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Effect of Ticagrelor Monotherapy vs Ticagrelor With Aspirin on Major Bleeding and Cardiovascular Events in Patients With Acute Coronary Syndrome

The TICO Randomized Clinical Trial

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IMPORTANCE Discontinuing aspirin after short-term dual antiplatelet therapy (DAPT) was evaluated as a bleeding reduction strategy. However, the strategy of ticagrelor monotherapy has not been exclusively evaluated in patients with acute coronary syndromes (ACS).

OBJECTIVE To determine whether switching to ticagrelor monotherapy after 3 months of DAPT reduces net adverse clinical events compared with ticagrelor-based 12-month DAPT in patients with ACS treated with drug-eluting stents.

DESIGN, SETTING, AND PARTICIPANTS A randomized multicenter trial was conducted in 3056 patients with ACS treated with drug-eluting stents between August 2015 and October 2018 at 38 centers in South Korea. Follow-up was completed in October 2019.

INTERVENTIONS Patients were randomized to receive ticagrelor monotherapy (90 mg twice daily) after 3-month DAPT (n = 1527) or ticagrelor-based 12-month DAPT (n = 1529).

MAIN OUTCOMES AND MEASURES The primary outcome was a 1-year net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, myocardial infarction, stent thrombosis, stroke, or target-vessel revascularization). Prespecified secondary outcomes included major bleeding and major adverse cardiac and cerebrovascular events.

RESULTS Among 3056 patients who were randomized (mean age, 61 years; 628 women [20%]; 36% ST-elevation myocardial infarction), 2978 patients (97.4%) completed the trial. The primary outcome occurred in 59 patients (3.9%) receiving ticagrelor monotherapy after 3-month DAPT and in 89 patients (5.9%) receiving ticagrelor-based 12-month DAPT (absolute difference, −1.98% [95% CI, −3.50% to −0.45%]; hazard ratio [HR], 0.66 [95% CI, 0.48 to 0.92]; *P* = .01). Of 10 prespecified secondary outcomes, 8 showed no significant difference. Major bleeding occurred in 1.7% of patients with ticagrelor monotherapy after 3-month DAPT and in 3.0% of patients with ticagrelor-based 12-month DAPT (HR, 0.56 [95% CI, 0.34 to 0.91]; *P* = .02). The incidence of major adverse cardiac and cerebrovascular events was not significantly different between the ticagrelor monotherapy after 3-month DAPT group (2.3%) vs the ticagrelor-based 12-month DAPT group (3.4%) (HR, 0.69 [95% CI, 0.45 to 1.06]; *P* = .09).

CONCLUSIONS AND RELEVANCE Among patients with acute coronary syndromes treated with drug-eluting stents, ticagrelor monotherapy after 3 months of dual antiplatelet therapy, compared with ticagrelor-based 12-month dual antiplatelet therapy, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year. The study population and lower than expected event rates should be considered in interpreting the trial.

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Visual Abstract

Supplemental content

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Patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) with drug-eluting stents are currently recommended dual antiplatelet therapy (DAPT), consisting of aspirin with a P2Y12 inhibitor for 12 months using a potent antiplatelet agent such as ticagrelor or prasugrel.[1-4] However, this strategy increases bleeding risk even in patients with a high thrombotic risk of ACS.[5-7] Although aspirin has proven benefits and has become the cornerstone for the antiplatelet therapy in secondary prevention of cardiovascular disease, discontinuing aspirin while maintaining administration of a P2Y12 inhibitor after DAPT was introduced to reduce the risk of bleeding.[8] Recent randomized trials also evaluated the aspirin-free strategies with ticagrelor monotherapy.[9,10] However, an investigation of ticagrelor monotherapy after short-term DAPT focusing on the patients with ACS including ST-elevation myocardial infarction who underwent PCI with newer-generation drug-eluting stents has not been performed.

Therefore, the trial of Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome (TICO) was performed to evaluate whether switching to ticagrelor monotherapy after 3 months of DAPT would reduce net adverse clinical events compared with ticagrelor-based 12-month DAPT among patients with ACS treated with drug-eluting stents.

Key Points

Question Does switching to ticagrelor monotherapy after 3 months of dual antiplatelet therapy reduce net adverse clinical events (a composite of major bleeding and major adverse cardiac and cerebrovascular events) among patients with acute coronary syndrome treated with drug-eluting stents?

Findings In this randomized clinical trial that included 3056 patients with acute coronary syndrome, ticagrelor monotherapy after 3 months of dual antiplatelet therapy, compared with ticagrelor-based 12-month dual antiplatelet therapy, significantly reduced net adverse clinical events at 1 year (3.9% vs 5.9%).

Meaning Among patients with acute coronary syndrome treated with new-generation drug-eluting stents, use of ticagrelor monotherapy after 3 months of dual antiplatelet therapy resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and adverse cardiac and cerebrovascular events at 1 year.

