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ORIGINAL RESEARCH

Ticagrelor Versus Clopidogrel in East Asian Patients With Acute Coronary Syndrome and Diabetes Mellitus

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ABSTRACT

BACKGROUND It is still unknown whether diabetes mellitus (DM) affects the relative safety and efficacy of ticagrelor vs clopidogrel in East Asian patients with acute coronary syndrome (ACS).

OBJECTIVES The authors sought to assess the safety and efficacy of ticagrelor vs clopidogrel according to the diabetic status of East Asian patients with ACS undergoing invasive management.

METHODS This prespecified analysis of the TICA KOREA (Clinically Significant Bleeding With Ticagrelor Versus Clopidogrel in Korean Patients With Acute Coronary Syndromes Intended for Invasive Management) trial included 800 Korean patients. The primary safety endpoint was clinically significant bleeding (PLATO [Platelet Inhibition and Clinical Outcomes] major or minor bleeding) at 12 months; the efficacy endpoint was major adverse cardiovascular events (cardiovascular death, myocardial infarction, and stroke).

RESULTS Of 800 patients, 216 (27.0%) had DM. The incidence of clinically significant bleeding within 12 months was significantly higher with ticagrelor than clopidogrel in the nondiabetic group (10.2% vs 4.3%; HR: 2.45; 95% CI: 1.27-4.70; $P = 0.007$) and tended to be higher in the diabetic group (13.8% vs 8.0%; HR: 1.87; 95% CI: 0.54-4.36; $P = 0.15$); there was no significant interaction between treatment-arm and DM (P for interaction $= 0.64$). The incidences of major adverse cardiovascular events were not significantly different after ticagrelor or clopidogrel both in the diabetic group (10.8% vs 6.0%; HR: 1.90; 95% CI: 0.71-5.07; $P = 0.20$) and in the nondiabetic group (8.5% vs 5.7%; HR: 1.51; 95% CI: 0.81-2.81; $P = 0.19$) without significant interaction (P-for-interaction $= 0.71$).

CONCLUSIONS In Korean ACS patients undergoing early invasive management, diabetes status did not affect the relative safety and efficacy of ticagrelor and clopidogrel. (Safety and Efficacy of Ticagrelor Versus Clopidogrel in Asian/Korean Patients With Acute Coronary Syndromes Intended for Invasive Management [TICA KOREA]; NCT02094963) (JACC: Asia 2022;2:666-674) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Because diabetes mellitus (DM) is associated with increased platelet reactivity and reduced response to antiplatelet drugs,[1-3] it is well known as a risk factor for subsequent ischemic events (ie, myocardial infarction [MI], stroke, or stent thrombosis) and cardiovascular mortality in patients with acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI).[4,5] Owing to the pathophysiological effect of DM on platelet activation, the safety and efficacy of antithrombotic therapies may differ between diabetic and nondiabetic patients; in other words, there is the possibility or clinical need that patients with DM may require more potent platelet inhibitors or alternative strategies.[6,7]

Although current practice guidelines recommend the preferential use of more potent $P2Y_{12}$ inhibitors (ie, ticagrelor and prasugrel) over clopidogrel for ACS with or without ST-segment elevation,[8,9] the relative safety and efficacy of potent $P2Y_{12}$ inhibitors in East Asian patients with a different bleeding or ischemic propensity are substantially different compared with Western patients.[10,11] This phenomenon has been demonstrated in several randomized clinical trials (RCTs).[12-14] In addition, although landmark RCTs in Western populations demonstrated a consistent treatment effect of potent ticagrelor and prasugrel over clopidogrel irrespective of diabetic status,[7,15] it is unclear whether the diabetic status affects the relative safety and efficacy of ticagrelor vs clopidogrel in East Asian patients with ACS. The TICA KOREA (Ticagrelor Versus Clopidogrel in Asian/Korean Patients with ACS Intended for Invasive Management) trial showed that ticagrelor was associated with higher incidence of clinically significant bleeding and numerically higher incidence of ischemic events than clopidogrel in Korean ACS patients.[16] Herein, we performed a prespecified subgroup analysis of the safety and efficacy of ticagrelor vs clopidogrel according to the diabetes status in the TICA KOREA trial.

