

# Comparison between ticagrelor versus clopidogrel in long term outcomes of Taiwanese diabetic subjects with acute coronary syndrome undergoing successful revascularization

## From TSOC ACS-DM registry

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### Abstract

Although previous clinical trials demonstrated that ticagrelor could reduce cardiovascular events and mortality versus clopidogrel in patients with acute coronary syndrome (ACS), the real-world evidence of its clinical impacts on East Asian Diabetic population has rarely been investigated.

Between November 2013 and June 2015, 1534 patients were recruited into the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology (TSOC ACS-DM registry). After propensity score matching, a total of 730 patients undergoing successful revascularization and discharged on ticagrelor (N=365) or clopidogrel (N=365) were analyzed. The primary and secondary endpoints were all-cause mortality and re-hospitalization, respectively. The all-cause death associated with ticagrelor vs clopidogrel was 3.6% vs 7.4% (adjusted hazard ratio (HR) 0.34 [0.15–0.80];  $P=.0138$ ) at 24 months. The re-hospitalization rate at 24 months was 38.9% vs 39.2% ( $P=.3258$ ).

For diabetic patients with ACS, ticagrelor provided better survival benefit than clopidogrel without an increase of re-hospitalization in 24 months after successful percutaneous coronary intervention. This study in real-world circumstance provided valuable complementary data to externally validate platelet inhibition and patient outcomes (PLATO) finding especially in Asian diabetic population.

**Abbreviations:** ACS = acute coronary syndrome, AMI = acute myocardial infarction, CI = confidence interval, DAPT = dual antiplatelet therapy, DM = diabetes mellitus, HR = hazard ratio, KAMIR-NIH = Korea Acute Myocardial Infarction Registry-National Institute of Health, NNT = number-needed-to-treat, OR = odds ratio, PCI = percutaneous coronary intervention, PLATO = platelet inhibition and patient outcomes, PSM = propensity score matching, STEMI = ST elevation myocardial infarction, THEMIS = Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study, TIMI = thrombolysis in myocardial infarction, TSOC ACS-DM registry = Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology.

**Keywords:** acute coronary syndrome, clopidogrel, diabetes, ticagrelor

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## 1. Introduction

The Asia-Pacific region is populated by more than 4.2 billion inhabitants, equivalent to 60% of the world's population. Acute coronary syndrome (ACS) is now a major cause of death and disability in this region with in-hospital mortality typically exceeding 5%.<sup>[1]</sup> Diabetes mellitus (DM) is one of the most important risk factors for coronary artery disease and the prevalence of which is increasing globally, especially in Asian countries. Moreover, in diabetic patients, platelet reactivity is increased providing a proinflammatory state, which is even much more pronounced during ACS.<sup>[2]</sup> Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor antagonist, especially in those undergoing percutaneous coronary intervention (PCI) has become one of the established standard of treatment for ACS.<sup>[3,4]</sup> Clopidogrel has been used extensively worldwide as the P2Y12 receptor antagonist with aspirin for more than a decade. A drawback of clopidogrel is that as a pro-drug, it needs liver metabolism to be activated. Moreover, this pathway is susceptible to genetic polymorphism, which may lead to unexpected variations in drug activity.<sup>[5,6]</sup> In particular, studies have consistently shown that some population, like Asian and DM patients have higher prevalence of impaired clopidogrel-induced antiplatelet effects compared with other population.<sup>[2,7,8]</sup>

In the global Phase III PLATO trial, ticagrelor, a novel and more potent P2Y12 receptor antagonist, has been demonstrated to reduce the composite of myocardial infarction, stroke and death from cardiovascular cause, without increasing overall major bleeding than clopidogrel in patients with ACS.<sup>[9]</sup> However, the efficacy and safety in the East Asian population have not been well established.<sup>[10]</sup> The studies showed that Asian patients are more susceptible to antithrombotics or fibrinolytics<sup>[11,12]</sup> and to be associated with a higher bleeding risk during management of ischemic heart diseases and antithrombotic therapy.<sup>[13]</sup> Although the subgroup analysis from PLATO study revealed consistent profile of effects and safety in Asian and in diabetic patients receiving ticagrelor and clopidogrel,<sup>[14]</sup> another phase III PHILO trial that was designed to mirror PLATO trial but only included East Asian population showed the event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in patient treated with ticagrelor compared with clopidogrel.<sup>[15]</sup> As such, we undertook the present observational study to evaluate outcomes in ACS DM patient, a very high risk population, after receiving percutaneous coronary intervention and treated with ticagrelor or clopidogrel, who were enrolled into the Acute Coronary Syndrome-Diabetes Mellitus Registry of the Taiwan Society of Cardiology (TSOC ACS-DM Registry).