Methods

Study Design

The trial protocol (Supplement 1) was approved by the institutional review board at each center, and all participants provided written informed consent. The rationale and design have been previously published.[11] This study was an investigator-initiated, multicenter, randomized, unblinded trial conducted at 38 centers in South Korea. Study coordination, data management, and site management services were performed at the Cardiovascular Research Center, Seoul, South Korea. The designated trial monitors reviewed the investigational data at appropriate intervals for accuracy and completeness and ensured protocol compliance.[11] This trial was performed in accordance with the principles of the Declaration of Helsinki.

Study Population

Patients who underwent successful PCI with ultrathin bioresorbable polymer sirolimus-eluting stents (Orsiro; Biotronik AG) for ACS (ST-elevation myocardial infarction, non-ST-elevation myocardial infarction, or unstable angina) were eligible for enrollment. Key exclusion criteria included increased risk of bleeding due to prior hemorrhagic stroke, traumatic brain injury or brain surgery within the past 6 months, internal bleeding within the past 6 weeks, need of oral anticoagulation therapy, and anemia (hemoglobin ≤8 g/dL). The full inclusion and exclusion criteria are listed in eTable 1 in Supplement 2.

Randomization and Study Procedures

After PCI, patients were randomly assigned in a 1:1 ratio to receive ticagrelor monotherapy after 3-month DAPT or ticagrelor-based 12-month DAPT. A web-response permuted-block randomization (mixed blocks of 4 or 6), which was conducted at each participating site, stratified the random assignment according to the presence of diabetes and ST-elevation myocardial infarction. The allocation sequence was computer generated by an external programmer who was not involved in the trial.

If patients were not taking aspirin or ticagrelor at the time of PCI, loading doses of aspirin (300 mg) and ticagrelor (180 mg) were administered. A single aspirin dose (100 mg per day) and 2 ticagrelor doses (90 mg per day) were maintained. After 3 months of DAPT, aspirin was discontinued in the patients who were assigned to receive ticagrelor monotherapy after 3 months of DAPT, and aspirin use was continued in patients who were randomized to receive ticagrelor-based DAPT for 12 months. The concomitant use of other antiplatelet agents or anticoagulants was not allowed. Other medical treatments were left to physician discretion, but guideline-directed medical therapy was strongly recommended.

Outcomes

The primary outcome was a net adverse clinical event, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events, within 12 months following PCI. Major bleeding was defined according to the Thrombolysis in Myocardial Infarction (TIMI) criteria: intracranial bleeding, hemorrhage with a hemoglobin decrease of at least 5 g/dL, or fatal bleeding that caused death within 7 days.[12] Major adverse cardiac and cerebrovascular events were defined as death, myocardial infarction, stent thrombosis, stroke, and target-vessel revascularization.

Secondary outcomes were major bleeding and major adverse cardiac and cerebrovascular events.[11] Other secondary outcomes were defined as major or minor bleeding,

death, myocardial infarction, stent thrombosis, stroke, and target-vessel revascularization. The composite of cardiac death or myocardial infarction, and the composite of cardiac death, myocardial infarction, stent thrombosis, or target-vessel revascularization were also assessed as prespecified secondary outcomes.

Cardiac death was defined as death due to myocardial infarction, cardiac perforation or pericardial tamponade; arrhythmia or conduction abnormality; stroke within 30 days of the procedure or related to the procedure; death due to a procedural complication; or any case of death in which a cardiac cause was not excluded by a clinical event committee.[11] Myocardial infarction after hospital discharge was defined as symptoms, electrocardiographic changes, or abnormal imaging findings, combined with a creatine kinase MB fraction above the upper normal limits or a troponin T or troponin I level greater than the 99th percentile of the upper normal limit.[13] Stent thrombosis was defined as definite or probable stent thrombosis according to the Academic Research Consortium definition.[14] Stroke was defined as an acute cerebrovascular event that caused death, a neurological deficit lasting more than 24 hours, or an acute infarction shown by imaging studies.[15] Stroke was further classified as an ischemic or hemorrhagic event. Target-vessel revascularization was defined as a repeat PCI or bypass surgery of the target vessel with either: (1) symptoms of ischemia or a positive stress test and angiographic diameter stenosis of greater than 50%; or (2) angiographic diameter stenosis of greater than 70% without symptoms of ischemia or a positive stress test.[11,16] In a post hoc analysis, the Bleeding Academic Research Consortium's definition of bleeding events was also used (eTable 2 in Supplement 2).[12]

Suspected adverse events, including bleeding and ischemic events, were reported on the electronic case report form with source documents. Monitoring by the study coordination center and local institutional review board was conducted to search for potential adverse events that were not reported. Adverse events were centrally collected, and any document that could lead to unblinding of treatment assignment was obliterated before submission to the clinical event committee. Outcomes were categorized according to predefined criteria by an independent clinical event committee blinded to the treatment assignments and primary results of the trial.[11]

