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REVIEW

De-escalating Dual Antiplatelet Therapy to Ticagrelor Monotherapy in Acute Coronary Syndrome

A Systemic Review and Individual Patient Data Meta-Analysis of Randomized Clinical Trials

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Background: The role of transitioning from short dual antiplatelet therapy (DAPT) to potent P2Y12 inhibitor monotherapy in patients with acute coronary syndrome (ACS) undergoing drug-eluting stent (DES) implantation remains inconclusive.

Purpose: To compare the effects of de-escalating DAPT to ticagrelor monotherapy versus standard DAPT from randomized clinical trials in patients with ACS.

Data Sources: PubMed, EMBASE, Scopus, and ClinicalTrials.gov from inception to 12 December 2024.

Study Selection: Randomized clinical trials comparing de-escalating DAPT to ticagrelor monotherapy versus ticagrelor-based standard DAPT for 12 months, specifically in patients with ACS undergoing DES implantation.

Data Extraction: The coprimary end points were an ischemic end point (composite of death, nonprocedural [spontaneous] myocardial infarction, or stroke) and a bleeding end point (Bleeding Academic Research Consortium types 3 or 5 bleeding).

Data Synthesis: Individual patient data were obtained from 3 trials (TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome], T-PASS [Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome], and ULTIMATE-DAPT [Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes]), including 9130 randomized patients with ACS; 3132 had ST-segment elevation myocardial infarction (STEMI), 3023 had non-STEMI (NSTEMI), and 2975 had unstable angina. The rate of the primary ischemic end point was not different between the ticagrelor monotherapy and standard DAPT groups (1.7% vs. 2.1%; hazard ratio [HR], 0.85 [95% CI, 0.63 to 1.16]). The rate of the primary bleeding end point was lower in the ticagrelor monotherapy group (0.8% vs. 2.5%; HR, 0.30 [CI, 0.21 to 0.45]). These findings were consistent in patients with STEMI, NSTEMI, and unstable angina.

Limitation: Other de-escalation strategies for modulating antiplatelet therapy were not included.

Conclusion: In patients with ACS undergoing DES implantation, de-escalating DAPT to ticagrelor monotherapy was associated with a lower risk for major bleeding compared with standard DAPT, without an increase in ischemic events, regardless of the type of ACS.

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Despite advances in revascularization strategies, antiplatelet therapy remains the cornerstone of pharmacologic treatment for preventing ischemic events in patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (1–3). The current standard of care for these patients is dual antiplatelet therapy (DAPT) consisting of aspirin and a P2Y12 inhibitor for 12 months after drug-eluting stent (DES) implantation (1, 2). Moreover, potent P2Y12 inhibitors, such as ticagrelor and prasugrel, are preferred over clopidogrel in patients with ACS, as randomized trials have shown that these agents are more effective at preventing ischemic and thrombotic events (1, 2, 4, 5). However, prolonged use of DAPT, particularly with potent P2Y12 inhibitors, comes at the expense of an increased risk for bleeding complications (4–8). To balance the risk for major bleeding and ischemic events, several de-escalation strategies for modulating antiplatelet therapy have been proposed (6–8). One approach that has gained popularity is transitioning after an obligate period of

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short DAPT to P2Y12 inhibitor monotherapy, which aims to reduce aspirin-associated bleeding while preserving the anti-ischemic benefits of antiplatelet therapy (6–15). Several meta-analyses have reaffirmed the effects of P2Y12 inhibitor monotherapy after DAPT de-escalation; however, these studies were limited by patient heterogeneity in clinical presentation, variations in P2Y12 inhibitor choice, differences in clinical end points of interest, and a lack of patient-level data (16, 17). The availability of individual patient data from a large cohort of randomized patients with ACS who had DES implantation and were treated with standard DAPT, including potent P2Y12 inhibitors as recommended by current guidelines, compared with de-escalation to potent P2Y12 inhibitor monotherapy, would allow for the use of uniform definitions for clinical end points and facilitate the assessment of the effects of potent P2Y12 inhibitor monotherapy across various subgroups, particularly those defined by the type of ACS (1, 2).

Toward this end, we aimed to conduct a systematic review and individual patient data meta-analysis of randomized clinical trials that compared the efficacy and safety of de-escalating DAPT to ticagrelor monotherapy versus ticagrelor-based standard DAPT in patients with ACS who had DES implantation. In addition, we sought to assess the consistency of these effects across different types of ACS.

METHODS

The study protocol was prospectively registered in PROSPERO (www.crd.york.ac.uk/prospero, CRD42024565855), and this meta-analysis was reported in accordance with the guidelines of the PRISMA-IPD (Preferred Reporting Items for Systematic reviews and Meta-Analyses of Individual Participant Data) (**Supplement 1**, available at Annals.org) (18).