METHODS

STUDY DESIGN AND POPULATION. The design and primary results of the TICA KOREA trial (NCT02094963) have been published previously.[16] In brief, a total of 800 patients hospitalized for ACS (unstable angina, non-ST-segment elevation myocardial infarction [MI], or ST-segment elevation MI) in whom invasive treatment was planned were assigned randomly at a 1:1 ratio to receive either ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) or clopidogrel (600 mg loading dose, 75 mg daily thereafter). The trial was conducted at 10 major centers in Korea and was approved by the investigational review board or ethics committee at each participating center. Written informed consent was obtained from all patients.

Patients were recorded as having DM if they were receiving active treatment with oral hypoglycemic agents or insulin at the index hospitalization. For patients diagnosed with DM who were on dietary therapy alone, documentation of abnormal fasting blood glucose or an abnormal result on a glucose tolerance test according to World Health Organization criteria was required. According to the presence or absence of DM, study participants were categorized into 2 groups: patients with DM (n = 216) and those without DM (n = 584).

STUDY ENDPOINTS AND FOLLOW-UP. The primary safety endpoint was the incidence of clinically significant bleeding at 12 months after randomization, which was defined as a composite of major or minor bleeding according to the PLATO (Platelet Inhibition and Clinical Outcomes) criteria.[16,17] Secondary safety endpoints included each individual component of major, minor, or fatal bleeding defined by the PLATO criteria. The primary efficacy endpoint was the incidence of major adverse cardiovascular events (MACE; defined as a composite of death from cardiovascular causes, nonfatal MI, or nonfatal stroke) at 12 months after randomization. Secondary efficacy endpoints included individual components of MACE; composite of cardiovascular death, spontaneous MI (excluding periprocedural MI), or stroke; composite of all-cause death, MI, or stroke; all-cause death; repeat revascularization; and stent thrombosis (definite). The definitions of these safety and efficacy outcome measures have previously been described in detail.[16] All primary and secondary endpoints of the TICA KOREA trial were confirmed by source documentation collected at each hospital and centrally adjudicated with the use of prespecified criteria by an independent clinical events committee.

Patients were followed up by hospital visit or telephone interview at 1, 3, 6, and 12 months after hospital admission for the first event, with a safety follow-up visit 1 month after the end-of-treatment visit. All serious adverse events and efficacy and safety endpoints in this trial were monitored onsite. The investigators and study center personnel noted adverse events, suspected clinical events, study medication status, and use of concomitant medication.

STATISTICAL ANALYSIS. The primary purpose of this study was to evaluate the relative safety and efficacy outcomes in diabetic and nondiabetic ACS

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

MACE = major adverse cardiovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

RCT = randomized controlled trial

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NOVEMBER 2022:666–674

TABLE 1 Baseline Characteristic of Patients Stratified by Randomized Treatment and Diabetes Status

