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ORIGINAL ARTICLE

Ticagrelor Monotherapy Versus Ticagrelor With Aspirin in Acute Coronary Syndrome Patients With a High Risk of Ischemic Events

Seung-Jun Lee, MD*; Yong-Joon Lee, MD*; Byeong-Keuk Kim, MD; Sung-Jin Hong, MD; Chul-Min Ahn, MD; Jung-Sun Kim, MD; Young-Guk Ko, MD; Donghoon Choi, MD; Myeong-Ki Hong, MD; Yangsoo Jang, MD

BACKGROUND: In patients with acute coronary syndrome (ACS) with a high risk of ischemia, the impact of ticagrelor monotherapy after short-term dual antiplatelet therapy (DAPT) has not been clearly elucidated.

METHODS: This post hoc analysis of the TICO trial (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) compared the impact of ticagrelor monotherapy after 3-month DAPT versus ticagrelor-based 12-month DAPT in patients with high-ischemic risk ACS, defined as any of the following: number of stents implanted ≥3, total stent length >60 mm, complex procedures (chronic total occlusion, left main occlusion, or bifurcation plaques remedied using the 2-stent technique), or a history of diabetes or chronic kidney disease. Ischemic (composite of death, myocardial infarction, stent thrombosis, stroke, and target vessel revascularization) and bleeding outcomes (major bleeding) were evaluated at 12 months.

RESULTS: Of the total population (N=3056), 1473 (48.2%) patients were identified as having high-ischemic risk ACS. The rate of the ischemic outcome was significantly higher in high-ischemic risk ACS patients than in nonhigh-ischemic risk ACS patients (3.9% versus 1.9%, hazard ratio, 2.14 [95% CI, 1.37–3.35], P=0.001). Furthermore, the risk of major bleeding (3.2% versus 1.5%, hazard ratio, 2.23 [95% CI, 1.36–3.68], P=0.001) and the composite ischemic and bleeding outcome (6.6% versus 3.3%, hazard ratio, 2.02 [95% CI, 1.44–2.84], P<0.001) were also higher in the high-risk ACS population. In ACS patients with or without high-ischemic risk, the effect of ticagrelor monotherapy after 3-month DAPT, as compared to that of 12-month DAPT, was consistent with ischemic (P_{int}=0.718), bleeding (P_{int}=0.092), and composite outcomes (P_{int}=0.094) without significant interactions.

CONCLUSIONS: There were no significant heterogeneities in the impact of ticagrelor monotherapy after 3-month DAPT compared with that of ticagrelor-based 12-month DAPT on clinical outcomes according to the presence of high-ischemic risk.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02494895.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: acute coronary syndrome ■ ischemia ■ myocardial infarction ■ stroke ■ ticagrelor

As prolonged dual antiplatelet therapy (DAPT) with aspirin and $P2Y_{12}$ receptor inhibitors has been recommended in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI), identifying and managing patients with high-risk features for ischemic events are important.[1–3]

Correspondence to: Byeong-Keuk Kim, MD, PhD, Division of Cardiology, Severance Cardiovascular Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, 03722, Seoul, South Korea. Email kimbk@yuhs.ac

*S.-J. Lee and Y.-J. Lee contributed equally.

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WHAT IS KNOWN

- After the percutaneous coronary intervention, the optimal duration of dual antiplatelet therapy should be tailored to individual patients to achieve balance between the bleeding and ischemic risk.

WHAT THE STUDY ADDS

- Ticagrelor monotherapy after short-duration dual antiplatelet therapy was not associated with increased risk of ischemic or bleeding events in high-ischemic risk acute coronary syndrome patients, harboring angiographically demonstrated, procedural, or clinical risk factors.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
DAPT	dual antiplatelet therapy
HR	hazard ratio
MACCE	major adverse cardiac and cerebrovascular event
PCI	percutaneous coronary intervention
TICO	Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome

Recently, the concept of high-ischemic risks comprising various lesion related or procedural complexities and clinical characteristics has been proposed as an aid to clinical decision-making for patients undergoing PCI.[3–5] Prolonged DAPT may be required to reduce adverse ischemic events in patients with high-ischemic risks; however, the risk of fatal bleeding events may increase as a consequence of prolonged DAPT.[6] Therefore, well thought-out decisions regarding optimal antiplatelet therapy strategies are crucial, especially for ACS patients with high-ischemic risks.

As novel antiplatelet agents, such as ticagrelor and prasugrel, with greater potency, rapid effect, and a more consistent effect have become available, experimental antiplatelet therapy strategies for maintaining the use of potent $P2Y_{12}$ receptor inhibitors after a short duration of DAPT have been suggested to reduce bleeding risk without increasing the ischemic risk.[7–10] However, the efficacy and safety of these strategies for patients with high-ischemic risks are limited and focused only on lesion or procedural characteristics.[11,12] The TICO trial (Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome) demonstrated that ticagrelor monotherapy after 3-month DAPT was associated with a lower incidence of the composite outcome of major bleeding and major adverse cardiac and cerebrovascular events (MACCE) at 1 year than the currently recommended ticagrelor-based 12-month DAPT in ACS patients treated with drug-eluting stents.[13] Thus, the aim of the present post hoc analysis of the TICO trial was to evaluate the impact of ticagrelor monotherapy after 3-month DAPT in patients with ACS who have high-ischemic risks, compared with that of ticagrelor-based 12-month DAPT.