Data Sources and Searches

We searched PubMed, EMBASE, Scopus, and ClinicalTrials.gov from inception to 12 December 2024, without language restrictions. The detailed search strategy is provided in **Table 1 of Supplement 2** (available at Annals.org). Two investigators (Y.-J.L. and S.-H.L.) independently determined whether the studies met the prespecified eligibility criteria, with a third investigator (M.-K.H.) involved in cases of disagreement. Only full-text published studies were included, and reference lists of retrieved articles were manually searched to identify additional relevant studies not captured in the initial search.

Study Selection

A systematic review and individual patient data meta-analysis of randomized clinical trials comparing de-escalating DAPT to ticagrelor monotherapy versus ticagrelor-based standard DAPT, specifically focusing on patients with ACS undergoing DES implantation and no restrictions on the type of ACS, was conducted. The inclusion criteria for this analysis were randomized clinical trial; enrollment of patients presenting with ACS and undergoing contemporary DES implantation; comparison between ticagrelor monotherapy after short (≤3 months) DAPT as the experimental group and ticagrelor-based standard (12 months) DAPT as the control group; follow-up period of at least 12 months after DES implantation; and central adjudication of clinical end points. The exclusion criteria were nonrandomized studies; any restrictions on the type of ACS (that is, ST-segment elevation myocardial infarction [STEMI], non-STEMI [NSTEMI], or unstable angina) for patient enrollment; inclusion of patients presenting with chronic coronary syndrome; inclusion of patients requiring concurrent oral anticoagulation; comparisons involving P2Y12 inhibitors other than ticagrelor; and ongoing trials.

Data Extraction and Quality Assessment

The principal investigators of the eligible trials were contacted to request individual patient data provided in an anonymized electronic data set. The collected data were thoroughly reviewed for completeness and consistency and cross-referenced with the results of the original publications. Any missing data or discrepancies identified during the integrity checks were addressed by reaching out to the principal investigators for clarification or additional information. Two investigators (Y.-J.L. and S.-H.L.) independently assessed the quality of the included trials using the Cochrane Risk of Bias 2 Tool (19). Any disagreements were initially resolved through discussion, with unresolved issues referred to a third investigator (M.-K.H) for arbitration. Each trial was approved by an ethics committee, and all patients provided written informed consent.

Study End Points

The prespecified coprimary end points were ischemic and bleeding end points. The primary ischemic end point was a composite of death, nonprocedural (spontaneous) myocardial infarction (MI), or stroke. The primary bleeding end point was Bleeding Academic Research Consortium (BARC) types 3 or 5 bleeding (20). The secondary end points were net adverse clinical events, defined as the composite of the primary ischemic or bleeding end point (death, nonprocedural MI, stroke, or BARC types 3 or 5 bleeding); composite of death, nonprocedural MI, stroke, stent thrombosis, or target vessel revascularization; composite of death from cardiac cause, nonprocedural MI, or stroke; death; death from cardiac cause; nonprocedural MI; stent thrombosis; stroke; target vessel revascularization; and BARC types 3 and 5 bleeding separately. We adhered to the definitions used in the original trials for all clinical end points (**Table 2 of Supplement 2**, available at Annals.org) (13–15). All clinical end points were centrally adjudicated in each trial by an independent clinical end point committee, and any case of death

in which a cardiac cause could not be clearly excluded was judged as potentially due to a cardiac cause in all trials (13–15). Procedural MIs were not included in the analysis because most occurred within 48 hours of the index PCI, during which DAPT was administered to all patients, and were moreover only included in 1 trial (15).

Data Synthesis and Analysis

A 1-stage approach was prespecified to model the data from all trials simultaneously in the intention-to-treat population. Categorical variables are presented as number (percentage) and compared using χ^2 test or Fisher exact test. Continuous variables are presented as mean (SD) or median (IQR) and compared using *t* test or Mann–Whitney U test, depending on their distribution. Time-to-event outcomes of the primary and secondary end points were estimated using the Kaplan–Meier method. All primary analyses were done with censoring of events that occurred during the initial DAPT phase after DES implantation, which was identical in both the experimental and control groups. Consequently, only events that occurred after the time point at which each trial mandated transition from DAPT to ticagrelor monotherapy in the experimental group were included. Data were analyzed up to the longest time point available, with ticagrelor monotherapy according to the protocol in the experimental group and DAPT in the control group. Treatment effects were derived as hazard ratios (HRs) along with their corresponding 95% CIs using a mixed-effects Cox proportional hazards regression model, with trial as random effect. Prespecified sensitivity analyses, including the initial DAPT phase after DES implantation in 2 trials where randomization was performed at the time of index PCI, were done. Subgroup analyses for the primary end points were done for prespecified subgroups based on trial, age, sex, hypertension, diabetes, chronic kidney disease, current smoking, type of ACS, multivessel disease, use of intravascular imaging, and total stent length.

Confirmatory sensitivity analyses for the primary end points, based on a 2-stage approach (study-level meta-analyses) using an inverse-variance fixed-effect model, were prespecified to combine trial-level estimates. Heterogeneity between trials was assessed using the I^2 statistic. No imputation was done to infer missing values. All statistical analyses were done using SPSS, version 25.0 (IBM Corporation), and R, version 4.2.2 (R Foundation for Statistical Computing).