	DM			Non-DM		
	Ticagrelor (n = 116)	Clopidogrel (n = 100)	*P* Value	Ticagrelor (n = 284)	Clopidogrel (n = 300)	*P* Value
Age, y	64.4 ± 10.6	65.8 ± 10.0	0.31	61.7 ± 11.5	61.1 ± 11.8	0.58
Male	80 (69.0)	70 (70.0)	0.99	217 (76.4)	232 (77.3)	0.87
Body mass index, kg/m^2	24.6 ± 3.0	25.4 ± 3.4	0.11	24.6 ± 3.0	24.7 ± 3.1	0.83
Hypertension	82 (70.7)	57 (57.0)	0.05	141 (49.6)	136 (45.3)	0.34
Current smoker	37 (31.9)	35 (35.0)	0.74	106 (37.3)	107 (35.7)	0.74
Hyperlipidemia	63 (54.3)	62 (62.0)	0.32	145 (51.1)	132 (44.0)	0.10
Previous MI	16 (13.8)	7 (7.0)	0.16	9 (3.2)	13 (4.3)	0.60
Previous PCI	22 (19.0)	13 (13.0)	0.32	19 (6.7)	18 (6.0)	0.86
Previous CABG	2 (1.7)	0 (0.0)	0.54	2 (0.7)	3 (1.0)	>0.99
History of stroke	14 (12.1)	5 (5.0)	0.11	10 (3.5)	11 (3.7)	>0.99
History of heart failure	7 (6.0)	2 (2.0)	0.26	3 (1.1)	4 (1.3)	>0.99
Peripheral artery disease	0 (0.0)	0 (0.0)	-	4 (1.4)	2 (0.7)	0.63
Chronic renal disease	5 (4.3)	0 (0.0)	0.10	1 (0.4)	1 (0.3)	>0.99
Chronic lung disease	2 (1.7)	1 (1.0)	>0.99	10 (3.5)	2 (0.7)	0.03
Previous gastrointestinal bleeding	1 (0.9)	0 (0.0)	>0.99	0 (0.0)	0 (0.0)	-
Clinical diagnosis			0.41			0.65
Unstable angina	19 (16.4)	25 (25.0)		50 (17.6)	47 (15.7)	
NSTEMI	47 (40.5)	40 (40.0)		101 (35.6)	115 (38.3)	
STEMI	46 (39.7)	32 (32.0)		124 (43.7)	124 (41.3)	
Others	4 (3.4)	3 (3.0)		9 (3.2)	14 (4.7)	
Final treatment			0.02			0.91
Percutaneous coronary intervention	91 (78.4)	92 (92.0)		235 (82.7)	250 (83.3)	
Coronary artery bypass grafting	6 (5.2)	2 (2.0)		5 (1.8)	4 (1.3)	
Medical treatment only	19 (16.4)	6 (6.0)		44 (15.5)	46 (15.3)	
Antithrombotic agents during index hospitalization						
Unfractionated heparin	73 (62.9)	73 (73.0)	0.15	186 (65.5)	198 (66.0)	0.97
Low-molecular-weight heparin	14 (12.2)	19 (19.0)	0.62	47(16.5)	44 (14.7)	0.23
Glycoprotein IIb/IIIa inhibitors	2 (1.7)	4 (4.0)	0.55	6 (2.1)	10 (3.3)	0.52
Discharge medications						
Aspirin	111 (96.5)	99 (99.0)	0.45	274 (96.5)	287 (95.7)	0.77
Beta-blocker	83 (71.6)	79 (79.0)	0.27	192 (67.6)	218 (72.7)	0.21
Calcium-channel blocker	25 (21.6)	25 (25.0)	0.66	65 (22.9)	65 (21.7)	0.80
ACE inhibitor or ARB	52 (44.8)	52 (52.0)	0.36	111 (39.1)	119 (39.7)	0.95
Statin	104 (89.7)	92 (92.0)	0.72	250 (88.0)	277 (92.3)	0.11
Proton-pump inhibitor	2 (1.7)	1 (1.0)	>0.99	10 (3.5)	7 (2.3)	0.54

Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; CABG = coronary artery bypass grafting; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

patients after randomized treatment with ticagrelor or clopidogrel. Continuous variables are presented as mean values with standard deviation and were compared using either the Student's *t*-test or the nonparametric Wilcoxon rank sum test. Categorical variables are presented as number with percentage and were compared using the chi-square statistics or Fisher exact test, as appropriate. The Kaplan-Meier method was used to compare the cumulative incidence of the safety and efficacy endpoints according to treatment arm (ticagrelor vs clopidogrel) in patients with or without DM, and the time to the first event was compared between groups using the log rank test. A Cox proportional hazards model was used to compare the rates of safety and efficacy outcomes after ticagrelor or clopidogrel in each group of diabetic and nondiabetic patients, and HRs were presented with 95% CIs. The assumptions of the Cox model were assessed statistically based on Schoenfeld residuals and graphically by log-log plots; they were found to be satisfied for all variables. To estimate the interactions between treatment arm (ticagrelor or clopidogrel) and DM status, an interaction term was entered into the Cox proportional hazards models.

