PS-matched cohort, stratified by metformin users and non-metformin users.

Characteristics	Overall Population (n = 1157)			PS-matched Cohort (n = 636)		
	Metformin (n = 676)	Non-metformin (n = 481)	P-value	Metformin (n = 318)	Non-metformin (n = 318)	P-value
	Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age, years	62.2 ± 11.6	67.5 ± 11.9	<0.0001	65.9 ± 10.8	65.6 ± 12.1	0.6818
BMI, kg/m^2	26.3 ± 4.0	26.3 ± 4.3	0.8500	26.3 ± 4.1	26.2 ± 4.0	0.8503
DM duration, years	8.4 ± 7.4	11.5 ± 8.6	<0.0001	9.9 ± 6.6	9.9 ± 6.2	0.9186
Hemoglobin A1c, %	8.6 ± 2.0	8.1 ± 1.8	0.0030	8.3 ± 1.5	8.3 ± 1.5	0.9009
LDL-C, mg/dL	104.8 ± 39.4	99.0 ± 37.5	0.0230	101.4 ± 33.7	100.5 ± 37.5	0.7401
	n (%)	n (%)		n (%)	n (%)	
Male sex	506(74.9)	328(68.2)	0.0130	234(73.6)	232(73.0)	0.8579
Hypertension	483(71.5)	398(82.7)	<0.0001	246(77.4)	246(77.4)	1.0000
Smoking	233(34.5)	136(28.3)	0.0259	103(32.4)	99(31.1)	0.7335
Previous HF	28(4.2)	53(11.0)	<0.0001	24(7.6)	26(8.2)	0.7684
CKD	228(33.7)	178(37.0)	0.2495	116(36.5)	126(39.6)	0.4145
Atrial fibrillation	35(5.2)	31(6.4)	0.3596	19(6.0)	21(6.6)	0.7441
Stroke	66(9.8)	57(11.9)	0.2563	40(12.6)	39(12.3)	0.9044
Peripheral vascular disease	14(2.1)	19(4.0)	0.0584	11(3.5)	5(1.6)	0.1290
ACS subtype			0.0002			0.7720
STEMI	236(35.0)	117(24.4)		84(26.4)	94(29.6)	
NSTEMI	279(41.3)	248(51.8)		150(47.2)	148(46.5)	
Unstable angina	160(23.7)	114(23.8)		84(26.4)	76(23.9)	
LVEF <40%	74(11.0)	78(16.2)	0.0089	42(13.2)	42(13.2)	1.0000
IABP or inotropic used	145(21.5)	121(25.2)	0.1398	78(24.5)	71(22.3)	0.5126
LM disease	47(7.0)	45(9.4)	0.1365	31(9.8)	27(8.5)	0.5820
Multi-vessel disease	387(57.3)	292(60.7)	0.2390	187(58.8)	187(58.8)	1.0000
PCI	585(86.5)	364(75.7)	<0.0001	255(80.2)	257(80.8)	0.8415
CABG	26(3.9)	19(4.0)	0.9282	17(5.4)	12(3.8)	0.3423
ACEI/ARB	504(74.6)	279(58.0)	<0.0001	218(68.6)	206(64.8)	0.3132
Beta-blocker	455(67.3)	311(64.7)	0.3475	205(64.5)	213(67.0)	0.5042
Dual antiplatelet therapy	599(88.6)	394(81.9)	0.0013	274(86.2)	277(87.1)	0.7268
Statin	567(83.9)	369(76.7)	0.0023	254(79.9)	251(78.9)	0.7688
Glucose lowering drug			<0.0001			0.2494
1 OHA	185(27.4)	162(33.7)		132(41.5)	114(35.9)	
≥2 OHA	357(52.8)	91(18.9)		77(24.2)	88(27.7)	
Insulin	134(19.8)	228(47.4)		109(34.3)	116(36.5)	

Abbreviations: ACEI: angiotensin-converting-enzyme inhibitor; ACS: acute coronary syndrome; ARB: angiotensin II receptor blocker; BMI: body mass index; CABG: coronary artery bypass grafting; CKD: chronic kidney disease; DM: diabetes mellitus; HF: heart failure; IABP: intra-aortic balloon pump; LDL-C: low-density lipoprotein cholesterol; LM: left main; LVEF: left ventricular ejection fraction; NSTEMI: Non-ST elevation myocardial infarction; OHA: oral hypoglycemic agent; PCI: percutaneous coronary intervention; PS: propensity score; SD: standard deviation; STEMI: ST-elevation myocardial infarction.

All analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All reported p-values were two-sided, and the significance level was set at 0.05.

3. Results

Among the 1157 patients enrolled, the mean age was 64.4 (standard deviation [SD] 12.0), and 72% of the patients were male. The mean HbA1c was 8.4% (SD 1.9%). The mean DM duration was 9.8 years, and the mean follow-up duration was 554 days. There were 676 patients (58%) who had received metformin therapy, whereas 481 patients (42%) comprised the non-metformin group. The baseline characteristics of the overall population and the PS-matched population are shown in Table 1. In brief, metformin users were younger, with a higher HbA1c and LDL-C, more likely to be smokers, more likely to suffer from STEMI, and had received more guideline-recommended therapy, including PCI, ACEI/ARB, DAPT, and statin therapy. In contrast, non-metformin users were more likely to be female, and more likely to have had a long DM duration, hypertension, heart failure, an NSTEMI subtype, an LVEF <40%, and insulin therapy (Table 1). After the PS-matching procedure, 318 matched pairs were selected between the metformin and non-metformin users. The differences in baseline characteristics, co-morbid status, and treatment measures were well balanced among the PS-matched population (Table 1).

The mortality rate in the overall population was 19.2 per 1000 person-years among the metformin users but 82.9 per 1000 person-years among the non-metformin users. This crude difference in the mortality rate between the two treatment groups reduced slightly after the PS-matching procedure (30.7 per 1000 person-years among the metformin users, and 59.0 per 1000 person-years among the non-metformin users) (Table 2). In the primary analysis, the risk of all-cause mortality was lower in metformin users than in non-metformin users (adjusted hazard ratio [aHR] 0.50, 95% confidence interval [CI] 0.26–0.95, p = 0.0346) among the PS-matched cohort. This result was consistent in the secondary analyses (aHR 0.30, 95% CI 0.17–0.54, p < 0.0001 using traditional Cox proportional hazards model with adjustment of all the pre-determined covariates; and aHR 0.34, 95% CI 0.19–0.59, p = 0.0002 using Cox proportional hazards model with adjustment of the quintiles of the PS [PS-stratification analysis]). Moreover, the survival benefit of metformin therapy was sustained in all the sensitivity analyses that excluded patients with a single oral

Table 2
Incidence of all-cause mortality among the overall population and PS-matched cohort, stratified by metformin users and non-metformin users.

	Metformin			Non-metformin		
Overall population	n = 676			n = 481		
	PY	Event number	IR*	PY	Event number	IR*
	1042.6	20	19.2	699.6	58	82.9
PS-matched cohort	n = 318			n = 318		
	PY	Event Number	IR*	PY	Event number	IR*
	489.2	15	30.7	474.6	28	59.0

Abbreviations: IR: incidence rate; PS: propensity score; PY: person-year.
* Per 1000 person-years.

Table 3
Adjusted hazard ratios of all-cause mortality in metformin users versus non-metformin users with different statistical models.

	aHR (95% CI)	P-value
Primary analysis		
Method 1: PS-matched analysis	0.50 (0.26–0.95)	0.0346
Secondary analyses		
Method 2: Traditional Cox regression model	0.30 (0.17–0.54)	<0.0001
Method 3: PS-stratification analysis	0.34 (0.19–0.59)	0.0002
Sensitivity analysis 1*		
Method 1: PS-matched analysis	0.43 (0.20–0.90)	0.0251
Method 2: Traditional Cox regression model	0.34 (0.17–0.69)	0.0026
Method 3: PS-stratification analysis	0.38 (0.20–0.72)	0.0030
Sensitivity analysis 2†		
Method 1: PS-matched analysis	0.47 (0.25–0.89)	0.0194
Method 2: Traditional Cox regression model	0.35 (0.19–0.63)	0.0005
Method 3: PS-stratification analysis	0.38 (0.21–0.68)	0.0011
Sensitivity analysis 3‡		
Method 1: PS-matched analysis	0.30 (0.15–0.63)	0.0013
Method 2: Traditional Cox regression model	0.28 (0.12–0.65)	0.0032
Method 3: PS-stratification analysis	0.33 (0.16–0.68)	0.0025