## 2. Methods

### 2.1. Study patients

All patients were participants in the TSOC ACS-DM Registry. This was a prospective, nationwide, multicenter, non-interventional, observational clinical registry-based study, and the recruitment procedure has been detailed elsewhere.<sup>[16]</sup> In brief, the inclusion criteria were patients

- 1) who were admitted to the hospital with ACS within the previous 30 days;
- 2) with a history of type 2 DM or newly diagnosed DM defined according to the world health organization criteria;
- 3) aged  $\geq 20$  years; and
- 4) agreed to provide informed consent.

The exclusion criteria were patients

- 1) who had crossover from clopidogrel to ticagrelor or from ticagrelor to clopidogrel during study;
- 2) who did not take clopidogrel and ticagrelor;
- 3) who did not receive primary PCI;
- 4) with serum creatinine over 5 mg/dL; and
- 5) with ACS accompanied by or precipitated by a significant comorbidity such as motor vehicle accidents, trauma, severe gastrointestinal bleeding, peri-operative or peri-procedural myocardial infarction, or those participating in an investigational drug study.

Therefore, a total of 1534 patients with existing or newly diagnosed DM and aged  $>20$  years with ACS within the previous 30 days were recruited from 2013 through 2015.

According to the regulations of the Taiwan National Health Insurance system, the use of dual antiplatelet therapy can be reimbursed during a period of no longer than 9 months after the index ACS event. Ticagrelor became available in Taiwan in the latter half of 2013. The inclusion period for the present study was selected so as to span the period when clopidogrel dominated until the time when ticagrelor was well established in clinical practice in Taiwan and was chosen a priori to achieve adequate statistical power.

In this study, the clopidogrel group ( $n=917$ ) and the ticagrelor group ( $n=450$ ) were categorized according to patients who received dual antiplatelet therapy with clopidogrel or ticagrelor at the discharge of their in-hospital procedures. The dosage of clopidogrel and ticagrelor was according to the current Taiwanese guideline.<sup>[17]</sup> Further, patients were eligible for this study if they received primary PCI. In order to reduce sample selection bias, propensity score matching (PSM), which is commonly used in observational studies,<sup>[18–20]</sup> was performed to result in similar baseline characteristics between the clopidogrel and ticagrelor groups. In this study, the propensity score was measured on the variables shown in Table 1. The detailed process of patient selection is presented in Figure 1. Baseline demographic information, clinical symptoms, biochemistry data, and in-hospital procedures and outcomes, including 6-month, 1-year, and 2-year mortality, were collected as described previously.<sup>[16]</sup> The primary endpoint was death from any causes. Re-hospitalization was the secondary endpoint in this study. All data were submitted electronically by study nurses to a central laboratory for verification.

Continuous variables were presented as means and standard deviations when they were normally distributed and were compared using the Student *t* test; otherwise they were shown as medians and interquartile ranges and were analyzed using the Mann–Whitney *U* test. Categorical data were provided as numbers and percentages were examined using the chi-square test. Kaplan–Meier estimates and log-rank tests were performed to evaluate survival over 1- and 2-year periods between the clopidogrel and ticagrelor groups. Cox proportional hazards models were applied to compare the mortality between the clopidogrel and ticagrelor groups. The potential risk factors were further adjusted in the multivariate Cox proportional hazards models. The stratified estimates of 1- and 2-year mortality risk were further performed. A low thrombolysis in myocardial infarction (TIMI) score was defined as  $<3$  for patients with ST elevation myocardial infarction (STEMI) and  $<5$  for patients with non-STEMI/unstable angina; a high TIMI score was defined as  $\geq 3$  for STEMI patients and  $\geq 5$  for non-STEMI/unstable angina