All reported *P* values were 2-sided, and $P < 0.05$ was considered significant for all tests. No adjustment for multiple testing was undertaken. Because of the

TABLE 2 Primary and Secondary Safety Endpoints at 12 Months Stratified by Randomized Treatment and Diabetes Status

	DM				Non-DM				
	Ticagrelor (n = 116)	Clopidogrel (n = 100)	HR (95% CI)	*P* Value	Ticagrelor (n = 284)	Clopidogrel (n = 300)	HR (95% CI)	*P* Value	*P* for Interaction
Clinically significant bleeding: primary safety endpoint[a]	16 (13.8)	8 (8.0)	1.87 (0.80–4.36)	0.15	29 (10.2)	13 (4.3)	2.45 (1.27–4.70)	0.007	0.64
Procedure-related	5 (4.3)	3 (3.0)	1.51 (0.36–6.30)	0.58	6 (2.1)	4 (1.3)	1.60 (0.45–5.67)	0.47	0.93
CABG-related	6 (5.2)	1 (1.0)	5.56 (0.67–46.15)	0.11	5 (1.8)	3 (1.0)	1.82 (0.44–7.63)	0.41	0.39
Not procedure- or CABG-related	5 (4.3)	4 (4.0)	1.20 (0.32–4.47)	0.79	18 (6.3)	6 (2.0)	3.33 (1.32–8.38)	0.01	0.23
PLATO major bleeding	12 (10.3)	7 (7.0)	1.59 (0.62–4.03)	0.33	17 (6.0)	9 (3.0)	2.05 (0.91–4.60)	0.08	0.70
Procedure-related	2 (1.7)	3 (3.0)	0.60 (0.10–3.61)	0.58	2 (0.1)	2 (0.7)	1.06 (0.15–7.52)	0.95	0.76
CABG-related	6 (5.2)	1 (1.0)	5.50 (0.66–45.64)	0.12	5 (1.8)	3 (1.0)	1.81 (0.43–7.58)	0.42	0.53
Not procedure- or CABG-related	4 (3.5)	3 (3.0)	1.26 (0.28–5.64)	0.76	10 (3.5)	4 (1.3)	2.73 (0.86–8.70)	0.09	0.71
PLATO minor bleeding	6 (5.2)	1 (1.00)	5.50 (0.66–45.60)	0.12	14 (4.9)	4 (1.3)	3.80 (1.25–11.50)	0.02	0.57
Procedure-related	4 (3.5)	0 (0.0)	NA	>0.99	4 (1.4)	2 (0.7)	2.13 (0.39–11.60)	0.38	NA
CABG-related	0 (0.0)	0 (0.0)	NA	NA	0 (0.0)	0 (0.0)	NA	NA	NA
Not procedure- or CABG-related	2 (1.7)	1 (1.0)	1.90 (0.17–20.93)	0.60	10 (3.5)	2 (0.7)	5.47 (1.20–25.00)	0.03	0.73
Fatal bleeding	1 (0.9)	0 (0.0)	NA	>0.99	3 (1.1)	0 (0.1)	NA	>0.99	NA

Values are n (%) unless otherwise indicated. The percentages are Kaplan-Meier estimates of the incidence of the end points at 12 months. HR, 95% CI, and corresponding *P* values were calculated by means of Cox regression analysis. [a]Clinically significant bleeding was defined as a composite of PLATO major or minor bleeding).

NA = not available; PLATO = Platelet Inhibition and Patient Outcomes trial; other abbreviations as in Table 1.

potential for type I error due to multiple comparisons, all findings of this study should be interpreted as exploratory. Statistical analyses were performed using SPSS software version 22.0 (IBM Corporation) and R software version 3.6.2. (R Foundation for Statistical Computing).