Role of the Funding Source

This study has no funding source.

RESULTS

Study Selection and Included Patients

Our initial search strategy identified 3015 unique citations. After screening of titles and abstracts, 16 studies were considered potentially eligible. Of these, 13 were excluded after full-text review: 2 involved patients presenting with not only ACS but also chronic coronary syndrome (9, 10), 7 were subgroup analyses or ancillary substudies of a randomized clinical trial (21–27), and 4 were reports on the study design of a randomized clinical trial (28–31). Consequently, 3 randomized clinical trials (TICO [Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome], T-PASS [Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome], and ULTIMATE-DAPT [Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes]) were deemed eligible, and individual patient data were requested and obtained from each (**Appendix Figure 1**, available at Annals.org) (13–15). Details regarding the study population, stratification criteria for randomization, randomized treatments, follow-up duration, primary end point, and the risk of bias for each trial are provided in **Table 3 of Supplement 2** and **Figure 1 of Supplement 2** (available at Annals.org). All trials specifically enrolled patients with ACS who had DES implantation, with no restrictions on the type of ACS. Clinical follow-up was done up to 12 months after PCI, with a mean follow-up duration of 358.7 (SD, 35.9) days. Clinical outcomes were compared between ticagrelor monotherapy after short (≤3 months) DAPT in the experimental group and ticagrelor-based standard (12 months) DAPT in the control group. The TICO and T-PASS trials were open-label, whereas the ULTIMATE-DAPT trial was double-blind and placebo-controlled. A total of 9306 patients were initially identified for the analysis; 38 (0.4%) were excluded due to premature study termination and 138 (1.5%) due to adverse events during the initial DAPT phase after DES implantation. Ultimately, 9130 patients were included in the primary analysis, with 4562 (50.0%) assigned to de-escalating DAPT to ticagrelor monotherapy (hereafter, ticagrelor monotherapy) and 4568 (50.0%) to ticagrelor-based standard DAPT (hereafter, standard DAPT) (Appendix Figure 2, available at Annals.org).

Patient Characteristics

The baseline characteristics of patients in the ticagrelor monotherapy and standard DAPT groups were not different (**Table 1**). The mean age of the patients was 60.9 (SD, 10.5) years, 1925 (21.1%) patients were women, 2679 (29.3%) had a history of diabetes, and 1027 (11.2%) had chronic kidney disease. At presentation, 3132 (34.3%) patients were diagnosed with STEMI, 3023 (33.1%) with NSTEMI, and 2975 (32.6%) with unstable angina. Transfemoral access was used in 2308 (25.3%) patients. Multivessel coronary artery disease was present in 4113 (45.0%) patients, and intravascular imaging was used in 2701 (29.6%) patients. Multilesion and multivessel interventions were performed

Table 1. Baseline Characteristics

Characteristics	Ticagrelor Monotherapy (*n* = 4562)	Standard DAPT (*n* = 4568)
Trial, *n* (%)		
TICO	1453 (31.9)	1462 (32.0)
T-PASS	1409 (30.9)	1406 (30.8)
ULTIMATE-DAPT	1700 (37.3)	1700 (37.2)
Mean age (SD), *y*	60.9 (10.6)	60.9 (10.4)
Women, *n* (%)	966 (21.2)	959 (21.0)
Country of enrollment, *n* (%)		
Korea	2862 (62.7)	2868 (62.8)
China	1476 (32.4)	1519 (33.3)
Pakistan	202 (4.4)	159 (3.5)
United Kingdom	12 (0.3)	11 (0.2)
Italy	10 (0.2)	11 (0.2)
Mean body mass index (SD), kg/m^2	25.1 (3.4)	25.1 (3.5)
Hypertension, *n* (%)	2436 (53.4)	2475 (54.2)
Diabetes, *n* (%)	1342 (29.4)	1337 (29.3)
Insulin-treated diabetes, *n* (%)	215 (4.7)	211 (4.6)
Chronic kidney disease, *n* (%)*	498 (10.9)	529 (11.6)
End-stage kidney disease on dialysis, *n* (%)	20 (0.4)	31 (0.7)
Dyslipidemia, *n* (%)	3097 (67.9)	3098 (67.8)
Current smoker, *n* (%)	1568 (34.4)	1576 (34.5)
Prior myocardial infarction, *n* (%)	230 (5.0)	228 (5.0)
Prior percutaneous coronary intervention, *n* (%)	394 (8.6)	388 (8.5)
Prior coronary bypass graft surgery, *n* (%)	13 (0.3)	16 (0.4)
Prior stroke, *n* (%)	254 (5.6)	258 (5.6)
Type of ACS at presentation, *n* (%)		
ST-segment elevation MI	1572 (34.5)	1560 (34.2)
Non–ST-segment elevation MI	1554 (34.1)	1469 (32.2)
Unstable angina	1436 (31.5)	1539 (33.7)
Transfemoral access, *n* (%)	1161 (25.4)	1147 (25.1)
Multivessel coronary artery disease, *n* (%)	2036 (44.6)	2077 (45.5)
Use of intravascular imaging, *n* (%)	1343 (29.4)	1358 (29. 7)
Use of intra-aortic balloon pump, *n* (%)	39 (0.9)	42 (0.9)
Use of percutaneous cardiopulmonary support, *n* (%)	9 (0.2)	11 (0.2)
Multilesion intervention, *n* (%)	1003 (22.0)	1036 (22.7)
Multivessel intervention, *n* (%)	837 (18.3)	876 (19.2)
Mean treated lesions per patient (SD), *n*	1.3 (0.5)	1.3 (0.5)
Mean total number of stents per patient (SD), *n*	1.4 (0.7)	1.4 (0.7)
Mean total stent length per patient (SD), *mm*	36.9 (21.0)	36.5 (21.0)

ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; MI = myocardial infarction; TICO = Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome; T-PASS = Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome; ULTIMATE-DAPT = Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes.

* Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 of body surface area.

in 2039 (22.3%) and 1713 (18.8%) patients, respectively, with a mean total stent length of 36.7 (SD, 20.9) mm. Angiographic and procedural characteristics of treated lesions at index PCI are presented in **Table 4 of Supplement 2** (available at Annals.org), with no differences between the 2 groups. The baseline characteristics according to individual trials are provided in **Table 5 of Supplement 2** (available at Annals.org).

Clinical End Points

The rate of the primary ischemic end point did not differ between the ticagrelor monotherapy and standard DAPT groups (1.7% vs. 2.1%; HR, 0.85 [95% CI, 0.63 to 1.16]) (**Table 2** and **Figure 1, *left***). The prespecified sensitivity analyses based on a 2-stage approach showed consistent results for the primary ischemic end point, with low between-trial heterogeneity (I^2 = 6%) (**Figure 2A of Supplement 2**, available at Annals.org). The rate of the primary bleeding end point was lower in the ticagrelor monotherapy group compared with the standard DAPT group (0.8% vs. 2.5%; HR, 0.30 [CI, 0.21 to 0.45]) (**Table 2** and **Figure 1, *right***). The 2-stage approach for the primary bleeding end point showed consistent results with no between-trial heterogeneity (I^2 = 0%) (**Figure 2B of Supplement 2**, available at Annals.org).

The rate of net adverse clinical events was lower in the ticagrelor monotherapy group compared with the standard DAPT group (2.3% vs. 4.2%; HR, 0.56 [CI, 0.44 to 0.72]) (**Table 2**). The rates of the composite of death, nonprocedural MI, stroke, stent thrombosis, or target vessel revascularization (2.8% vs. 3.5%; HR, 0.80 [CI, 0.63 to 1.03]) and of the composite of death from cardiac cause, nonprocedural MI, or stroke (1.5% vs. 1.8%; HR, 0.87 [CI, 0.62 to 1.21]) did not differ between the groups. The rates of death (0.7% vs. 0.8%; HR, 0.88 [CI, 0.53 to 1.45]) and death from cardiac cause (0.4% vs. 0.4%; HR, 0.94 [CI, 0.46 to 1.90]) did not differ between the groups. The rates of other individual clinical end points, including nonprocedural MI, stent thrombosis, stroke, target vessel revascularization, and BARC type 5 bleeding were not different between the groups. However, the rate of BARC type 3 bleeding was lower in the ticagrelor monotherapy group compared with the standard DAPT group (0.7% vs. 2.4%; HR, 0.29 [CI, 0.19 to 0.43]). Prespecified sensitivity analyses, including the initial DAPT phase after DES implantation in the TICO and T-PASS trials, yielded consistent results for the primary and secondary end points (**Table 6 of Supplement 2**, available at Annals.org).

Subgroup Analyses

The effects of ticagrelor monotherapy versus standard DAPT for the primary end points were consistent across all prespecified subgroups, including the type of ACS (**Figure 2**). In the subgroup of patients with STEMI (a prespecified, stratified subgroup in all trials), the rate of the primary ischemic end point did not differ between the ticagrelor monotherapy and standard DAPT groups (2.1% vs. 1.8%; HR, 1.17 [CI, 0.70 to 1.97]), but ticagrelor monotherapy was associated with lower rate of the primary bleeding end point (0.6% vs. 2.2%; HR, 0.32 [CI, 0.16 to 0.65]) (**Figure 3 of Supplement 2**, available at Annals.org). Similarly, no difference in the rate of the