METHODS

The data that support the findings of this study would be provided when approval is obtained through discussion of the corresponding author and multicenter research committee upon appropriate request.

Study Population

The study design and rationale for the TICO trial have been described in detail previously.[13] In total, 3056 patients with ACS enrolled in the TICO trial were classified into 2 groups (high-ischemic risk ACS versus nonhigh-ischemic risk ACS). High-ischemic risk ACS was defined according to the modified version of previously proposed criteria[4,5] and included at least one of the following procedural or clinical risk factors: (1) number of stents implanted ≥3, (2) total stent length >60 mm, (3) complex procedure defined in the current study that includes chronic total occlusion, left main occlusion, or bifurcation plaques as target lesions using the 2-stent technique, or a history of (4) diabetes or (5) chronic kidney disease. The study protocol, coordination, data management, and site management services have been previously provided.[13] The trial protocol was approved by the institutional review board at each participating center, and all participants provided written informed consent. For the comparison of clinical impacts of ticagrelor monotherapy among patients with and without features of complex PCI, complex PCI was defined according to the previous studies[6,12]: (1) number of stents implanted ≥3, (2) number of lesions treated ≥3, (3) 3-vessels treated, (4) bifurcation PCI with 2 stents, (5) total stent length ≥60 mm, or (6) chronic total occlusion.

Study Outcomes and Definitions

The primary ischemic outcome was a MACCE, defined as a composite of all-cause death, myocardial infarction, stent thrombosis, stroke, or target vessel revascularization within 12 months after index PCI. The key secondary outcomes were major bleeding and net adverse clinical events, defined as a composite of major bleeding and MACCE. Major bleeding was defined in accordance with the Thrombolysis in Myocardial Infarction criteria.[14] Detailed definitions of the events are provided in the Data Supplement. The presence of diabetes was determined based on the physician's diagnosis, and data on serum glucose or hemoglobin A1c levels were not routinely collected. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min per 1.73 m^2 of the body surface area including end-stage renal disease with renal replacement therapy.

Statistical Analysis

Primary analyses were performed in an intention-to-treat manner. Categorical variables were reported as the number (percentage) and compared using the χ^2 test or Fisher exact test. Continuous variables were reported as mean±SD and compared using the Student *t* test. Event rates regarding study end points were estimated using the Kaplan-Meier survival analysis and compared using log-rank tests. Hazard ratios (HRs) with 95% CIs were computed using Cox regression analysis. To assess the differential therapy effects by high-ischemic risks, Cox regression analysis with tests for interaction was performed. The Haldane-Anscombe correction was used for calculation of hazard ratios in bleeding outcomes by landmark analysis at 3 months after PCI. All tests were 2-sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed using IBM SPSS, version 23.0 (IBM Corporation, New York) and R 3.5.3 software (R foundations for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

Among 3056 patients included in the TICO trial, 1473 (48.2%) were identified as having high-ischemic risk ACS. The prevalence of the individual components of high-ischemic risk ACS is shown in Figure 1: ≥3 stents were implanted in 13.8% of patients, total stent length was >60 mm in 23.0% of patients, complex procedures defined in the current study were performed in 14.9% of patients, diabetes history was present in 56.7% of patients, and chronic kidney disease history was present in 42.1% of patients. The baseline characteristics of the high-ischemic risk ACS patients and nonhigh-ischemic risk ACS patients are shown in Table 1, which did not differ between the patients who received ticagrelor monotherapy after 3-month DAPT and ticagrelor-based 12-month DAPT within the high-ischemic risk ACS and nonhigh-ischemic risk ACS patient groups.

Clinical Outcomes by High-Ischemic Risks

The clinical outcomes due to high-ischemic risks are shown in Figure I in the Data Supplement. The rate of the ischemic outcome was significantly higher in high-ischemic risk ACS patients than in nonhigh-ischemic risk ACS patients (3.9% versus 1.9%, HR, 2.14 [95% CI, 1.37–3.35], $P=0.001$). Furthermore, major bleeding occurred more frequently in high-ischemic risk ACS patients than in nonhigh-ischemic risk ACS patients (3.2% versus 1.5%, HR, 2.23 [95% CI, 1.36–3.68], $P=0.001$). The rate of the composite outcome including MACCE and major bleeding was significantly higher in high-ischemic risk ACS patients than in nonhigh-ischemic risk ACS patients (6.6% versus 3.3%, HR, 2.02 [95% CI, 1.44–2.84], $P<0.001$).