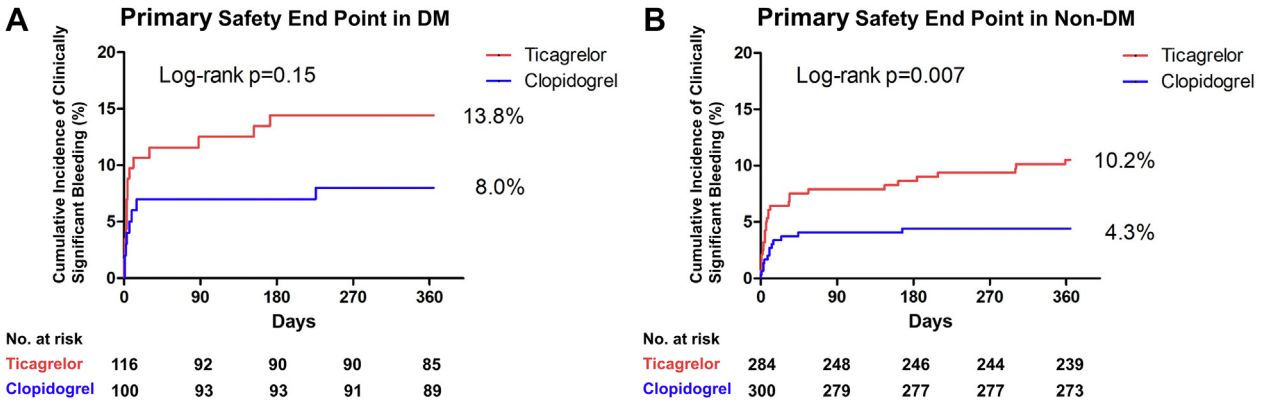
RESULTS

STUDY POPULATION AND BASELINE CHARACTERISTICS. A total of 800 patients at 10 major centers in Korea were enrolled in the TICA KOREA trial between July 5, 2014, and June 30, 2017. We randomly assigned 400 patients to receive ticagrelor therapy and 400 patients to receive clopidogrel therapy add-on aspirin. Among 800 randomized patients, 216 patients (27.0%) had DM and 584 patients did not. In patients with DM, 116 patients were assigned to ticagrelor and 100 patients to clopidogrel. In patients without DM, 284 patients were assigned to ticagrelor and 300 patients to clopidogrel. Baseline demographic, clinical characteristics, treatment, and medication data stratified by randomized group and diabetic status are shown in Table 1. In patients with DM, baseline characteristics did not differ significantly according to study drug (ticagrelor or clopidogrel), with the exception of a higher proportion of hypertension and a lower proportion of PCI treatment in ticagrelor-assigned patients. In patients without DM, baseline characteristics were well-balanced, with the exception of a higher proportion of chronic lung disease in the ticagrelor arm.

SAFETY ENDPOINTS ACCORDING TO DIABETIC STATUS. The median follow-up duration was 365 days (IQR: 365-365 days) in patients with DM and 365 days (IQR: 365-365. days) in patients without DM ($P = 0.81$). Twelve-month follow-up was completed for most patients except for 7 patients (3.2%) in the DM group and 9 patients (1.5%) in the non-DM group ($P = 0.22$). Primary and secondary safety endpoints after randomized treatment with ticagrelor or clopidogrel stratified by diabetes status are summarized in Table 2. In patients with DM, the 12-month incidence of the primary safety endpoint of clinically significant bleeding tended to be higher in the ticagrelor group than in the clopidogrel group (13.8% vs 8.0%, respectively; HR: 1.87; 95% CI: 0.54-4.36) (Figure 1). In patients without DM, the incidence of clinically significant bleeding was also significantly higher after ticagrelor than after clopidogrel (10.2% vs 4.3%, respectively; HR: 2.45; 95% CI: 1.27-4.70). There was no significant treatment arm-by-diabetic status interaction (*P* for interaction = 0.64). This trend was consistent with respect to each component of major, minor, or fatal bleeding, without a significant interaction between treatment arm and diabetic status.

EFFICACY ENDPOINTS ACCORDING TO DIABETIC STATUS. Primary and secondary efficacy outcomes after ticagrelor or clopidogrel stratified by diabetic

FIGURE 1 Cumulative Incidence of the Primary Safety Endpoint at 12 Months



Kaplan Meier curves showing rates of the primary safety endpoint of PLATO (Platelet Inhibition and Patient Outcomes) major or minor after ticagrelor or clopidogrel in patients with diabetes mellitus (DM) **(A)** and in those without DM **(B)**.

status are shown in Table 3. In patients with DM, the primary efficacy endpoint of MACE at 12 months was not significantly different between the ticagrelor group than in the clopidogrel group (10.3% vs 6.0%, respectively; HR: 1.90; 95% CI: 0.71-5.07) (Figure 2). Similarly, in patients without DM, the 12-month incidence of MACE was also not significantly different after ticagrelor or clopidogrel (8.5% vs 5.7%, respectively; HR: 1.51; 95% CI: 0.81-2.81). Thus, there was no significant interaction between treatment arm and diabetes status with regard to the primary efficacy outcome of MACE incidence (P for interaction = 0.71). These findings with regard to secondary efficacy outcomes were also similar irrespective of diabetic status.