Table 2. Clinical End Points*

Clinical End Points	Ticagrelor Monotherapy (*n* = 4562), *n* (%)	Standard DAPT (*n* = 4568), *n* (%)	HR (95% CI)
Primary end points			
Ischemic end point (composite of death, nonprocedural MI, or stroke)	75 (1.7)	88 (2.1)	0.85 (0.63–1.16)
Bleeding end point (BARC types 3 or 5 bleeding)	33 (0.8)	108 (2.5)	0.30 (0.21–0.45)
Secondary end points			
Net adverse clinical events (composite of death, nonprocedural MI, stroke, or BARC types 3 or 5 bleeding)	100 (2.3)	178 (4.2)	0.56 (0.44–0.72)
Death, nonprocedural MI, stroke, stent thrombosis, or target vessel revascularization	115 (2.8)	143 (3.5)	0.80 (0.63–1.03)
Death from cardiac cause, nonprocedural MI, or stroke	63 (1.5)	73 (1.8)	0.87 (0.62–1.21)
Death	29 (0.7)	33 (0.8)	0.88 (0.53–1.45)
Death from cardiac cause	15 (0.4)	16 (0.4)	0.94 (0.46–1.90)
Nonprocedural MI	24 (0.6)	25 (0.6)	0.96 (0.55–1.68)
Stent thrombosis	7 (0.2)	6 (0.1)	1.17 (0.39–3.48)
Definite	4	5	
Probable	3	1	
Stroke	30 (0.7)	35 (0.8)	0.86 (0.53–1.40)
Ischemic	18	24	
Hemorrhagic	7	5	
Uncertain	5	6	
Target vessel revascularization	50 (1.3)	61 (1.6)	0.82 (0.56–1.19)
BARC type 3 bleeding	30 (0.7)	104 (2.4)	0.29 (0.19–0.43)
Type 3a	19	48	
Type 3b	6	51	
Type 3c	5	5	
BARC type 5 bleeding	3 (0.1)	4 (0.1)	0.74 (0.17–3.33)

BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction.
*The listed percentages were estimated using the Kaplan–Meier method, so values might not calculate mathematically.

primary ischemic end point was observed between the 2 groups among patients with NSTEMI (1.8% vs. 2.3%; HR, 0.80 [CI, 0.47 to 1.34]) (**Figure 4A of Supplement 2**, available at Annals.org) and among those with unstable angina (1.3% vs. 2.2%; HR, 0.62 [CI, 0.35 to 1.11]) (**Figure 5A of Supplement 2**, available at Annals.org). However, ticagrelor monotherapy was associated with a lower rate of the primary bleeding end point among patients with NSTEMI (0.7% vs. 3.6%; HR, 0.19 [CI, 0.10 to 0.37]) (**Figure 4B of Supplement 2**, available at Annals.org) and unstable angina (0.9% vs. 1.9%; HR, 0.52 [CI, 0.27 to 0.99]) (**Figure 5B of Supplement 2**, available at Annals.org).

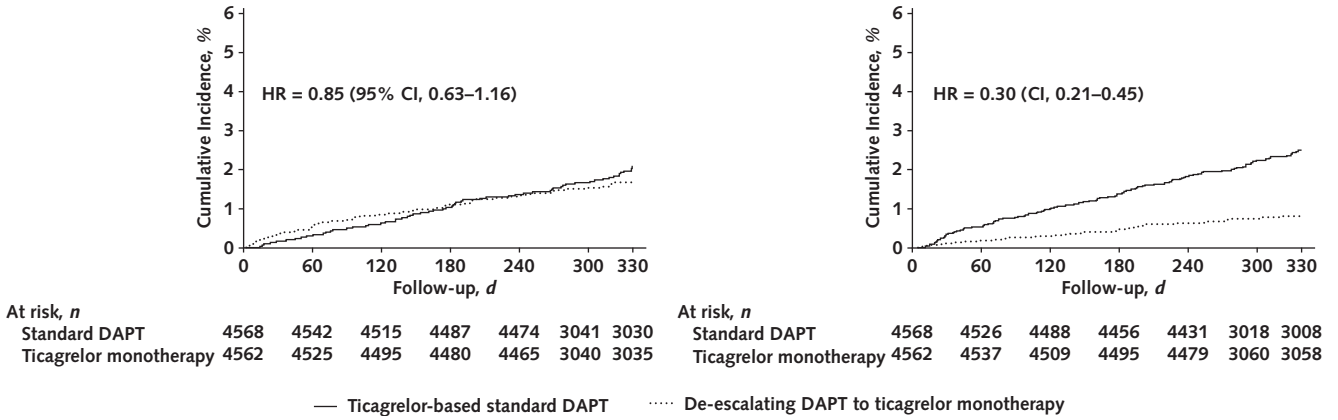
Discussion

In this meta-analysis, we analyzed individual patient data from 3 randomized clinical trials that specifically enrolled patients with ACS undergoing DES implantation, with no restrictions on the type of ACS. The analysis included 9130 patients presenting with an ACS, with approximately 3000 patients each having STEMI, NSTEMI, and unstable angina. All patients were randomly assigned to either standard DAPT for 12 months or de-escalation to ticagrelor monotherapy starting at a few weeks to up to 3 months after PCI. Compared with standard DAPT, ticagrelor monotherapy was associated with a lower risk for major bleeding without increasing the risk for ischemic events. Notably, these treatment effects were consistent across various subgroups, including the type of ACS, and persisted in sensitivity analyses using the 2-stage approach. Overall, our findings suggest that de-escalating DAPT to ticagrelor monotherapy will reduce aspirin-associated major bleeding while preserving the anti-ischemic benefits of antiplatelet therapy for patients with ACS of all types undergoing DES implantation.