**Table 1****Baseline characteristics of the patients who take clopidogrel and ticagrelor, respectively.**

Characteristics	Clopidogrel group (N = 365)	Ticagrelor group (N = 365)	Standardized mean difference*
Age, mean (SD), yr	63.0 (11.9)	62.7 (11.6)	0.023
Male sex, n (%)	274 (75.1)	273 (74.8)	0.006
BMI, mean (SD), kg/m <sup>2</sup>	26.1 (4.4)	26.2 (4.0)	0.013
SBP, mean (SD), mm Hg	141.7 (31.5)	141.6 (30.5)	0.003
DBP, mean (SD), mm Hg	83.1 (18.8)	82.9 (19.5)	0.011
Cardiovascular risk factors, n (%)			
Current smoker	136 (38.2)	134 (37.5)	0.014
Hypertension	272 (74.5)	268 (73.4)	0.025
Dyslipidemia	169 (46.3)	170 (46.6)	0.005
Other past history, n (%)			
Myocardial infarction	48 (13.1)	45 (12.3)	0.025
Percutaneous coronary intervention	71 (19.5)	70 (19.2)	0.007
Coronary-artery bypass grafting	5 (1.4)	7 (1.9)	0.043
Arterial fibrillation	13 (3.6)	11 (3.0)	0.031
Heart failure	18 (4.9)	18 (4.9)	0.000
Chronic obstructive pulmonary disease	6 (1.6)	6 (1.6)	0.000
ECG findings at study entry, n (%)			
Normal	40 (11.0)	58 (15.9)	0.145
ST-elevation	170 (46.6)	158 (43.3)	0.066
ST-depression	82 (22.5)	80 (21.9)	0.013
T-wave only	27 (7.4)	25 (6.9)	0.021
Missing	46 (12.6)	44 (12.1)	0.017
Killip classification			
I	198 (54.3)	209 (57.3)	0.061
II	84 (23.0)	90 (24.7)	0.039
III	48 (13.2)	24 (6.6)	0.222
IV	23 (6.3)	22 (6.0)	0.011
Missing	12 (3.3)	20 (5.5)	0.107
Peak_CK, median (IQR), U/L	582 (1362)	715 (1412)	0.104
Peak_CKMB, median (IQR), μg/L	42.0 (117.0)	47.5 (121.0)	0.042
Peak_Trop, median (IQR), μg/L	7.42 (44.9)	10.2 (44.0)	0.047
HbA1c, mean (SD), %	8.5 (2.0)	8.3 (1.9)	0.087
Total cholesterol, mean (SD), mg/dL	169.7 (51.0)	172.6 (44.5)	0.061
HDL, mean (SD), mg/dL	38.5 (10.3)	38.7 (10.0)	0.024
LDL, mean (SD), mg/dL	104.2 (40.1)	105.8 (37.2)	0.042
Triglyceride, median (IQR), mg/dL	131.5 (118.0)	141.0 (111.0)	0.038
Creatinine, mean (SD), mg/dL	1.15 (0.58)	1.18 (0.63)	0.051

BMI=body mass index, CK=creatinine kinase, DBP=diastolic blood pressure, ECG=electrocardiogram, HDL=high density lipoprotein, IQR=inter quartile range, LDL=low density lipoprotein, SBP=systolic blood pressure, SD=standard deviation.

\*Standardized mean differences of <0.10 likely denote a negligible imbalance between case patients and their matched controls.

patients. All statistical analyses were performed using statistical analysis system version 9.4 (SAS Institute Inc., Cary, NC), and a *P*-value <.05 was considered statistically significant.

### 3. Results

Table 1 shows the baseline characteristics of clopidogrel and ticagrelor groups after PSM. These 2 groups exhibited non-significant differences for all covariates. The mean age was  $63.0 \pm 11.9$  and  $62.7 \pm 11.6$  for patients who took clopidogrel and ticagrelor, respectively. Around 75% subjects were male in both groups.

The culprit artery territories, left ventricle ejection fraction, number of diseased vessel, use of an intra-aortic balloon pump, stent type, PCI, implantable cardioverter defibrillator, and medication use among the clopidogrel and ticagrelor groups were comparable (Table 2). Patients in the ticagrelor group reported taking coronary artery bypass grafting surgery significantly less frequently than did those in the clopidogrel group. In addition, the mean durations of treatment in the

clopidogrel and ticagrelor groups were  $7.8 \pm 3.6$  months vs  $6.7 \pm 3.2$  months ( $P < .0001$ ). Table 3 shows the in-hospital bleeding status, patients in the ticagrelor group presented a higher rate of bleeding according to the TIMI criteria<sup>[21]</sup> during the ACS admission, but the 2 groups did not differ significantly with respect to the rates of major or minor bleeding type.