DISCUSSION

In this prespecified clinical trial analysis, we assessed whether diabetes status influenced the relative safety and efficacy outcomes with ticagrelor vs clopidogrel among East Asian (Korean) ACS patients who were intended for early invasive management. The major findings are summarized as follows: 1) compared with clopidogrel, ticagrelor was associated with a higher incidence of clinically significant bleeding at 12 months in the nondiabetic group and in diabetic group (although not statistically significant in this group); 2) the incidence of MACE and ischemic events at 12 months were not significantly different after ticagrelor and clopidogrel both in diabetic and nondiabetic patients; and 3) there was no significant treatment effect-by-diabetes status interaction demonstrating that DM did not affect the relative safety and efficacy of ticagrelor and clopidogrel in Korean ACS patients (Central Illustration).

The evidence on the relative safety and efficacy of ticagrelor or prasugrel compared to clopidogrel in diabetic patients with ACS undergoing PCI were controversial.[15,18] In TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38), diabetic patients compared with nondiabetic patients tended to have a greater reduction in ischemic events without an increase in TIMI major bleeding.[18] Thus, the net benefit of prasugrel over clopidogrel in this trial (a composite of the incidence of ischemic and bleeding events) was greater in patients with DM than those without DM (P for interaction = 0.05). By contrast, in the subgroup analysis of the PLATO trial,[15] the reduction in the incidence of ischemic events by ticagrelor in patients with DM was consistent with the overall cohort, without significant interactions between diabetic status and treatment arm. However, the magnitude of ischemic benefit of ticagrelor was enhanced in patients with levels of glycated hemoglobin or glucose higher than the median, albeit without any interaction between treatments. However, the direct applicability of these trials findings to Asian population may be limited owing to <10% of enrolled patients. Although it is unanimously agreed that patients with ACS and DM require strong platelet inhibition, it is still questioned whether this concept could be directly applicable to East Asian patients with a higher bleeding tendency. In our prespecified analysis of TICA KOREA, the

TABLE 3 Primary and Secondary Efficacy Endpoints at 12 Months Stratified by Randomized Treatment and Diabetes Status

	DM				Non-DM				
	Ticagrelor (n = 116)	Clopidogrel (n = 100)	HR (95% CI)	*P* Value	Ticagrelor (n = 284)	Clopidogrel (n = 300)	HR (95% CI)	*P* Value	*P* for Interaction
MACE: primary efficacy end point									
Composite of cardiovascular death, MI, or stroke	12 (10.3)	6 (6.0)	1.90 (0.71–5.07)	0.20	24 (8.5)	17 (5.7)	1.51 (0.81–2.81)	0.19	0.71
Post hoc: composite of cardiovascular death, spontaneous MI, or stroke	6 (5.2)	6 (6.0)	0.92 (0.30–2.87)	0.89	15 (5.3)	11 (3.7)	1.45 (0.66–3.15)	0.35	0.52
Other secondary efficacy endpoints									
Composite of all-cause death, MI, or stroke	12 (10.3)	8 (8.0)	1.43 (0.58–3.50)	0.43	25 (8.8)	19 (6.3)	1.41 (0.77–2.55)	0.26	0.99
All-cause death	4 (3.4)	4 (4.0)	0.94 (0.23–3.75)	0.93	12 (4.2)	6 (2.0)	2.14 (0.80–5.70)	0.13	0.33
Cardiovascular death	4 (3.4)	2 (2.0)	1.87 (0.34–10.19)	0.47	11 (3.9)	4 (1.3)	2.94 (0.94–9.24)	0.06	0.66
Noncardiovascular death	0 (0.0)	2 (2.0)	NA	>0.99	1 (0.4)	2 (0.7)	0.53 (0.05–5.89)	0.61	NA
MI	8 (6.9)	3 (3.0)	2.47 (0.66–9.32)	0.18	12 (4.2)	13 (4.3)	0.98 (0.45–2.15)	0.96	0.25
Stroke	3 (2.6)	1 (1.0)	2.84 (0.30–27.34)	0.37	3 (1.1)	4 (1.3)	0.81 (0.18–3.60)	0.78	0.37
Repeat revascularization	4 (3.4)	5 (5.0)	0.74 (0.20–2.75)	0.65	6 (2.1)	7 (2.3)	0.92 (0.31–2.75)	0.89	0.80
Stent thrombosis	0 (0.0)	2 (2.0)	NA	>0.99	2 (0.7)	2 (0.7)	1.07 (0.15–7.56)	0.95	NA

Values are n (%) unless otherwise indicated. The percentages are Kaplan-Meier estimates of the incidence of the endpoints at 12 months. HR, 95% CI, and corresponding *P* values were calculated by means of Cox regression analysis.