Current guidelines recommend 12 months of DAPT with aspirin and a potent P2Y12 inhibitor for patients with ACS undergoing DES implantation (1, 2). However, prolonged DAPT increases the risk for bleeding complications, which has led to the development of various strategies for de-escalating antiplatelet therapy (6–8). Among these, de-escalation by discontinuation (that is, transitioning from a short period of DAPT to single antiplatelet therapy [either aspirin or a P2Y12 inhibitor]) has been investigated in previous randomized clinical trials (6, 7, 9–15, 32, 33). However, de-escalation to aspirin monotherapy in the SMART-DATE (Safety of 6-Month Duration of Dual Antiplatelet Therapy After Percutaneous Coronary Intervention in Patients With Acute Coronary Syndromes) trial and clopidogrel monotherapy in the STOPDAPT-2 ACS (Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt-Chromium Stent-2) trial was associated with a higher risk for ischemic events compared with 12 months of standard DAPT in patients with ACS (32, 33).

De-escalation to potent P2Y12 inhibitor monotherapy (mostly with ticagrelor) has also been studied in ACS (13–15). Ticagrelor is a reversible and direct-acting oral antagonist of the P2Y12 receptor that provides greater, faster, and more consistent platelet inhibition than clopidogrel (34). Although ACS subgroup analyses have been done in the TWILIGHT (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention) and GLOBAL LEADERS (GLOBAL LEADERS: A Clinical Study Comparing Two Forms of Antiplatelet Therapy After Stent Implantation) trials, which included patients with ACS as well as chronic coronary syndrome, the safety and efficacy of de-escalating DAPT to ticagrelor monotherapy specifically in patients with ACS have been examined in the previous TICO, T-PASS, and

Figure 1. Time-to-event curves for the primary end points.



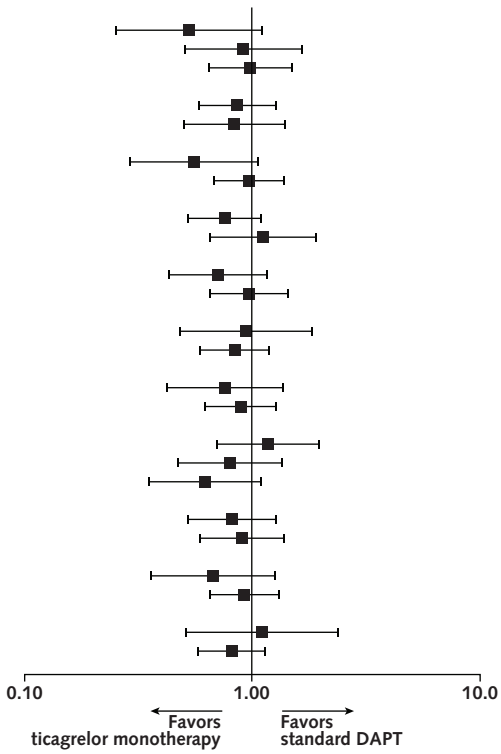
Kaplan–Meier survival curves for the (*left*) primary ischemic end point (composite of death, nonprocedural myocardial infarction, or stroke) and (*right*) primary bleeding end point (BARC types 3 or 5 bleeding). BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; HR = hazard ratio.

ULTIMATE-DAPT trials (13–15, 21, 22). These 3 randomized clinical trials were similar in enrolling patients with ACS undergoing contemporary DES implantation, had no restrictions on the type of ACS, included a control group that received ticagrelor-based 12 months of standard DAPT after DES implantation, and had all clinical end points centrally adjudicated by an independent clinical end point committee (13–15). However, the timing of randomization and primary end point varied across these 3 trials (13–15). In the ULTIMATE-DAPT trial, all eligible patients received 1 month of treatment with aspirin and ticagrelor after the index PCI, and randomization was done at 1 month only in those free of major bleeding or ischemic events (15). In contrast, randomization was done at the time of the index PCI in the TICO and T-PASS trials, and the data analysis included events that occurred during the common early period of DAPT treatment, which might have diluted both ischemic and bleeding events to the null (13, 14). In addition, although the definitions of the individual clinical end points were mostly consistent, the trials used different primary composite end points (13–15). To account for these differences, we conducted an individual patient data meta-analysis from these 3 trials and considered only events occurring after DAPT was discontinued in the experimental group. We also prespecified primary end points related to major bleeding and ischemic events and performed subgroup analyses on the basis of the type of ACS, offering insights into the effects of de-escalating DAPT to ticagrelor monotherapy across the spectrum of ACS presentations. Our study has demonstrated that after DES implantation in patients presenting with ACS, de-escalating DAPT with aspirin and ticagrelor at several weeks to up to 3 months post-PCI to ticagrelor alone will reduce major bleeding without increasing adverse ischemic events. These effects were consistent across all examined subgroups, including the type of ACS (STEMI, NSTEMI, or unstable angina).