Figure 2 compares the all-cause mortality rate and re-hospitalization rate at 2 years between patients in the clopidogrel and ticagrelor groups. Compared with the patients who received clopidogrel, those who received ticagrelor had lower incidences of all-cause death at 2 years (log-rank test  $P = .0404$ ), with adjusted hazard ratios (HRs) of 0.34 (95% confidence interval [CI], 0.15–0.80;  $P = .0138$ ) (Table 4). However, the results did not reach statistical significance for re-hospitalization at 2 years. In stratified analyses based on gender, age, TIMI score, and ACS diagnosis status, a prominently lower 2-year mortality risk was observed among females and patients aged  $\geq 65$  years in the ticagrelor group compared with patients in the clopidogrel group (Fig. 3).

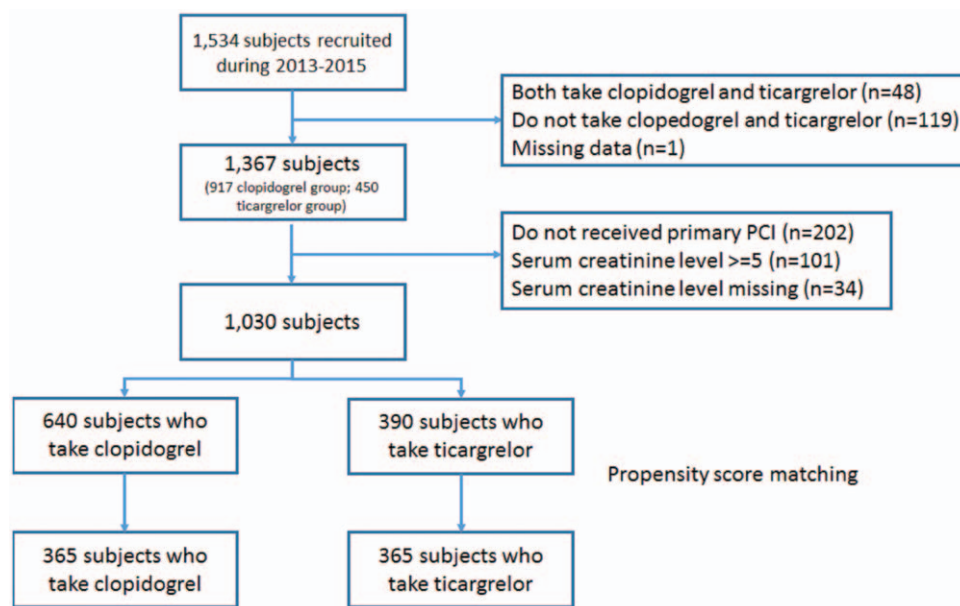


Figure 1. Participant selection flow chart.

Table 2

## Treatments and procedures of the patients who take clopidogrel and ticagrelor, respectively.

Characteristics	Clopidogrel Group (N = 365)		Ticagrelor Group (N = 365)	P-value
Culprit artery territory, n (%)				
LM	8 (2.2)	4 (1.1)		0.4030
LAD	162 (44.4)	155 (42.5)		
LCx	61 (16.7)	72 (19.7)		
RCA	106 (29.0)	114 (31.2)		
Unknown	28 (7.7)	20 (5.5)		
Ejection fraction				
Normal	152 (51.4)	167 (59.2)		0.1451
Mild (40–50%)	86 (29.1)	69 (24.5)		
Moderate (30–40%)	34 (11.5)	31 (11.0)		
Severe (<30%)	23 (7.8)	12 (4.3)		
Not done	1 (0.3)	3 (1.1)		
Disease vessel				
0	1 (0.3)	4 (1.2)		0.0019
1	109 (32.9)	156 (45.5)		
2	96 (29.0)	87 (25.4)		
3	125 (37.8)	96 (28.0)		
Intra aortic balloon pump, n (%)	72 (19.7)	62 (17.0)		0.3390
Stent type, n (%)				
BMS	131 (36.0)	119 (32.6)		0.0035
DES	153 (42.0)	185 (50.7)		
Both	12 (3.3)	7 (1.9)		
Others (bioresorbable)	1 (0.3)	9 (2.5)		
None/unknown	67 (18.4)	45 (12.3)		
PCI lesions successfully treated, n (%)	295 (97.0)	323 (97.9)		0.5009
Coronary artery bypass grafting status, n (%)	10 (2.7)	2 (0.6)		0.0199
ICD, n (%)	2 (0.6)	1 (0.3)		1.0000
Medications, n (%)				
Aspirin	337 (92.3)	345 (94.5)		0.2322
GP IIb/IIIa inhibitors	24 (6.6)	26 (7.1)		0.7695
ACE inhibitor	150 (41.1)	154 (42.2)		0.7639
Angiotensin II receptor blocker	113 (31.0)	119 (32.6)		0.6334
Oral beta blocker	252 (69.0)	264 (72.3)		0.3292
Statin	290 (79.5)	300 (82.2)		0.3472
Ca <sup>2+</sup> antagonist	78 (21.4)	63 (17.3)		0.1596
Medication duration, mo, mean (SD)	7.8 (3.6)	6.7 (3.2)		<0.0001