Abbreviations as in Tables 1 and 2.

relative safety and efficacy outcomes of ticagrelor and clopidogrel were not substantially modulated by the presence or absence of DM. Without further clinical evidence through large-sized RCTs, no confirmative recommendation can be drawn as to whether ticagrelor or prasugrel should be the preferred antiplatelet strategy in East Asian patients with DM presenting with ACS.

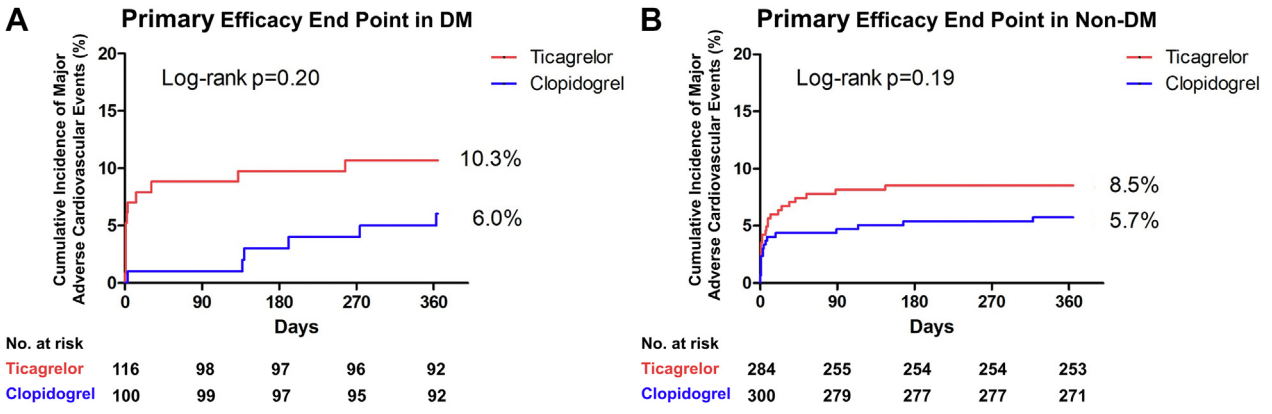
A number of mechanisms may contribute to impaired clopidogrel response in patients with DM.[2] Available evidence suggests that ticagrelor may be particularly advantageous in patients with DM undergoing PCI.[19-21] However, our study showed that ticagrelor showed a higher risk of safety outcomes and a similar risk of efficacy outcomes compared to clopidogrel, irrespective of diabetic status. Compared to previous study findings,[15,18] it is poorly understood the reason why potent $P2Y_{12}$ inhibitor of ticagrelor did not show superior efficacy (compared with clopidogrel) in the diabetic subset of Korean ACS patients. Such discrepant findings might be explained in part by marked interethnic differences in intrinsic thrombogenicity, the pharmacokinetic and pharmacodynamic profiles of the $P2Y_{12}$ inhibitors, and differing propensity for bleeding complications between Western and East Asian patients.[22,23] In addition unlike Caucasians, East Asian patients are more prone to bleeding events than ischemic events, especially with potent $P2Y_{12}$ inhibitors.[11,24] Therefore, in terms of net benefit of bleeding and thrombotic events, ticagrelor showed a higher bleeding tendency without any additional preventive effect on ischemic events compared with clopidogrel, especially in East Asian populations, irrespective of DM.

STUDY LIMITATIONS. First, although our analysis of outcomes according to diabetes status was prespecified in the setting of the TICA KOREA trial, its findings may be vulnerable to the known limitations of subgroup analyses in general, and its results should be considered as exploratory or hypothesis-generating only. Second, owing to the relatively small number of patients, this study did not have sufficient statistical power to detect clinically significant differences in safety and efficacy outcomes in each subgroup. Also, analyses of outcome measures were not adjusted for multiple comparisons. Third, although baseline characteristics were relatively well-balanced between diabetic and nondiabetic patients, randomization was not performed according to diabetic status, and consequently unidentified confounders cannot entirely be ruled out. Lastly, data on glycemic control (ie, glycated hemoglobin levels) and concomitant antidiabetes medications were not available. Therefore, we could not assess the impact of the quality of glycemic control and antiglycemic drug effect on the safety and efficacy of the antiplatelet agents.