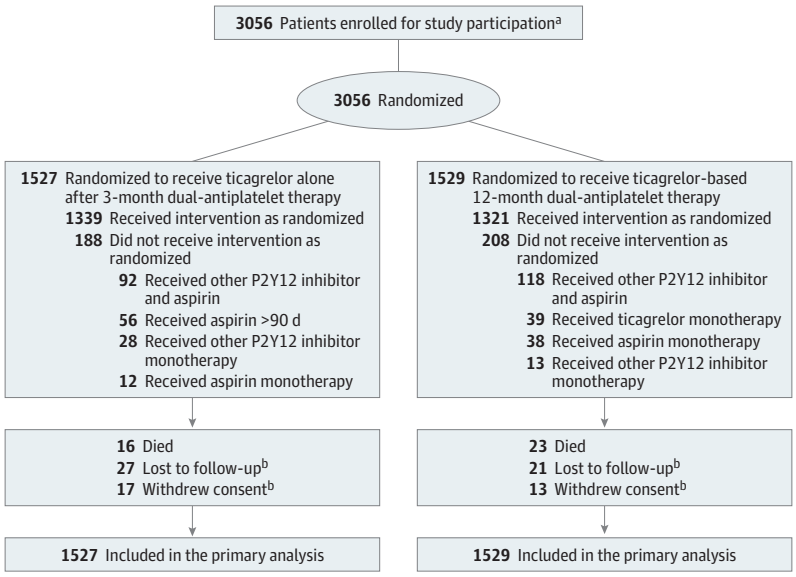
Statistical Analysis

Sample size and power calculations were based on a superiority assumption for the primary outcome. Assuming an 18% incidence of net adverse clinical events at 1 year in the patients with ticagrelor-based 12-month DAPT,[4,11] a sample size of 3056 was chosen. This sample size provided 90% power to detect a 25% difference (4.5% absolute difference) with a type I error rate of .05 and 10% follow-up loss.[11,17] A minimal clinically important difference of 25% was chosen based on previous meta-analyses showing the benefit regarding the major bleeding in the short-term DAPT vs 1-year DAPT (hazard ratio [HR], 0.58 [95% CI, 0.47 to 0.72]),[18] but it was chosen as a more conservative difference because ticagrelor monotherapy rather than aspirin monotherapy was given in the experimental group in this study. In November 2017, when 1967 patients (64%) were enrolled and 795 patients (26%) had completed the 1-year follow-up, a discussion among the members of the data and safety monitoring board found that the event rate of the primary outcome was reported to be 6.5% for all patients, which was lower than expected. Recalculation of the sample size, with an expected primary outcome of 9% with a detection of 25% difference, revealed that 6688 patients were needed to provide the original study power. However, considering the rate of enrollment, the steering committee reached a consensus to not change the sample size. In September 2019, after the meeting of the data and safety monitoring board, a consensus was reached to not expand the study duration, despite the event rates being lower than expected, in order to report the results in a timely manner.

The primary analysis was performed to determine whether the patients receiving ticagrelor monotherapy after 3 months of DAPT would be superior to those receiving ticagrelor-based 12 months of DAPT, with respect to the primary outcome. All patients enrolled were analyzed according to their randomization group, and those with missing outcome data were censored at the time of loss to follow-up or withdrawal of consent. Kaplan-Meier estimates were used to determine the cumulative incidences of the primary and secondary outcomes. HRs and 95% CIs were generated using Cox proportional hazards models. To assess the validity of the proportional hazards assumption, the assumption was assessed by log-minus-log-survival function and found to hold. To confirm the assumption of proportionality, time-dependent covariate analysis was used. The time-dependent covariate was not statistically significant, suggesting the proportional hazard assumption was reasonable. Although patients could experience more than 1 component of the composite primary outcome, each patient was assessed until the occurrence of their first event and only once during the analysis.

Because the same treatment was given in both groups during the first 3 months, prespecified 3-month landmark analyses were performed after excluding the patients who experienced adverse events within this period. Post hoc analyses were performed for the patients in the per-protocol population who adhered to the allocated therapy after excluding patients who did not receive the allocated therapy and for the as-treated population considering the actual treatments received. A mixed-effects model was constructed with site as a random effect for the primary outcome in a post hoc analysis. Subgroup analyses, according to the prespecified subgroups (age, sex, diabetes, hypertension, chronic kidney disease, clinical presentation, presence of multivessel disease, total stent length), were performed. The heterogeneity of effects in subgroups was assessed using interaction terms in a Cox proportional hazard model. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory. The findings of subgroup analyses should also be interpreted as exploratory because of lack of adjustment for multiple testing of subgroups.

Figure 1. Participant Flow in the TICO Randomized Clinical Trial



[a] Study sites were not required to provide screening logs. Data regarding reasons for ineligibility are not available.

[b] Outcomes of patients who were lost to follow-up or withdrew consent were included to the point of final contact. Their time-to-event measure was censored at the last contact date.

Categorical variables are reported as numbers and percentages, and compared using a χ^2 test or Fisher exact test. Continuous variables are reported as mean (SD) or median interquartile range (IQR) values (as appropriate) and compared using a *t* test or Mann-Whitney test. SAS version 9.2 (SAS Institute Inc) was used for all analyses. All tests were 2-sided, and a *P* value of less than .05 was considered statistically significant.