The primary goal of de-escalating DAPT to ticagrelor monotherapy is to reduce bleeding complications while not increasing adverse ischemic events, thereby favorably affecting their offsetting effects (6–8). This approach is grounded in the understanding that the risk for ischemia or thrombosis is highest immediately after PCI and decreases over time, whereas the risk for bleeding is less time dependent (3, 6, 7, 35). In our meta-analysis using individual patient data from 3 trials involving 9130 patients with ACS, the prespecified primary ischemic end point, the composite of death, nonprocedural MI, or stroke during the period of de-escalation to ticagrelor monotherapy versus continued DAPT, did not differ between the groups. This finding supports the notion that aspirin is not necessary to prevent future ischemic events in patients with ACS undergoing DES implantation who are treated with ticagrelor alone after a short initial period of DAPT. Notably, the upper bound of the 95% CI for the hazard of the primary ischemic end point between the groups was 1.16, meaning that it is unlikely that ticagrelor monotherapy could increase relative ischemic event rates by more than 16% (an absolute difference of approximately 0.3%, given the observed control arm event rate). These results are consistent with the findings from a pharmacodynamic substudy from the TWILIGHT trial, which demonstrated that ticagrelor monotherapy has a similar antithrombotic effect to that of ticagrelor plus aspirin (36). Therefore, our findings support the approach of transitioning from short DAPT to ticagrelor monotherapy to reduce the risk for bleeding without increasing ischemic risk in patients with ACS undergoing DES implantation. Meanwhile, differences in adherence to ticagrelor between the randomized clinical trial population and the general population should be considered, particularly given its twice-daily dosing requirement; nonetheless, even when accounting for

Figure 2. Subgroup analyses for the primary end points.

Subgroup	Patients, *n/N (%)*		HR (95% CI)
	Ticagrelor Monotherapy	Standard DAPT	
Trial			
TICO	11/1453 (0.8)	21/1462 (1.5)	0.53 (0.25-1.09)
T-PASS	21/1409 (1.5)	23/1406 (1.6)	0.91 (0.51-1.65)
ULTIMATE-DAPT	43/1700 (2.5)	44/1700 (2.6)	0.98 (0.64-1.49)
Age			
≥65 y	47/1802 (2.8)	54/1785 (3.3)	0.86 (0.58-1.28)
<65 y	28/2760 (1.0)	34/2783 (1.3)	0.83 (0.50-1.37)
Sex			
Female	14/966 (1.5)	25/959 (2.8)	0.56 (0.29-1.07)
Male	61/3596 (1.8)	63/3609 (1.9)	0.97 (0.68-1.38)
Hypertension			
Yes	47/2436 (2.0)	63/2475 (2.8)	0.76 (0.52-1.10)
No	28/2126 (1.4)	25/2093 (1.3)	1.11 (0.65-1.90)
Diabetes			
Yes	27/1342 (2.1)	38/1337 (3.1)	0.71 (0.43-1.16)
No	48/3220 (1.5)	50/3231 (1.7)	0.97 (0.65-1.43)
Chronic kidney disease			
Yes	16/498 (3.5)	18/529 (4.2)	0.94 (0.48-1.84)
No	59/4064 (1.5)	70/4039 (1.9)	0.84 (0.59-1.19)
Current smoking			
Yes	19/1568 (1.2)	25/1576 (1.7)	0.76 (0.42-1.38)
No	56/2994 (2.0)	63/2292 (2.3)	0.89 (0.62-1.28)
Type of ACS			
STEMI	31/1572 (2.1)	26/1560 (1.8)	1.17 (0.70-1.97)
NSTEMI	26/1554 (1.8)	31/1469 (2.3)	0.80 (0.47-1.34)
Unstable angina	18/1436 (1.3)	31/1539 (2.2)	0.62 (0.35-1.11)
Multivessel disease			
Yes	35/2036 (1.8)	44/2077 (2.4)	0.81 (0.52-1.27)
No	40/2526 (1.7)	44/2491 (1.9)	0.90 (0.59-1.38)
Use of intravascular imaging			
Yes	16/1343 (1.2)	24/1358 (1.9)	0.67 (0.36-1.27)
No	59/3219 (1.9)	64/3210 (2.2)	0.92 (0.65-1.31)
Total stent length			
>60 mm	14/599 (2.5)	12/571 (2.3)	1.11 (0.51-2.40)
≤60 mm	61/3963 (1.6)	76/3997 (2.1)	0.81 (0.58-1.14)