Clinical Outcomes by High-Ischemic Risks and Antiplatelet Therapy Strategy

The effects of ticagrelor monotherapy after 3-month DAPT compared with ticagrelor-based 12-month DAPT in high- and nonhigh-ischemic risk ACS patients are presented in Figure 2 and Table 2. Ticagrelor monotherapy after 3-month DAPT compared with ticagrelor-based 12-month DAPT showed consistent effects on the ischemic outcome between the high-ischemic risk

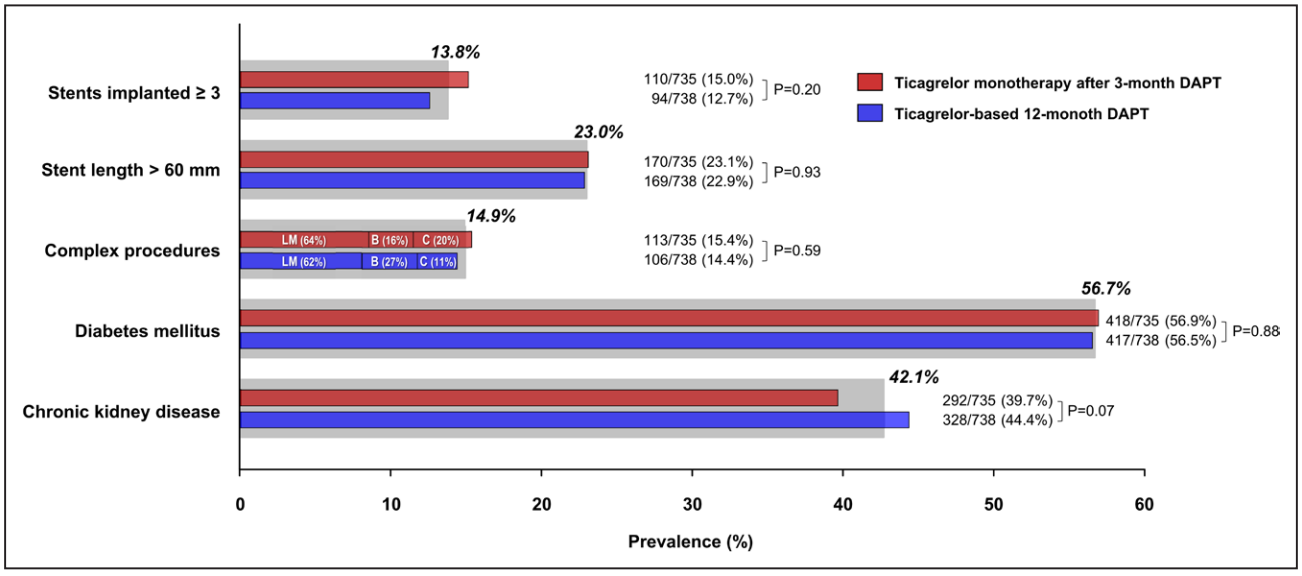


Figure 1. Prevalence of the individual components of high-ischemic risk in patients with acute coronary syndrome (ACS). The prevalence indicates the number of patients divided by the total high-ischemic risk ACS population (N=1473, gray bar, bold-italic letters), those prescribed with ticagrelor monotherapy after 3-mo dual antiplatelet therapy (DAPT; N=735, red bar), and those with ticagrelor-based 12-mo DAPT (N = 738, blue bar), respectively. B indicates bifurcation using 2-stent techniques; C, chronic total occlusion; and LM, left main.