Results

Between August 2015 and October 2018, 3056 patients were enrolled; 1527 patients were randomized to receive ticagrelor monotherapy after 3-month DAPT, and 1529 patients were randomized to receive ticagrelor-based 12-month DAPT (**Figure 1**). Randomization was primarily done within 1 day after PCI (95% on day 0 and 3.7% on day 1 after PCI) (eTable 3 in Supplement 2). In the patients who received ticagrelor monotherapy after 3 months of DAPT, 1339 patients (88%) adhered to the treatment regimen compared with 1321 (86%) patients in the group receiving ticagrelor-based 12-month DAPT, with no significant difference between groups (Figure 1). Details regarding the antiplatelet therapy and reasons for nonadherence are provided in eTable 4 and eTable 5 in Supplement 2. Despite the disallowing of the concomitant use of other antiplatelet agents, clopidogrel or prasugrel was used in the 8.2% of the patients receiving ticagrelor monotherapy after 3-month DAPT and in 8.9% of patients receiving ticagrelor-based 12-month DAPT (*P* = .49). At the time of the database lock (November 2019), 39 patients died, and clinical follow-up was completed for all except 78 patients (2939/3017; 97.4%) of whom 48 (1.6%) were lost to follow-up and 30 (1.0%) withdrew consent.

Baseline characteristics are provided in **Table 1**; the mean age was 61 years, 80% of the patients were men, and 27% had diabetes. Most patients (2107 patients [69%]) were admitted via the emergency department. The distribution of ACS among patients was 926 (30%) for unstable angina, 1027 (34%) for non-ST-elevation myocardial infarction, and 1103 (36%) for ST-elevation myocardial infarction. Primary PCI was performed in 1052 patients (34%). Detailed angiographic and procedural characteristics for treated lesions and the uses of medications during the study period are presented in eTable 6 and eTable 7 in Supplement 2; there were no significant differences between the study groups.

The primary outcome of a net adverse clinical event occurred in 59 patients (3.9%) receiving ticagrelor monotherapy after 3-month DAPT and in 89 patients (5.9%) receiving ticagrelor-based 12-month DAPT (absolute difference, −1.98% [95% CI, −3.50% to −0.45%]; HR, 0.66 [95% CI, 0.48 to 0.92]; *P* = .01) (**Figure 2**A and **Table 2**). On prespecified 3-month landmark analyses between 3 and 12 months, a net adverse clinical event occurred in 21 patients (1.4%) receiving ticagrelor monotherapy after 3-month DAPT and in 51 patients (3.5%) receiving ticagrelor-based 12-month DAPT (HR, 0.41 [95% CI, 0.25 to 0.68]; *P* = .001) (Figure 2B; eTable 8 in Supplement 2).

The secondary outcome of major bleeding occurred in 25 patients (1.7%) receiving ticagrelor monotherapy after 3-month DAPT and in 45 patients (3.0%) receiving ticagrelor-based 12-month DAPT (HR, 0.56 [95% CI, 0.34 to 0.91]; *P* = .02) (Table 2). Between months 3 and 12, major bleeding occurred in 3 patients (0.2%) receiving ticagrelor monotherapy after 3-month DAPT and in 23 patients (1.6%) receiving ticagrelor-based 12-month DAPT (HR, 0.13 [95% CI, 0.04 to 0.44]; *P* = .001) (eTable 8 in Supplement 2). Incidences of bleeding events, according to the Bleeding Academic

Table 1. Patient, Lesion, and Procedural Characteristics

Characteristics	No. (%)[a]	
	Ticagrelor monotherapy after 3-mo DAPT (N = 1527)	Ticagrelor-based 12-mo DAPT (N = 1529)
Age, mean (SD), y	61 (11)	61 (11)
Men	1204 (79)	1224 (80)
Women	323 (21)	305 (20)
Body mass index, mean (SD)[b]	24.9 (3.2)	24.9 (3.3)
Comorbid conditions		
Dyslipidemia	924 (61)	922 (60)
Hypertension	760 (50)	781 (51)
Current smoker	555 (36)	587 (38)
Diabetes	418 (27)	417 (27)
Chronic kidney disease[c]	292 (19)	328 (22)
Prior percutaneous coronary intervention	135 (9)	127 (8)
Prior stroke	60 (4)	66 (4)
Prior myocardial infarction	64 (4)	49 (3)
Prior coronary bypass graft	8 (1)	10 (1)
Admission via emergency department	1068 (70)	1039 (68)
Clinical presentation		
Unstable angina	442 (29)	484 (32)
Non–ST-elevation myocardial infarction	539 (35)	488 (32)
ST-elevation myocardial infarction	546 (36)	557 (36)
Antithrombotic drug before intervention[d]		
Unfractionated heparin	947 (62)	951 (62)
Low-molecular-weight heparin	125 (8)	142 (9)
Glycoprotein IIb/IIIa inhibitors	100 (7)	97 (6)
Antiplatelet drug before intervention[d]		
Aspirin	1470 (96)	1451 (95)
Clopidogrel	545 (36)	499 (33)
Ticagrelor	1108 (73)	1063 (70)
Prasugrel	3 (<1)	4 (<1)
Primary percutaneous coronary intervention[e]	523 (34)	529 (35)
Transradial approach	837 (55)	861 (56)
Multivessel coronary artery disease	842 (55)	861 (56)
Multilesion intervention	306 (20)	312 (20)
Multivessel intervention	253 (17)	267 (18)
Treated lesions per patient, mean (SD)	1.23 (0.50)	1.24 (0.51)
Total No. of stents per patient, mean (SD)	1.37 (0.67)	1.37 (0.66)
Total stent length per patient, mean (SD), mm	35 (20)	35 (21)

Abbreviation: DAPT, dual antiplatelet therapy.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] Calculated as weight in kilograms divided by height in meters squared.