Abbreviations: aHR: adjusted hazard ratio; CI: confidence interval; PS: propensity score.
* excluding patients with single oral anti-diabetic agent.
† Excluding patients with mortality during index hospitalization.
‡ Excluding incident metformin users with metformin initiated during index hospitalization.

anti-diabetes agent, excluded patients with mortality during index hospitalization, and excluded incident metformin users with metformin initiated during index hospitalization (Table 3). None of the baseline characteristics that had been considered in the subgroup analyses significantly modified the relationship between metformin therapy and the risk of mortality (Fig. 1).

4. Discussion

This study found that metformin was associated with lower all-cause mortality in type 2 DM patients with ACS. This result was consolidated using different statistical models and additional sensitivity analyses that excluded patients with less severe DM, that is, those who received only one oral hypoglycemic agent, and patients who had suffered mortality during index hospitalization. This survival benefit associated with metformin was consistent in the subgroup analyses in relation to old age, normal weight, and advanced DM severity, which might otherwise have cast doubt on the wider potential beneficial effects of metformin [8,17]. Moreover, similar mortality benefits were found in patients at risk of lactic acidosis, such as those with left ventricular systolic dysfunction and CKD [18].

Intensive blood-glucose control with metformin resulted in better survival benefits for patients than either those in the sulfonylurea or insulin control groups in the United Kingdom Prospective Diabetes Study (UKPDS) [8]. However, this survival benefit of metformin was not reproducible in type 2 DM patients with established coronary heart disease. Hong et al. stated that metformin had reduced the risk of a cardiovascular event by 46% in patients with stable coronary heart disease during a 5-year follow-up in a randomized control trial. Nevertheless, there was no benefit on mortality when compared with sulfonylurea [9]. Conversely, another large retrospective observational study showed that metformin reduced 2-year mortality in patients with atherosclerotic disease by 24% after adjusting covariates with the PS method [10]. Moreover, most systematic reviews and meta-analysis reports have not included clinical studies concerning patients with established coronary heart disease while evaluating the efficacy of metformin [17].