Table 1. Baseline Characteristics

	High-ischemic ACS (n=1473)			Nonhigh-ischemic ACS (n=1583)		
	Ticagrelor monotherapy after 3-mo DAPT (n=735)	Ticagrelor-based 12-mo DAPT (n=738)	*P* value	Ticagrelor monotherapy after 3-mo DAPT (n=792)	Ticagrelor-based 12-mo DAPT (n=791)	*P* value
Age, y	62.9±10.3	63.0±10.6	0.751	58.7±10.8	59.4±10.6	0.205
Male	560 (76.2)	572 (77.5)	0.591	644 (81.3)	652 (82.4)	0.610
Body mass index, kg/m^2	24.9±3.1	25.0±3.3	0.541	24.9±3.2	24.8±3.3	0.557
Hypertension	441 (60.0)	449 (60.8)	0.782	319 (40.3)	332 (42.0)	0.526
Diabetes	418 (56.9)	417 (56.5)	0.929	0	0	-
Chronic kidney disease	292 (39.7)	328 (44.4)	0.075	0	0	-
Dyslipidemia	468 (63.7)	458 (62.1)	0.557	456 (57.6)	464 (58.7)	0.699
Prior MI	33 (4.5)	32 (4.3)	0.987	31 (3.9)	17 (2.1)	0.057
Prior percutaneous coronary intervention	71 (9.7)	80 (10.8)	0.509	64 (8.1)	47 (5.9)	0.117
Prior coronary bypass graft	7 (1.0)	6 (0.8)	0.994	1 (0.1)	4 (0.5)	0.370
Clinical presentation			0.537			0.160
Unstable angina	229 (31.2)	247 (33.5)		213 (26.9)	237 (30.0)	
Non–ST-segment–elevation MI	266 (36.2)	249 (33.7)		273 (34.5)	239 (30.2)	
ST-segment–elevation MI	240 (32.7)	242 (32.8)		306 (38.6)	315 (39.8)	
Transradial approach	392 (53.3)	392 (53.1)	0.975	445 (56.2)	469 (59.3)	0.230
2- or 3-vessel diseases	490 (66.7)	507 (68.7)	0.436	352 (44.4)	354 (44.8)	0.942
Multilesion intervention	227 (30.9)	216 (29.3)	0.536	79 (10.0)	96 (12.1)	0.197
Multivessel intervention	189 (25.7)	184 (24.9)	0.776	64 (8.1)	83 (10.5)	0.117
Total number of stents per patient	1.60±0.83	1.57±0.82	0.493	1.16±0.36	1.18±0.39	0.156
Total stent length per patient, mm	42.1±25.0	41.7±25.6	0.760	27.5±11.3	28.6±11.4	0.052
Mean stent diameter, mm	3.12±0.42	3.13±0.41	0.826	3.18±0.45	3.18±0.41	0.834

Data are presented as mean±SD or n (%). ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; and MI, myocardial infarction.

ACS (HR, 0.73 [95% CI, 0.43–1.23]) and nonhigh-ischemic risk ACS patients (HR, 0.61 [95% CI, 0.29–1.30]) without significant interaction (P_{int}=0.718). The impact of ticagrelor monotherapy on bleeding (P_{int}=0.092) or composite outcome (P_{int}=0.094) was also consistent without group interaction. Among patients with and without features of complex PCI,[6,12] the impact of ticagrelor monotherapy after 3-month DAPT, as compared with ticagrelor-based 12-month DAPT, was also consistent (Figure II in the Data Supplement). Landmark analyses at 3 months after index PCI also demonstrated consistent effects of ticagrelor monotherapy on ischemic, bleeding, and composite outcomes, without significant heterogeneity between the high-ischemic and nonhigh-ischemic ACS patients (Figure III in the Data Supplement).

Clinical Outcomes According to Individual Components of High-Ischemic Risk ACS

When considering the risks of ischemic, bleeding, and composite outcome according to antiplatelet strategies and the individual components of high-ischemic risk ACS, there were no significant heterogeneities in the effects of ticagrelor monotherapy after 3-month DAPT compared with those of ticagrelor-based 12-month DAPT across the individual components of high-ischemic risk ACS (Figure 3). The incidence of ischemic, bleeding, and composite outcomes gradually increased as the number of high-ischemic risk factors increased in overall population (all P<0.05), and the effect of ticagrelor monotherapy after 3-month DAPT was also consistent regardless of the number of ischemic risk factors (Figure 4).

DISCUSSION

The main findings of the present post hoc analysis were as follows: (1) in patients with ACS, the presence of high-ischemic risks was significantly associated with a higher rate of not only the ischemic outcome but also the bleeding and composite outcomes; (2) the effect of ticagrelor monotherapy after 3-month DAPT, compared with that of ticagrelor-based 12-month DAPT, on ischemic events and bleeding was similar among patients who had high-ischemic risks or underwent complex PCI and those who did not; and (3) in high-ischemic risk ACS patients, the effects of ticagrelor monotherapy after 3-month DAPT on clinical outcomes were similar across the individual components of high-ischemic risk ACS, including angiographic, procedural, or clinical complexities.