ACE=angiotensin-converting-enzyme, BMS=bare metal stent, DES=drug eluting stent, ICD=implantable cardioverter defibrillators, LAD=left anterior descending coronary artery, LCx=left circumflex coronary artery, LM=left main coronary artery, PCI=percutaneous coronary intervention, RCA=right coronary artery, SD=standard deviation.

**Table 3****The in-hospital bleeding status of the patients who take clopidogrel and ticagrelor, respectively.**

		Clopidogrel (N = 365)	Ticagrelor (N = 365)	P-value
In hospital TIMI bleed	No	350 (95.9)	363 (99.5)	.0014
	Yes	15 (4.1)	2 (0.6)	
TIMI major/minor bleed type	Major	12 (80.0)	2 (100.0)	1.0000
	Minor	3 (20.0)	0 (0)	
Blood transfusion	No	353 (96.7)	363 (99.5)	.0070
	Yes	12 (3.3)	2 (0.6)	

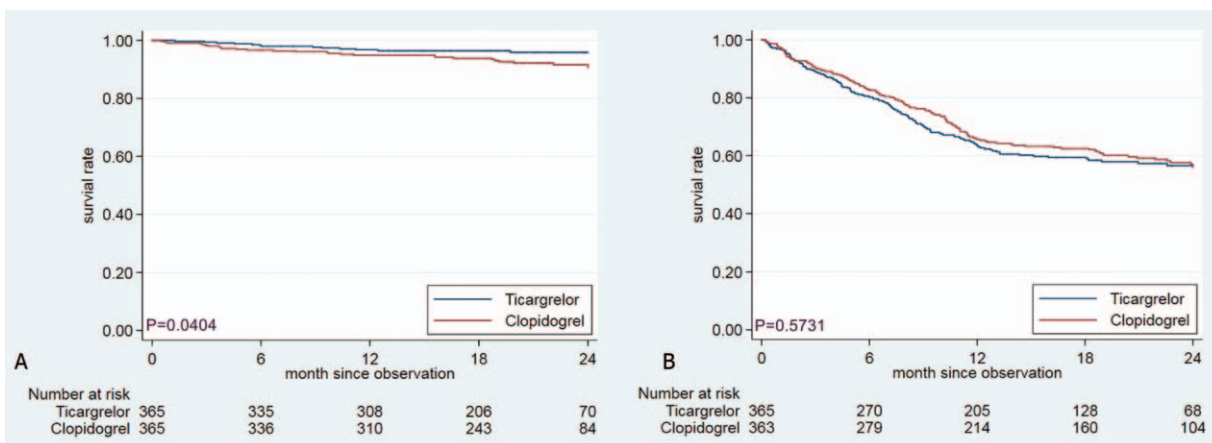
#### 4. Discussion

This study from sub-analysis of the nationwide, multicenter registry was conducted to compare the real-world outcome of East Asian diabetes population, mostly Taiwanese patients with ACS treated with ticagrelor versus clopidogrel after PCI. The main finding is that patients treated on ticagrelor post PCI had lower all-cause mortality without increasing any hospitalization. And the survival benefit persisted up to 2 years after. Therefore, ticagrelor might be an appropriate antiplatelet agent in addition to aspirin in East Asian diabetes population with ACS after PCI.