[c] Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 of body surface area.

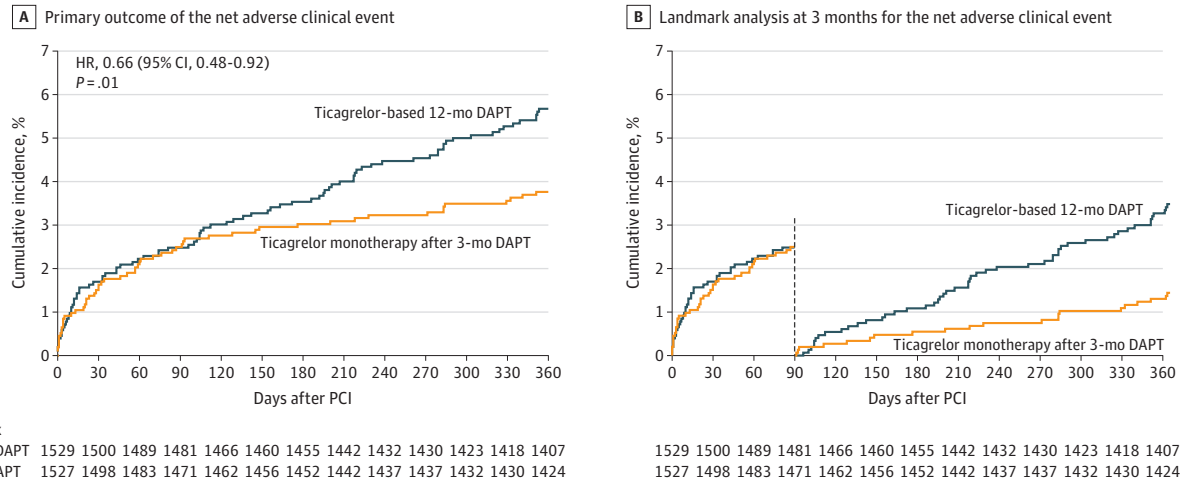
[d] Drugs before intervention were what were given in the hospital immediately before the procedure.

[e] Primary percutaneous coronary intervention was defined as an emergent percutaneous coronary intervention without previous fibrinolytic treatment.

Research Consortium definition, are provided in eTable 9 in Supplement 2. Another secondary outcome of major adverse cardiac and cerebrovascular events occurred in 35 (2.3%) patients receiving ticagrelor monotherapy after 3-month DAPT and in 51 (3.4%) patients receiving ticagrelor-based 12-month DAPT, with no significant difference between the groups (HR, 0.69 [95% CI, 0.45 to 1.06]; *P* = .09) (Table 2). Between months 3 and 12, the incidence of major adverse cardiac and cerebrovascular events did not significantly differ between the groups (HR, 0.58 [95% CI, 0.33 to 1.04]; *P* = .07) (eTable 8 in Supplement 2).

There was no significant difference in the occurrence of death between the 2 groups (16 [1.1%] in the group receiving ticagrelor monotherapy after 3-month DAPT vs 23 [1.5%] in the group receiving ticagrelor-based 12-month DAPT; HR, 0.70 [95% CI, 0.37 to 1.32]; *P* = .27). There was no significant difference in the occurrence of stent thrombosis, which occurred in 6 (0.4%) patients receiving ticagrelor monotherapy after 3-month DAPT and in 4 (0.3%) patients receiving ticagrelor-based 12-month DAPT (HR, 1.51 [95% CI, 0.43 to 5.33]; *P* = .53). Comparisons between the group receiving ticagrelor monotherapy after 3-month DAPT vs the group

Figure 2. Time-to-Event Curves for the Primary Outcome and Landmark Analysis at 3 Months



No. at risk

12-mo DAPT	1529	1500	1489	1481	1466	1460	1455	1442	1432	1430	1423	1418	1407
3-mo DAPT	1527	1498	1483	1471	1462	1456	1452	1442	1437	1437	1432	1430	1424

1529 1500 1489 1481 1466 1460 1455 1442 1432 1430 1423 1418 1407
1527 1498 1483 1471 1462 1456 1452 1442 1437 1437 1432 1430 1424

A net adverse clinical event was defined as a composite of major bleeding by the Thrombolysis in Myocardial Infarction criteria or major adverse cardiac and cerebrovascular event. Between 3 and 12 months, the hazard ratio (HR) was 0.41 (95% CI, 0.25-0.68; *P* = .001). Reported HRs are for the patients with ticagrelor monotherapy after 3-month dual antiplatelet therapy (DAPT). The median observation periods were 365 days (interquartile range, 365-365) for both study groups.