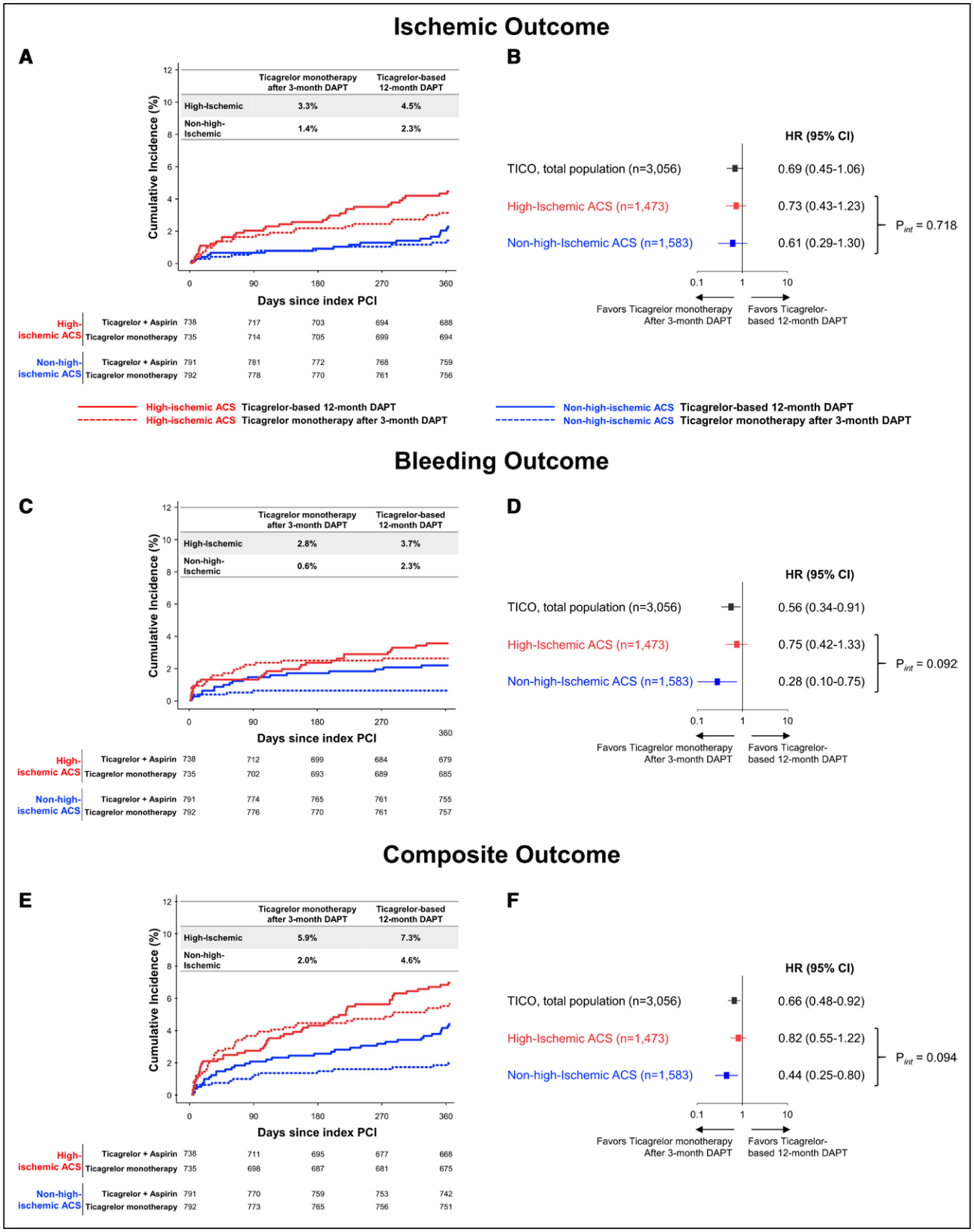


Figure 2. Time-to-event curves and risks of clinical outcomes by high-ischemic risk and antiplatelet therapy strategy. Kaplan-Meier estimates and relative risks for major adverse cardiac and cerebrovascular events (**A** and **B**), major bleeding (**C** and **D**), and net adverse clinical events (**E** and **F**) are presented. There was no significant interaction between the treatment strategy and the presence of high-ischemic risk factors. P_{int} indicates *P* values from Cox regression test of therapy × high-ischemic risk interaction. ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; HR, hazard ratio; PCI, percutaneous coronary intervention; and TICO, Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome.

Table 2. Clinical Outcomes by High-Ischemic Risks and Antiplatelet Therapy Strategy

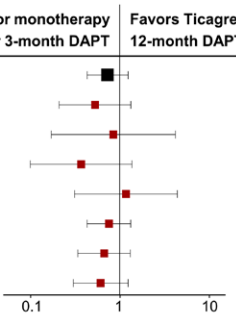
	High-ischemic ACS (n=1473)			Nonhigh-ischemic ACS (n=1583)			*P* value for interaction
	Ticagrelor monotherapy after 3-mo DAPT (n=735)	Ticagrelor-based 12-mo DAPT (n=738)	HR (95% CI)	Ticagrelor monotherapy after 3-mo DAPT (n=792)	Ticagrelor-based 12-mo DAPT (n=791)	HR (95% CI)	
Primary and key secondary outcome							
Major adverse cardiac and cerebrovascular events	24 (3.3)	33 (4.5)	0.73 (0.43–1.23)	11 (1.4)	18 (2.3)	0.61 (0.29–1.30)	0.718
Major bleeding	20 (2.8)	27 (3.7)	0.75 (0.42–1.33)	5 (0.6)	18 (2.3)	0.28 (0.10–0.75)	0.092
Net adverse clinical events	43 (5.9)	53 (7.3)	0.82 (0.55–1.22)	16 (2.0)	36 (4.6)	0.44 (0.25–0.80)	0.094
Individual events							
Death	12 (1.6)	20 (2.7)	…	4 (0.5)	3 (0.4)	…	…
Cardiac	6 (0.8)	12 (1.6)	…	1 (0.1)	0 (0)	…	…
Noncardiac	6 (0.8)	8 (1.1)	…	3 (0.4)	3 (0.4)	…	…
Myocardial infarction	6 (0.8)	7 (1.0)	…	1 (0.1)	0 (0)	…	…
Stent thrombosis	5 (0.7)	4 (0.5)	…	1 (0.1)	0 (0)	…	…
Subacute	3 (0.4)	2 (0.3)	…	1 (0.1)	0 (0)	…	…
Late	2 (0.3)	2 (0.3)	…	0 (0)	0 (0)	…	…
Stroke	4 (0.6)	4 (0.6)	…	4 (0.5)	7 (0.9)	…	…
Target vessel revascularization	5 (0.7)	5 (0.7)	…	3 (0.4)	5 (0.6)	…	…
Major or minor bleeding	38 (5.2)	49 (6.8)	…	15 (1.9)	34 (4.3)	…	…