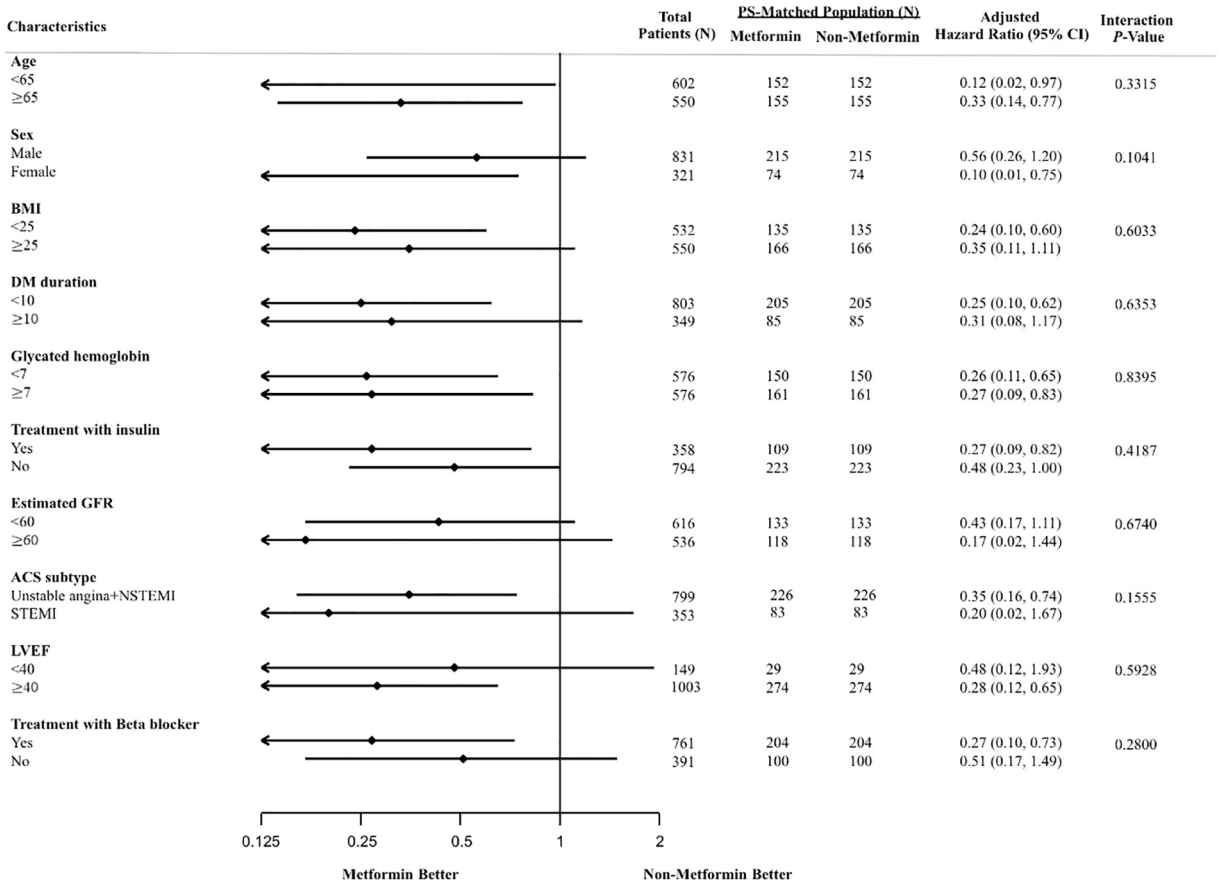

Fig. 1. Forest plot concerning effects of metformin therapy versus non-metformin therapy on all-cause mortality, stratified by different baseline characteristics. Abbreviations: ACS: acute coronary syndrome; BMI: body mass index; DM: diabetes mellitus; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; NSTEMI: non-ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction.

There have been several retrospective analyses that have evaluated the survival benefits of metformin for patients with type 2 DM and ACS. Jørgensen et al. extracted data from the Danish National Patient Registry and found a 2.5-fold increase in all-cause mortality in glyburide monotherapy among patients with myocardial infarction who had undergone emergent PCI, compared with metformin. Nevertheless, the study was limited to a relatively small sample size in both groups (129 participants and 47 participants received metformin and glyburide therapy, respectively), and there was no covariant adjustment for renal function, DM duration, HbA1c, serum LDL-C level, antiplatelet therapy, and smoking status [12]. Inzucchi et al. collected data from the National Heart Care Project in the United States. They found that neither metformin nor thiazolidinedione alone, but a combined therapy of both medications reduced mortality by 48% in comparison with a non-insulin sensitizer [11]. Another post-hoc analysis of the Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) 2 trial, a prospective, randomized trial that compared three different hyperglycemia management strategies in type 2 DM patients with suspected ACS, reported that metformin reduced the 4-year mortality rate by 35%, compared with the non-metformin group. However, a high proportion of patients using insulin therapy in the comparison group weakened the conclusion [13]. All of these studies, apart from the Danish registry study, were initiated prior to the era of primary PCI, with a low rate of primary PCI of <10%. The definition of emergency PCI in the Danish registry was 'a procedure performed within 48 hours after admission', which differed significantly from the current guideline recommendations [19]. In addition, most patient managements in these earlier studies did not conform to current clinical practice. For example, both DAPT and statin therapy were not mandatory for ACS management according to guideline recommendations in these earlier ACS study periods [20]. Thus, the prescription rates for DAPT and statin therapy in these studies were low.

Interpretation of the survival benefits associated with metformin in this very high-risk population requires a multi-axial approach. In addition to the baseline characteristics and DM severity, we also prospectively collected detailed results concerning ACS severity and the burden of atherosclerosis. These details have usually been absent in previous retrospective studies and in recent clinical trials [5,6,11–13]. Compared with one recent clinical trial, the 2-year mortality rate was higher in our study [5]. This may have been due to a higher mean age, CKD, and DM severity, and a lower guideline-recommended medication prescription rate in our study. Conversely, a higher coronary revascularization rate and DAPT rate were identified in our study, compared to two recent clinical trials [5,6]. These differing rates reflect the diversity between clinical trials and real-world registries in terms of disease severity and clinical management.