Table 2. Clinical Outcomes at 1 Year

Outcomes	No. of patients with event (% cumulative incidence)[a]		Absolute difference, % (95% CI)	Hazard ratio (95% CI)	*P* value[b]
	Ticagrelor monotherapy after 3-mo DAPT (n = 1527)	Ticagrelor-based 12-mo DAPT (n = 1529)			
Primary outcome					
Net adverse clinical event[c]	59 (3.9)	89 (5.9)	−1.98 (−3.50 to −0.45)	0.66 (0.48 to 0.92)	.01
Secondary outcomes					
TIMI					
Major bleeding	25 (1.7)	45 (3.0)	−1.33 (−2.40 to −0.27)	0.56 (0.34 to 0.91)	.02
Major or minor bleeding	53 (3.6)	83 (5.5)	−2.06 (−3.52 to −0.60)	0.64 (0.45 to 0.90)	.01
Major adverse cardiac and cerebrovascular event[d]	35 (2.3)	51 (3.4)	−1.05 (−2.23 to 0.13)	0.69 (0.45 to 1.06)	.09
Cardiac death or acute MI	13 (0.9)	22 (1.5)	−0.59 (−1.35 to 0.16)	0.59 (0.30 to 1.18)	.14
Cardiac death, acute MI, stent thrombosis, or target-vessel revascularization	18 (1.2)	30 (2.0)	−0.79 (−1.68 to 0.10)	0.60 (0.34 to 1.08)	.09
Death	16 (1.1)	23 (1.5)	−0.46 (−1.26 to 0.35)	0.70 (0.37 to 1.32)	.27
Cardiac	7	12			
Noncardiac	9	11			
Acute MI	6 (0.4)	11 (0.7)	−0.34 (−0.87 to 0.19)	0.55 (0.20 to 1.48)	.24
Stent thrombosis	6 (0.4)	4 (0.3)	0.13 (−0.27 to 0.54)	1.51 (0.43 to 5.33)	.53
Subacute	4	2			
Late	2	2			
Stroke	8 (0.5)	11 (0.7)	−0.20 (−0.76 to 0.37)	0.73 (0.29 to 1.81)	.50
Ischemic	5	9			
Hemorrhagic	3	2			
Target-vessel revascularization	8 (0.5)	10 (0.7)	−0.13 (−0.69 to 0.42)	0.80 (0.32 to 2.03)	.64

Abbreviations: DAPT, dual antiplatelet therapy; MI, myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

[a] Percentages are Kaplan-Meier estimates at day 365.

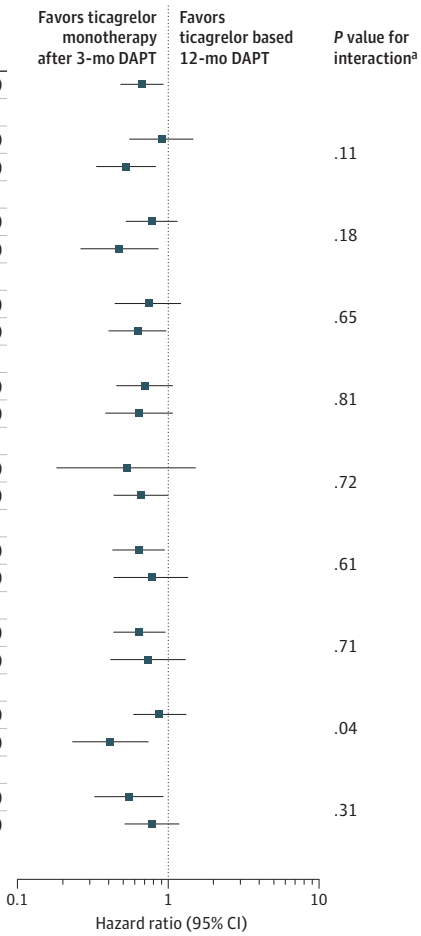
[b] *P* values are derived from Cox proportional hazards model.

[c] Net adverse clinical event included the composite of major bleeding and major adverse cardiac and cerebrovascular events.

[d] Major adverse cardiac and cerebrovascular event included the composite of death, MI, stent thrombosis, stroke, or target-vessel revascularization.