Data are presented as n (% of the cumulative rates at 12 mo according to Kaplan-Meier event rates). *P* values are from the Cox regression test of therapy × high-ischemic risks interaction. ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; HR, hazard ratio; and MI, myocardial infarction.

Discontinuation of DAPT has been shown to increase the risk of ischemic events after PCI in patients with clinical or procedural risk factors,[6,15] suggesting that the use of a single antiplatelet agent, especially aspirin monotherapy after DAPT, would not be sufficient in patients with a high risk of recurrent ischemic events. Nevertheless, long-duration DAPT has raised many concerns since it definitely increases the risk of bleeding.[16] Thus, maintaining potent $P2Y_{12}$ receptor inhibitor monotherapy after a short duration of DAPT has been proposed to balance the risks of ischemic or bleeding events in patients with ACS,[9,10] but there are still ongoing concerns associated with increased ischemic risks in ACS patients, especially those with additional ischemic burdens due to angiographic and procedural complexities or clinical risk factors.[3,6] Some randomized clinical trials using potent $P2Y_{12}$ inhibitor monotherapy after PCI have looked at the secondary effects of lesion or procedural complexities.[11,12] In the post hoc analysis of the subset of patients who underwent complex PCI from the GLOBAL-LEADERS trial (A Clinical Study Comparing Two Forms of Anti-Platelet Therapy After Stent Implantation), which evaluated the impact of an experimental antiplatelet therapy strategy (23 months of ticagrelor monotherapy following 1-month DAPT) versus a conventional strategy, the experimental strategy was associated with a lower rate of ischemic events (all-cause death, any stroke, any myocardial infarction, or any revascularization), and no differences between groups were observed in Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding events.[11] However, in contrast to the TICO trial, the GLOBAL-LEADERS trial included patients undergoing PCI for ACS (46.9%) and stable coronary artery disease (53.1%).[9] In a post hoc analysis of complex PCI from the TWILIGHT trial (Ticagrelor With or Without Aspirin in High-Risk Patients After PCI) that examined the effect of ticagrelor monotherapy following 3-month DAPT versus a conventional 12-month DAPT strategy, ticagrelor monotherapy following 3-month DAPT was associated with a lower rate of BARC type 2, 3, or 5 bleeding events, and no group difference was observed in ischemic events.[12] Similar to the GLOBAL-LEADERS trial, the patients in the TWILIGHT trial included those who underwent PCI for ACS (64.8%) and stable angina (28.7%) or asymptomatic patients (6.4%); patients with ST-segment–elevation myocardial infarction were excluded.[10] The TICO trial exclusively focused on the effects of ticagrelor monotherapy after 3-month DAPT in patients presenting with all subsets of ACS, including ST-segment–elevation myocardial infarction, who underwent PCI using only thin-strut-based bioresorbable polymer sirolimus-eluting stents.[13] Among patients with ACS enrolled in the TICO trial, the present post hoc analysis investigated whether the impact of ticagrelor monotherapy after short-term DAPT is still comparable in patients with ACS having high-ischemic risks, which were defined according to the latest version of the proposed criteria that includes clinical risk factors as well as lesion or procedural complexities.[5] Considering that

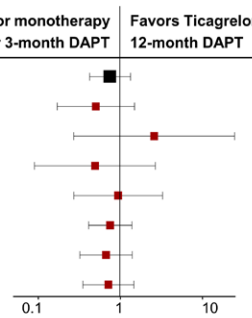
A Ischemic Outcome

	No. / Total (%)		HR (95% CI)	Favors Ticagrelor monotherapy after 3-month DAPT	Favors Ticagrelor-based 12-month DAPT
	Ticagrelor monotherapy after 3-month DAPT	Ticagrelor-based 12-month DAPT			
Overall	24/735 (3.3%)	33/738 (4.5%)	0.73 (0.43-1.23)		
Any procedural risk factor	7/270 (2.6%)	12/247 (4.9%)	0.52 (0.21-1.33)		
Number of stents implanted ≥3	3/110 (2.7%)	3/94 (3.2%)	0.84 (0.17-4.17)		
Total stent length >60 mm	3/170 (1.8%)	8/169 (4.7%)	0.36 (0.10-1.37)		
Complex procedures	5/113 (4.4%)	4/106 (3.8%)	1.17 (0.31-4.37)		
Any clinical risk factor	21/586 (3.6%)	29/608 (4.8%)	0.75 (0.43-1.32)		
Diabetes Mellitus	14/418 (3.3%)	21/417 (5.0%)	0.66 (0.34-1.31)		
Chronic kidney disease	12/292 (4.1%)	22/328 (6.7%)	0.61 (0.30-1.23)		