The pleiotropic effects of metformin have been proposed for decades. However, most of these effects have been demonstrated in animal studies. Metformin reduces inflammatory marker secretion in smooth muscle cells, endothelial cells, macrophages, and hepatocytes [21,22]. Moreover, chronic treatment with metformin prevents ischemic ventricular fibrillation in metabolically normal pigs. This protective effect may be partially explained as the preservation of myocardial energetics during ischemia [23]. Moreover, metformin reduces ischemic-reperfusion injury in animal models with and without DM [24]. In addition, metformin treatment can result in attenuated post-MI cardiac remodeling, reduced new onset heart failure presentation, or heart failure progression via the AMP-activated protein kinase pathway that may decrease the risk of sudden cardiac death and all-cause mortality [23,25]. Our study comprised a complex and very high-risk population; therefore, the protective effect of metformin is likely to be multi-faceted, and likely to include anti-inflammatory and anti-thrombotic effects, and preserved endothelial function [26].

Concerns have been raised regarding metformin therapy in the ACS population, especially for older age group patients, and for those with concomitant heart failure and CKD, and regarding exposure to contrast medium during PCI in this population [18,27]. In our subgroup analyses, we did not observe any interaction between these stratifying factors and the main effect of metformin therapy.

Another important issue involves adherence to guideline recommendations. The prescription rate for metformin in our cohort was only 58%, even with the exclusion of patients with advanced kidney disease and of lean stature (BMI <18.5 kg/m^2). In contrast, 67% of the ACS population had received metformin therapy in recent clinical trials, [5,6] while a high metformin prescription rate ranging from 75% to 90% has been reported in real-world cohort studies [27,28]. The disparity in metformin prescription rates between the general population with type 2 DM and an ACS cohort might reflect the unconfirmed beneficial effects and safety concerns regarding metformin therapy in this very high-risk population. Current DM guidelines, as well as ACS guidelines, recommend metformin therapy for patients with ASCVD, but do not mention any recommendations concerning metformin therapy for the ACS population [19,29,30]. It is unlikely that a placebo-controlled trial with a mortality endpoint among people with DM and ACS will be forthcoming. Thus, our study addresses a knowledge gap concerning this very high-risk population, especially in the modern PCI era.

4.1. Limitations

This study has important limitations that should be acknowledged. Firstly, this is an observational study that provides only an inference of association rather than establishes causation between metformin therapy and mortality; hence, our findings need to be interpreted with caution. Secondly, the possibility of confounding by indication could not be ignored in this study. For example, patients with advanced age, frailty, multiple co-morbidities, or reduced life expectancy were more likely to be prescribed non-metformin anti-diabetic agents as revealed in our study and other studies [27,28]. Vice versa, metformin-treated patients were more likely to undergo revascularization, had shorter duration of diabetes and better LVEF, and received more guideline-recommended therapy in our study. Even though imbalances in baseline characteristics were well controlled using robust statistical methods, residual confounding effects might still exist. Thirdly, the proportion of patients receiving sulphonylureas or meglitinide was 46.0% ($n = 311$) in the metformin group and 49.5% ($n = 238$) in the non-metformin group ($p = 0.244$) among the overall cohort (data not shown). Since sulphonylureas have been reported to be associated with adverse outcomes in several registry studies, we could not distinguish whether metformin was beneficial or one of the comparators was detrimental in our study. Fourthly, empagliflozin and liraglutide have been shown to provide survival benefits in recent clinical trials, whereas only a few patients ($n = 15$) were prescribed sodium-glucose cotransporter 2 inhibitors, and none was prescribed glucagon-like peptide-1 agonists in our study. Thus, we considered that this factor would not affect our conclusion. Fifthly, because this study was based on the Taiwanese (Chinese) population, we recommend caution in extrapolating these findings to Caucasian populations. Lastly, the adherence to metformin therapy after 1-year of follow-up in our study was only 68%, however, which was similar to another clinical trial [5].

5. Conclusions

Based on a national registry in Taiwan in the modern PCI era, our study demonstrated that metformin was associated with lower all-cause mortality among patients with type 2 DM and ACS. This encouraging result might increase adherence of guideline recommendation on metformin therapy, especially in this very high-risk population.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.03.021.

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