Figure 3. Subgroup Analyses for the Primary Outcome

Subgroup	No./total (%) Ticagrelor monotherapy after 3-mo DAPT	Ticagrelor-based 12-mo DAPT	Absolute difference, (95% CI)	Hazard ratio (95% CI)	*P* value for interaction[a]
All patients	59/1527 (3.9)	89/1529 (5.9)	-1.98 (-3.50 to -0.45)	0.66 (0.48 to 0.92)	
Age, y					
<65	32/945 (3.4)	35/926 (3.8)	-0.41 (-2.10 to 1.28)	0.90 (0.55 to 1.45)	.11
≥65	27/582 (4.7)	54/603 (9.0)	-4.31 (-7.17 to -1.45)	0.52 (0.33 to 0.82)	
Sex					
Men	43/1204 (3.6)	57/1224 (4.7)	-1.11 (-2.69 to 0.48)	0.77 (0.52 to 1.14)	.18
Women	16/323 (5.0)	32/305 (10.5)	-5.52 (-9.70 to -1.34)	0.47 (0.26 to 0.85)	
Diabetes					
Yes	26/418 (6.2)	36/417 (8.7)	-2.48 (-6.05 to 1.09)	0.73 (0.44 to 1.20)	.65
No	33/1109 (3.0)	53/1112 (4.8)	-1.79 (-3.40 to -0.18)	0.62 (0.40 to 0.96)	
Hypertension					
Yes	35/760 (4.7)	52/781 (6.7)	-2.07 (-4.37 to 0.24)	0.69 (0.45 to 1.06)	.81
No	24/767 (3.2)	37/748 (5.0)	-1.84 (-3.84 to 0.15)	0.63 (0.38 to 1.06)	
Chronic kidney disease[b]					
Yes	23/292 (8.0)	35/328 (10.9)	-2.87 (-7.46 to 1.72)	0.53 (0.18 to 1.51)	.72
No	36/1235 (2.9)	54/1201 (4.5)	-1.59 (-3.09 to -0.08)	0.65 (0.43 to 0.99)	
Body mass index[c]					
<25	38/798 (4.8)	62/827 (7.6)	-2.77 (-5.11 to -0.44)	0.63 (0.42 to 0.94)	.61
≥25	21/729 (2.9)	27/702 (3.9)	-0.97 (-2.85 to 0.91)	0.77 (0.43 to 1.34)	
Clinical presentation					
Unstable angina/NSTEMI	39/981 (4.0)	61/972 (6.3)	-2.33 (-4.29 to -0.36)	0.63 (0.43 to 0.95)	.71
STEMI	20/546 (3.7)	28/557 (5.1)	-1.36 (-3.78 to 1.06)	0.73 (0.41 to 1.29)	
Multivessel disease					
Yes	43/842 (5.2)	51/861 (6.0)	-0.84 (-3.22 to 1.54)	0.86 (0.58 to 1.30)	.04
No	16/685 (2.4)	38/668 (5.7)	-3.37 (-5.47 to -1.27)	0.41 (0.23 to 0.73)	
Total stent length, mm					
<30	21/790 (2.7)	37/754 (5.0)	-2.30 (-4.22 to -0.38)	0.54 (0.32 to 0.92)	.31
≥30	38/737 (3.2)	52/775 (6.8)	-1.53 (-3.92 to 0.85)	0.77 (0.51 to 1.17)	



Numbers and percentages shown are number of patients with event/number of patients at risk and incidences at 1 year. NSTEMI indicates non–ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.

[a] *P* values for interaction were calculated using interaction terms in a Cox proportional hazard model.

[b] Chronic kidney disease was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2 of body surface area.

[c] Calculated as weight in kilograms divided by height in meters squared.

receiving ticagrelor-based 12-month DAPT showed no significant differences in the incidence of acute myocardial infarction (6 [0.4%] vs 11 [0.7%]; HR, 0.55 [95% CI, 0.20 to 1.48]; *P* = .24), stroke (8 [0.5%] vs 11 [0.7%]; HR, 0.73 [95% CI, 0.29 to 1.81]; *P* = .50), or target-vessel revascularization (8 [0.5%] vs 10 [0.7%]; HR, 0.80 [95% CI, 0.32 to 2.03]; *P* = .64) (Table 2).

From the post hoc analysis model, with site as a random effect, the results for the primary outcome were consistent with the main prespecified analysis (3.9% in the group receiving ticagrelor monotherapy after 3-month DAPT vs 5.9% in the group receiving ticagrelor-based 12-month DAPT; HR, 0.66 [95% CI, 0.48 to 0.92]; *P* = .01). Baseline characteristics for the per-protocol population and the as-treated population are presented in eTable 10 and eTable 11 in Supplement 2. As for the primary outcomes, the results were consistent in the per-protocol population (3.6% in the group receiving ticagrelor monotherapy after 3-month DAPT vs 5.7% in the group receiving ticagrelor-based 12-month DAPT; HR, 0.63 [95% CI, 0.43 to 0.90]; *P* = .01) (eFigure 1A and eTable 12 in Supplement 2), and in the as-treated population (3.6% in the group receiving ticagrelor monotherapy after 3-month DAPT vs 6.1% in the group receiving ticagrelor-based 12-month DAPT; HR, 0.61 [95% CI, 0.43 to 0.86]; *P* = .005) (eFigure 1B and eTable 12 in Supplement 2). Post hoc analyses of secondary outcomes for the per-protocol population and the as-treated population are presented in eTable 12 in Supplement 2.

A prespecified subgroup analysis showed that ticagrelor monotherapy after 3-month DAPT had a consistent effect on the primary outcome across subgroups except in the subset of patients with multivessel disease (**Figure 3**). Ticagrelor monotherapy after 3-month DAPT was more favored over ticagrelor-based 12-month DAPT in the subset of the patients without multivessel disease than in those without (*P* value for interaction = .04). Subgroup analyses for the secondary outcome in post-hoc analyses showed a consistent effect across subgroups (eFigure 2 and eFigure 3 in Supplement).