B Bleeding Outcome

	No. / Total (%)		HR (95% CI)	Favors Ticagrelor monotherapy after 3-month DAPT	Favors Ticagrelor-based 12-month DAPT
	Ticagrelor monotherapy after 3-month DAPT	Ticagrelor-based 12-month DAPT			
Overall	20/735 (2.8%)	27/738 (3.7%)	0.75 (0.42-1.33)		
Any procedural risk factor	5/270 (1.9%)	9/247 (3.6%)	0.50 (0.17-1.49)		
Number of stents implanted ≥3	3/110 (2.7%)	1/94 (1.1%)	2.57 (0.27-24.68)		
Total stent length >60 mm	2/170 (1.2%)	4/169 (2.4%)	0.49 (0.09-2.68)		
Complex procedures	5/113 (4.4%)	5/106 (4.7%)	0.94 (0.27-3.26)		
Any clinical risk factor	18/586 (3.1%)	25/608 (4.1%)	0.75 (0.41-1.38)		
Diabetes Mellitus	12/418 (2.9%)	18/417 (4.3%)	0.67 (0.32-1.39)		
Chronic kidney disease	12/292 (4.1%)	19/328 (5.8%)	0.71 (0.35-1.47)		



C Composite Outcome

	No. / Total (%)		HR (95% CI)	Favors Ticagrelor monotherapy after 3-month DAPT	Favors Ticagrelor-based 12-month DAPT
	Ticagrelor monotherapy after 3-month DAPT	Ticagrelor-based 12-month DAPT			
Overall	43/735 (4.9%)	53/738 (7.3%)	0.82 (0.55-1.22)		
Any procedural risk factor	12/270 (4.4%)	17/247 (6.9%)	0.63 (0.30-1.32)		
Number of stents implanted ≥3	6/110 (5.5%)	4/94 (4.3%)	1.28 (0.36-4.55)		
Total stent length >60 mm	5/170 (2.9%)	10/169 (5.9%)	0.49 (0.17-1.43)		
Complex procedures	10/113 (8.8%)	7/106 (6.6%)	1.35 (0.51-3.55)		
Any clinical risk factor	38/586 (6.5%)	48/608 (7.9%)	0.83 (0.54-1.27)		
Diabetes Mellitus	26/418 (6.2%)	36/417 (8.6%)	0.73 (0.44-1.20)		
Chronic kidney disease	23/292 (7.9%)	35/328 (10.7%)	0.74 (0.44-1.25)		

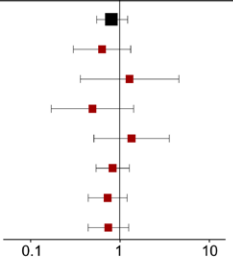


Figure 3. Risks of clinical outcomes according to antiplatelet strategies and the individual components of high-ischemic risk acute coronary syndrome.

Risks of (**A**) major adverse cardiac and cerebrovascular events, (**B**) major bleeding, and (**C**) net adverse clinical events according to antiplatelet strategy and the individual components of high-ischemic risk are presented. Hazard ratios (HRs) are for patients administered ticagrelor monotherapy after 3 mo of dual antiplatelet therapy (DAPT) vs ticagrelor-based 12-mo DAPT.

both procedural[11,12] and clinical risk factors[15,17] significantly contribute to the occurrence of ischemic events, the high-ischemic risk ACS population defined in this post hoc analysis could be considered to have the highest risk among patients who underwent PCI. Given the concern that ticagrelor monotherapy after short-term DAPT might not be sufficient for the prevention of recurrent ischemic events in patients with ACS having high-ischemic risks, we conducted post hoc analyses comparing the impact of this strategy with that of ticagrelor-based 12-month DAPT and demonstrated consistent effects on the occurrence of ischemic events in patients with high-ischemic risk ACS.