DAPT is a cornerstone of therapy for patients with acute coronary syndrome.<sup>[3]</sup> Clopidogrel has been used extensively worldwide for more than a decade. However, a drawback of clopidogrel is that it is a pro-drug, which means that it needs to be activated by liver metabolism.<sup>[22]</sup> In diabetes patients with ACS, the drug metabolism may be hampered by these specific circulatory circumstances and delay the antiplatelet effect especially in those patients undertaking PCI.<sup>[2,23]</sup> Furthermore, this pathway is susceptible to genetic polymorphism, which may lead to unexpected variations in drug activity. Besides, Asian patients have been reported as poor clopidogrel metabolizers due to the prevalence of cytochrome P450 2C19 (CYP2C19) loss-of-function alleles.<sup>[24–26]</sup>

Ticagrelor is an oral, direct-acting antiplatelet agent that binds reversibly to the P2Y<sub>12</sub> receptor and has a more rapid onset and robust antiplatelet effect compared with clopidogrel.<sup>[27]</sup> Ticagrelor is recommended by current ACS guidelines based on the PLATO trial.<sup>[4]</sup> Although the use of ticagrelor for ACS has been increasing across Asia, there is a paucity of evidence regarding the efficacy and safety of ticagrelor in this population.<sup>[28]</sup> The PHILO

study was a multicenter, randomized, double-blind study which was designed as PLATO and conducted in Japan and East Asian countries (Japan, 90%; South Korea, 6%; Taiwan, 4%).<sup>[15]</sup> But ticagrelor failed to demonstrate the benefit in PHILO study. The incidence of the composite primary end point (cardiovascular death, myocardial infarction, and stroke) was 10.2% (34 events) per year with ticagrelor and 8.1% (24 events) per year with clopidogrel (odds ratio (OR) 1.47, 95% CI 0.88–2.44). However, a retrospective nationwide cohort study compared clinical outcome of ticagrelor and clopidogrel in acute myocardial infarction (AMI) patients by using Taiwan National Health Insurance Database found the primary efficacy endpoint rate, including death from any cause, AMI, or stroke was 22% lower in the ticagrelor group than in the clopidogrel group (10.6% and 16.2%, respectively; adjusted hazard ratio (HR), 0.779; 95% CI: 0.684–0.887).<sup>[29]</sup> Another nationwide retrospective cohort study from Korean health insurance review and assessment data also revealed that ticagrelor had a significant effect on reduction of all-cause death without increasing major bleeding than clopidogrel in AMI patients after PCI.<sup>[30]</sup> To clarify the survival benefit of ticagrelor in East Asian ACS population after successful PCI in the real-world circumstance, we designed current study from the nationwide TSOC ACS DM registry. We found a lower all-cause mortality rate in the ticagrelor group than in the clopidogrel group (3.3% versus 4.9%) at 1 year follow up. A study from Korea Acute Myocardial Infarction Registry-National Institute of Health (KAMIR-NIH) included 2754 AMI patients after successful PCI and evaluated the short-term outcome of ticagrelor and clopidogrel. No difference in the composite of cardiac death, myocardial infarction, stroke, or target vessel revascularization at



**Figure 2.** Cumulative Kaplan–Meier estimates of the time to death (A) and hospitalization (B) at 2yr, respectively, between the patients who take clopidogrel and ticagrelor.