Discussion

In this randomized clinical trial of patients with ACS treated with drug-eluting stents, ticagrelor monotherapy after 3-months of DAPT compared with ticagrelor-based DAPT for 12 months resulted in a significant 2% absolute reduction in the composite outcome of 1-year net adverse clinical events, with a significant association with reduced risk of major bleeding and no significant association with risk of major adverse cardiac and cardiovascular events. These findings suggest that ticagrelor monotherapy after short-term DAPT could be an optimal strategy that balances both ischemic and bleeding risks for patients with ACS treated with drug-eluting stents.

Current guidelines recommend 12-month DAPT with potent antiplatelet agents for patients with ACS.[1,2] However, the risk of increased bleeding has raised concerns,[5-7] and the timepoint to switch to single-antiplatelet therapy and which antiplatelet agent should be stopped are still uncertain. Although previous studies had evaluated short-term DAPT,[19,20] these were limited because of the small number of enrolled patients with ACS who had implanted drug-eluting stents that were no longer commercially available. Although 3 recent randomized clinical trials have evaluated the efficacy of short-term DAPT targeting only for ACS,[21-23] these studies included substantial proportions of patients (41% to 81%) receiving clopidogrel-based DAPT. Therefore, in the post-clopidogrel and new-generation drug-eluting stent era, the present trial investigated the effectiveness of short-term DAPT followed by ticagrelor monotherapy for patients with the whole spectrum of ACS.

Four randomized trials evaluated stopping aspirin instead of the P2Y12 inhibitor.[9,10,24,25] Ticagrelor monotherapy was used in the GLOBAL LEADERS trial and the TWILIGHT trial.[9,10] The GLOBAL LEADERS trial found that ticagrelor with aspirin for 1 month followed by ticagrelor alone for 23 months did not reduce the risk of mortality or myocardial infarction 2 years after PCI, compared with 12 months of DAPT followed by 12 months of aspirin alone.[9] The TWILIGHT trial had the same experimental strategy as the present trial and found that ticagrelor monotherapy was associated with a lower incidence of clinically relevant bleeding than ticagrelor plus aspirin in high-risk patients who underwent PCI.[10] Similar to the results of the present trial, type 3 or 5 bleeding, defined by the Bleeding Academic Research Consortium, was significantly lower in the ticagrelor monotherapy group in the TWILIGHT trial. A higher incidence of bleeding events in the present trial compared with the TWILIGHT trial may be attributed to the events between the index PCI and 3 months, racial differences, and enrollment of the patients with ST-elevation myocardial infarction.[5,20] In line with the previous studies, this trial provides confirmatory findings and expands the existing knowledge on the safety and feasibility of an aspirin-free approach and the use of a P2Y12 inhibitor monotherapy strategy for patients with ACS. However, this study differs from previous trials by including only patients presenting with ACS. More than two-thirds of the patients were admitted via emergency department, and one-third presented with ST-elevation myocardial infarction requiring primary PCI. Also, this trial differs from the TWILIGHT trial because this trial excluded the patients with a high bleeding risk, whereas the TWILIGHT trial enrolled the patients with a high bleeding risk. Thus, the differences in bleeding events between the groups may have been more easily achieved in the TWILIGHT trial.

There was a significant interaction between the antiplatelet therapy strategy and the presence of multivessel disease for the occurrence of the primary outcome. Although it is known that atherosclerotic burden and procedural complexities might affect the strategies of antiplatelet therapy,[26] these relationships have not been well investigated in patients with ACS.

Considering the new-generation drug-eluting stents, thin-strut based bioresorbable polymer sirolimus-eluting stents are expected to reduce thrombogenicity and vascular injury, as well as accelerate endothelialization, leading to the superior clinical outcomes.[27,28] The improved clinical performances of stents might have influenced the positive results of the ticagrelor monotherapy after short-term DAPT in the present trial. Because this study was performed exclusively in patients who received these ultrathin sirolimus-eluting stents, extrapolation of the results to other drug-eluting stents requires caution.

Limitations

This study has several limitations. First, study power was calculated by estimating the occurrence of net adverse clinical events, the composite outcome. Comparisons of the occurrence of each component, particularly major adverse cardiac and cerebrovascular events, could be underpowered. Second, this study was an open-label trial and not placebo-controlled, and drug adherence was not monitored. However, clinical outcomes were assessed by members of an independent clinical event committee, and statistical analyses were performed by independent statisticians. Third, although the primary outcome met the superiority assumption, the lower than anticipated event rate of the primary outcome led to a lower than expected power. Fourth, patients at high risk of bleeding, which generally account for approximately 40% of patients undergoing PCI in a real-world setting, were excluded. Fifth, randomization was performed after the index PCI, not at 3 months after PCI. However, the superiority comparison was initially designed with an estimated event rate including the first 3 months after PCI. Furthermore, prespecified 3-month landmark analyses showed results that were consistent with the main results. Sixth, this study was conducted only in South Korea. Caution is needed in extrapolating these results outside of South Korea.

Conclusions

Among patients with ACS treated with drug-eluting stents, ticagrelor monotherapy after 3-month DAPT, compared with ticagrelor-based 12-month DAPT, resulted in a modest but statistically significant reduction in a composite outcome of major bleeding and cardiovascular events at 1 year. The study population and lower than expected event rates should be considered in interpreting the trial.

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Data Sharing Statement: See Supplement 3.

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