CONCLUSIONS

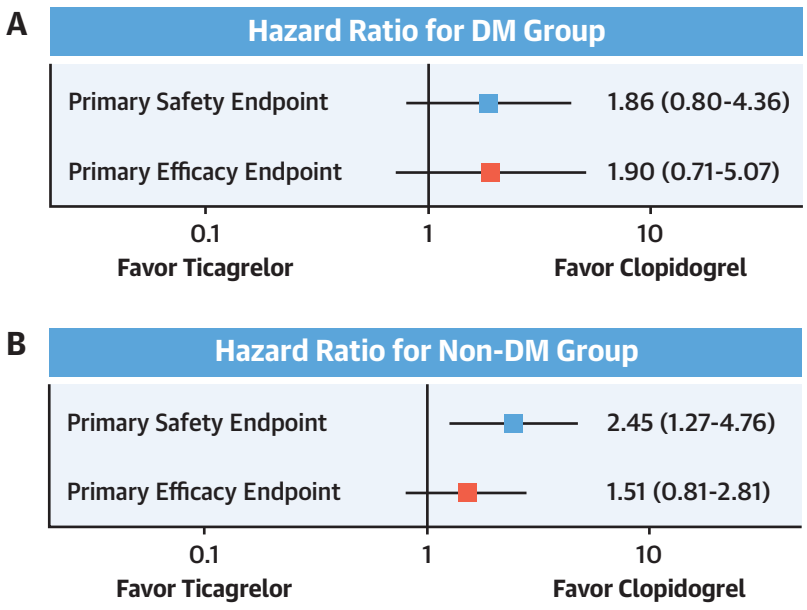
In this prespecified analysis of the TICA KOREA trial, the presence or absence of DM did not affect the relative safety and efficacy of ticagrelor and clopidogrel in East Asian (Korean) patients with ACS who

FIGURE 2 **Cumulative Incidence of the Primary Efficacy Endpoint at 12 Months**



Kaplan-Meier curves showing rates of the primary efficacy endpoint of major adverse cardiovascular events in patients with diabetes mellitus (DM) **(A)** and in those without DM **(B)**. Major adverse cardiovascular events were defined as a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

CENTRAL ILLUSTRATION **HRs for the Primary Endpoint According to Diabetes Status**



$P_{interaction}$ for Primary Safety Endpoint = 0.64
$P_{interaction}$ for Primary Efficacy Endpoint = 0.71
between treatment arms and DM status

Choi Y, et al. JACC: Asia. 2022;2(6):666–674.

HR (95% CI) for the primary safety and efficacy endpoint in the diabetes mellitus (DM) group **(A)**, and in the non-DM group **(B)**.

were intended for early invasive strategy. Compared with clopidogrel, ticagrelor use was associated with a higher incidence of clinically significant bleeding in nondiabetic patients and diabetic patients (although not statistically significant in this group). The rates of ischemic events were not significantly different after ticagrelor and clopidogrel in the diabetic and nondiabetic groups. Finally, DM did not affect the relative safety and efficacy of ticagrelor and clopidogrel in Korean ACS patients.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Owing to an increased platelet reactivity, reduced response to antiplatelet drugs, and a higher risk for thrombotic and ischemic events and mortality in patients with DM presenting with ACS, a more potent antiplatelet strategy is recommended. However, it is unknown whether this strategy is applicable to East Asian patients with a different bleeding and ischemic propensity.

TRANSLATIONAL OUTLOOK: This prespecified analysis of the TICA KOREA trial provides data on the safety and efficacy of ticagrelor vs clopidogrel in Korean patients with and without DM. The study showed that ticagrelor use was associated with a higher incidence of clinically significant bleeding and tended to be associated with a higher risk of ischemic MACE irrespective of diabetes status. Further specifically designed, sufficiently powered RCTs are needed to establish the most optimal antithrombotic therapy in diabetic East Asian patients undergoing invasive therapy for ACS.

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