**Table 4**  
Endpoints of the patients who take clopidogrel and ticagrelor, respectively.

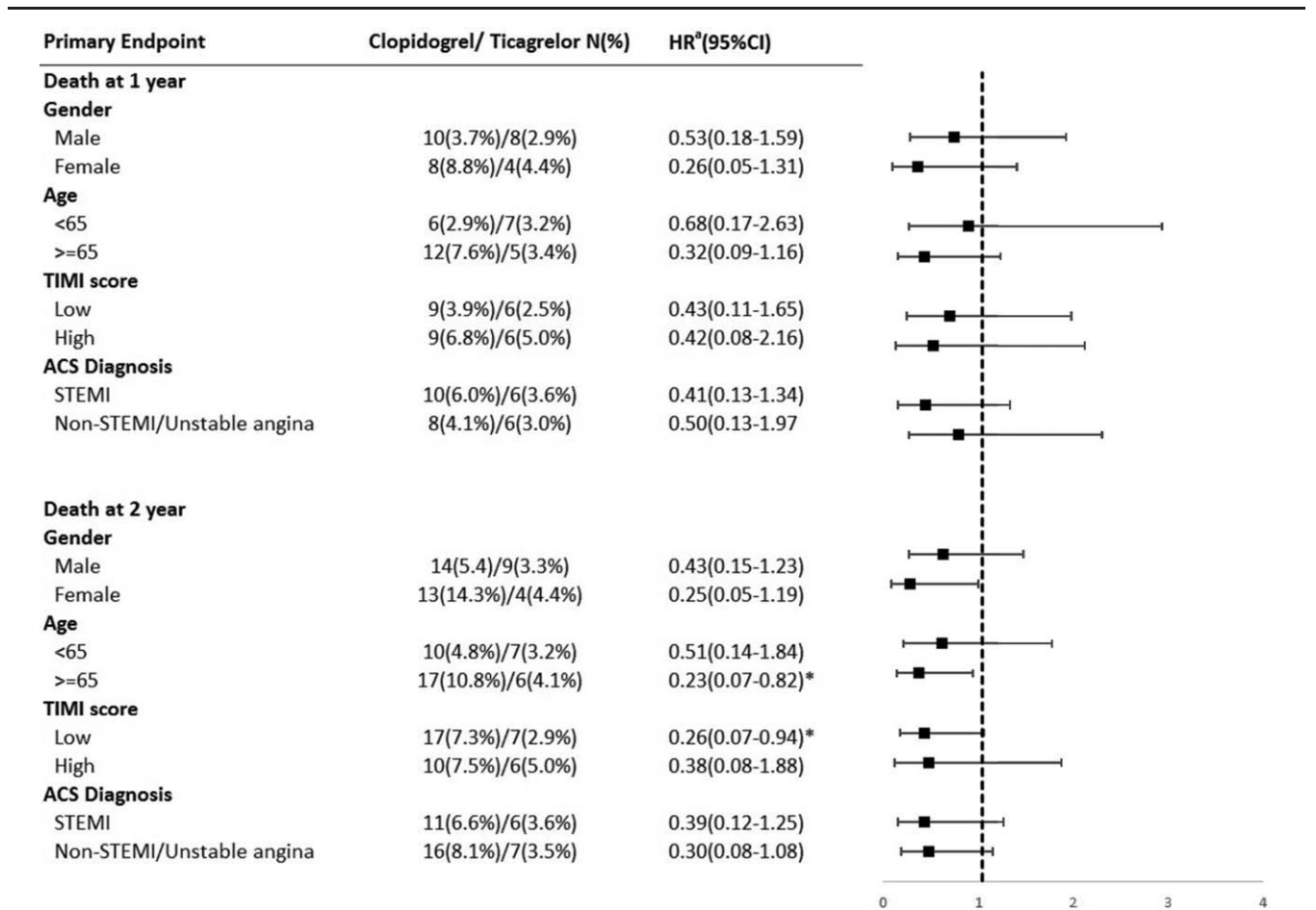
	Clopidogrel group (N = 365)	Ticagrelor group (N = 365)	HR	95% CI	P-value	HR*	95% CI	P-value
<b>All-cause mortality (N, %)</b>								
6 mo	12 (3.3)	7 (1.9)	0.63	0.25–1.60	.3301	0.61	0.22–1.71	.3476
1 yr	18 (4.9)	12 (3.3)	0.67	0.32–1.39	.2799	0.43	0.18–1.05	.0652
2 yr	27 (7.4)	13 (3.6)	0.51	0.26–0.98	.0444	0.34	0.15–0.80	.0138
<b>Hospitalized (N, %)</b>								
6 mo	74 (20.3)	88 (24.1)	1.30	0.95–1.77	.1030	1.62	1.14–2.30	.0077
1 yr	119 (32.6)	131 (35.9)	1.17	0.91–1.49	.2311	1.24	0.94–1.64	.1295
2 yr	143 (39.2)	142 (38.9)	1.05	0.83–1.33	.6786	1.14	0.88–1.48	.3258

\* Adjustment for ECG findings at study entry, Killip classification, Peak CK, stent type, coronary artery bypass grafting status, and disease vessels.

6 months was observed between 2 groups (4.2% vs 4.9%,  $P = .499$ ).<sup>[31]</sup> Both KAMIR-NIH and TSOC ACS-DM registry mainly included relatively stable patients with ACS after successful revascularization. One of the differences between our study and KAMIR-NIH is that our study population consisted entirely of diabetic ACS patients, which is a very high-risk diseased population requiring aggressive intervention. The beneficial effect of any intervention in the high-risk population could be subsequently translated into a smaller number-needed-to-treat (NNT) as compared to that in the general population. For

example, by using ticagrelor vs clopidogrel, the NNT for 1-year and 2-year all-cause mortality in our study was 63 and 27, respectively.