High-risk ACS patients, who constituted about 48% of the TICO trial population, were characterized by a higher risk of ischemic events; moreover, the incidence of bleeding and the composite outcome was also significantly higher. Considering that most bleeding risk prediction scores are positively correlated with the overall risk,[18] it is difficult to judge whether ischemic risks and bleeding risks exist independently in real-world clinical practice.[19] Therefore, antiplatelet treatment strategies for

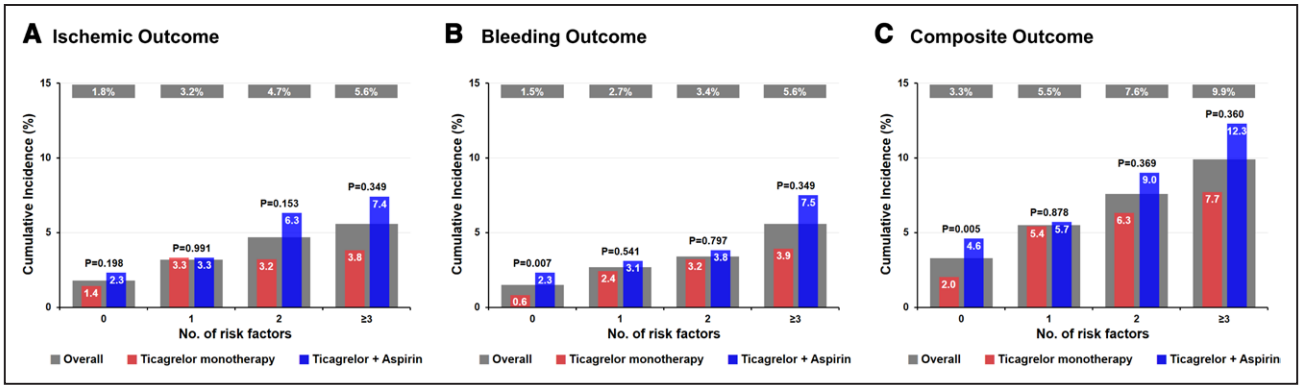


Figure 4. Incidence of clinical outcomes by the number of high-ischemic acute coronary syndrome (ACS) risk factors and antiplatelet strategy.

Cumulative incidence of major adverse cardiac and cerebrovascular events (**A**), major bleeding (**B**), and net adverse clinical events (**C**). **P* value for the comparison of the cumulative incidences of the events by the number of high-ischemic ACS risk factors.

bleeding reduction are important clinically, as well as for the prevention of recurrent ischemic events. In the present post hoc analyses, we demonstrated that the therapeutic impact of ticagrelor monotherapy after 3-month DAPT, compared with that of 12-month DAPT, was also consistent with the bleeding and composite outcomes. Taken together, even in high-risk ACS patients, ticagrelor monotherapy after short-term DAPT could be considered as a reasonable therapeutic approach that could strike a balance between the ischemic and bleeding risks.

The efficacy of treatment of ticagrelor monotherapy on each outcome was consistent among patients with each component of high-ischemic risk and those with multiple risk factors. Similar to the findings of the current analysis, post hoc analyses of the GLOBAL-LEADERS trial demonstrated an augmented risk of ischemic events in a subset of patients with diabetes and chronic kidney disease.[20,21] However, the therapeutic effect of the potent $P2Y_{12}$ inhibitor after short-term DAPT was consistent in these patients. Among high-ischemic risk ACS patients in the TICO trial, the incidence of ischemic, bleeding, and composite outcomes gradually increased as the number of high-ischemic risk factors increased. However, the therapeutic effect of ticagrelor monotherapy after 3-month DAPT on the occurrence of MACCE was consistent across each component of high-ischemic risk ACS and with an increasing number of risk factors, consistent with the findings of the TWILIGHT trial.[12] In addition, the current analysis revealed that these results were consistent with the findings of major bleeding and composite outcomes including MACCE and bleeding. Thus, ticagrelor monotherapy after short-term DAPT might be considered in patients with ACS across various ischemic risks, including angiographically demonstrated, procedural, and clinical risk factors.

Limitations

This study has several limitations. First, the present study was not prespecified in the TICO trial protocol. Therefore, our findings need to be interpreted only in the context of hypothesis generation. Second, the definition of high-ischemic risk ACS is arbitrary and differs among studies including the present study. In this regard, considering the specified definition for high-ischemic risk ACS used in this post hoc analysis, care should be taken to interpret our results and adopt the results of these analyses for the management of patients with ACS. Third, the lower-than-expected event rate of the primary outcome noted in the TICO trial may have limited the power of the present post hoc analysis, particularly for the ischemic outcomes or stent thrombosis. Finally, the diagnosis of diabetes was based on physicians' reports and not on the findings of routine tests for fasting plasma glucose, routine tests for glycated hemoglobin, or the oral glucose tolerance test. In conclusion, among patients with ACS, there were no significant heterogeneities in the impact of ticagrelor monotherapy after 3-month DAPT compared with that of ticagrelor-based 12-month DAPT on ischemic or bleeding outcomes according to whether high-ischemic risks existed or not.

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Affiliation

Severance Cardiovascular Hospital, Yonsei University College of Medicine, Seoul, South Korea.

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Disclosures

None.

Supplemental Materials

Expanded Methods
Online Figures I–III
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