Besides, in diabetic and ACS patients, platelet reactivity is increased given a proinflammatory state and the clopidogrel-mediated platelet inhibitory effects may be deteriorated in DM patients.<sup>[2,32]</sup> Compared with clopidogrel and prasugrel, ticagrelor achieved not only faster, enhanced platelet inhibition and reduced high on-treatment platelet reactivity rates, but also significantly decreased inflammatory cytokines and increased



**Figure 3.** Primary endpoint at 1 yr and 2 yr between the patients who take clopidogrel and ticagrelor by gender, age, TIMI score, and ACS diagnosis. a: adjustment for ECG findings at study entry, Killip classification, Peak CK, stent type, coronary artery bypass grafting status, and disease vessels. Low TIMI score defined as a TIMI score <3 for STEMI patients and <5 for non-STEMI/unstable angina patients whereas a TIMI score ≥3 for STEMI patients and ≥5 for non-STEMI/unstable angina patients were defined as high TIMI score group. \* $P < .05$ .

circulating endothelial progenitor cells, contributing to improved arterial endothelial function in diabetic acute coronary syndrome patients.<sup>[23,33]</sup> Another difference is that our study provided long term outcome up to 2 years. We noted lower mortality rate trend of ticagrelor group at 6 months and 12 months (1.9% versus 3.3% and 3.3% versus 4.9%). And we also noted the difference in survival benefit is consistent and significant at the analysis of 24 months (3.6% versus 7.4%; adjusted HRs=0.46; 95% CI: 0.23–0.92;  $P=0.0271$ ), although the treatment period of ticagrelor group is  $6.7 \pm 3.2$  months only, which is less than clopidogrel group. The possible explanation is that the pleiotropic effects of ticagrelor on longer-term clinical course beyond its potent antiplatelet effects such as restoration of endothelial function or tissue perfusion could contribute to additional clinical benefits in the study population.<sup>[27]</sup> Our study showed a lower 2-year mortality risk in females and patients aged  $\geq 65$  years in the ticagrelor group. Yaseen et al found diabetes mellitus, hypertension, obesity, and male sex were the major independent predictors for clopidogrel non-responder. They also found younger age was a protective factor.<sup>[35]</sup> These findings can explain why females and elderly patients had better outcome in the ticagrelor group.

In our study, the incidence of in-hospital bleeding including TIMI major or minor bleeding are relatively low in both ticagrelor and clopidogrel group, which may be attributable to missing information or incomplete patient records. Because minor bleeding events were possibly not fully reported and incomplete in the registry, the total bleeding events might be underestimated in the present study. However, ticagrelor had consistent similar re-hospitalization rate with clopidogrel during follow up period.

Recently, topline results of Ticagrelor on Health Outcomes in Diabetes Mellitus Patients Intervention Study (THEMIS) study has been early released.<sup>[35]</sup> By enrolling 19,271 patients with diabetes and established coronary artery disease but no history of myocardial infarction or stroke, ticagrelor has been shown to reduce major adverse cardiovascular events as compared to placebo. To be noted, there are some key differences between our study and THEMIS including study population (DM with ACS vs DM) and intervention strategy. As such, the indispensable role of our study as a real-world evidence to inform clinical decisions with complementary data to randomized controlled trials still exists.

There are some key limitations in the present study. First, our study was a non-randomized study, but based on a prospective, observational registry, therefore, selection bias was hardly avoidable, which opens the possibility of residual confounding which is a known potential source of error in registry studies. Even though it was partial compensated by multivariate Cox proportional hazard models. Second, the absolute risk of bleeding is lower in the registry than the risk seen in clinical trials. It is conceivable that this relates to underreporting of bleeding events in the registry. Third, we could not accurately evaluate other adverse effects of P2Y12 inhibitors including dyspnea, heart block, or bruising. Fourth, the actual treatment duration and attrition are unavailable in the present analysis which is based on intention to treat. However, as more patients in the ticagrelor arm discontinued their study drug than in the clopidogrel arm, we still found the survival benefit of ticagrelor over clopidogrel up to 2 years follow up. Fifth, there was no data for clopidogrel non-response or semi-response in TSOC ACS-DM registry. Although we excluded all patients needed to shift

clopidogrel to ticagrelor, the clopidogrel non-/semi-response might still interfere our study.

In conclusion, ticagrelor versus clopidogrel treatment at discharge in diabetic patients with ACS after PCI was associated with a lower adjusted risk of death without an increase in the rate of overall re-hospitalization during 24-months follow-up. This study in real-world circumstance provided important complementary data to externally validate PLATO finding especially in the high-risk Asian diabetic population.

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