Subgroup	Patients, *n/N (%)*		HR (95% CI)
	Ticagrelor Monotherapy	Standard DAPT	
Trial			
TICO	13/1453 (0.9)	41/1462 (2.8)	0.32 (0.17-0.59)
T-PASS	9/1409 (0.6)	39/1406 (2.8)	0.23 (0.11-0.47)
ULTIMATE-DAPT	11/1700 (0.6)	28/1700 (1.7)	0.39 (0.20-0.79)
Age			
≥65 y	20/1802 (1.1)	63/1785 (3.7)	0.31 (0.19-0.51)
<65 y	13/2760 (0.5)	45/2783 (1.8)	0.29 (0.16-0.54)
Sex			
Female	8/966 (0.9)	21/959 (2.3)	0.38 (0.17-0.85)
Male	25/3596 (0.7)	87/3609 (2.6)	0.29 (0.18-0.45)
Hypertension			
Yes	22/2436 (0.9)	65/2475 (2.8)	0.34 (0.21-0.55)
No	11/2126 (0.5)	43/2093 (2.2)	0.25 (0.13-0.49)
Diabetes			
Yes	12/1342 (0.9)	39/1337 (3.0)	0.30 (0.16-0.58)
No	21/3220 (0.7)	69/3231 (2.3)	0.30 (0.19-0.50)
Chronic kidney disease			
Yes	6/498 (1.2)	23/529 (4.9)	0.27 (0.11-0.67)
No	27/4064	85/4039 (2.2)	0.31 (0.20-0.48)
Current smoking			
Yes	10/1568 (1.2)	29/1576 (2.0)	0.34 (0.17-0.70)
No	56/2994 (2.0)	79/2292 (2.8)	0.29 (0.18-0.46)
Type of ACS			
STEMI	10/1572 (0.6)	31/1560 (2.2)	0.32 (0.16-0.65)
NSTEMI	10/1554 (0.7)	50/1469 (3.6)	0.19 (0.10-0.37)
Unstable angina	13/1436 (0.9)	27/1539 (1.9)	0.52 (0.27-0.99)
Multivessel disease			
Yes	16/2036 (0.8)	58/2077 (3.1)	0.28 (0.16-0.49)
No	17/2526 (0.7)	50/2491 (2.1)	0.33 (0.19-0.58)
Use of intravascular imaging			
Yes	6/1343 (0.5)	27/1358 (2.0)	0.22 (0.09-0.54)
No	27/3219 (0.8)	81/3210 (2.8)	0.33 (0.21-0.51)
Total stent length			
>60 mm	6/599 (1.1)	20/571 (3.7)	0.28 (0.11-0.70)
≤60 mm	27/3963 (0.7)	88/3997 (2.4)	0.31 (0.20-0.47)

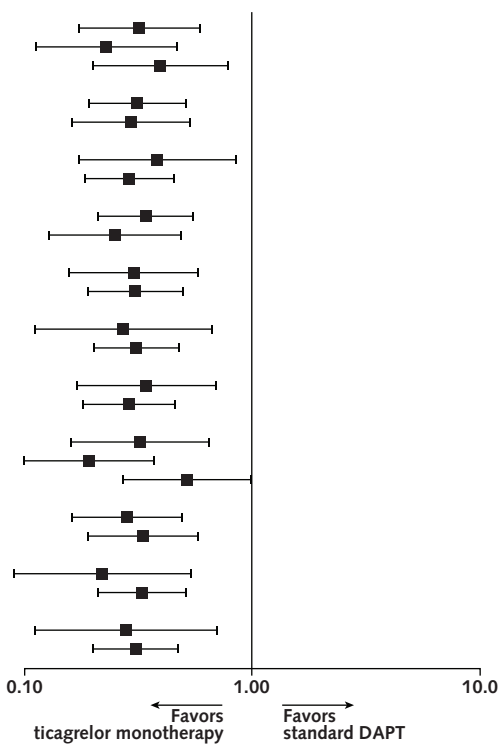


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***Figure 2*–Continued.**

Subgroup analyses for the (*top*) primary ischemic end point and (*bottom*) primary bleeding end point for the prespecified subgroups, including those classified by the type of ACS. ACS = acute coronary syndrome; DAPT = dual antiplatelet therapy; HR = hazard ratio; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TICO = Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome; T-PASS = Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome; ULTIMATE-DAPT = Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes.

the most common dosing omissions of missing a single dose, ticagrelor's effect on platelet inhibition remained acceptable (37, 38).

The current study overcomes the limitations of 3 prior meta-analyses of DAPT de-escalation to P2Y12 inhibitor monotherapy (16, 39, 40). Although these prior studies included an ACS subcohort, they also included patients with chronic coronary syndromes or those treated with various P2Y12 inhibitors, making it difficult to assess outcomes specifically in patients with ACS who require potent P2Y12 inhibitors (1, 2, 16, 39, 40). Two recent meta-analyses using individual patient data from randomized clinical trials specifically focused on the effects of ticagrelor monotherapy after short DAPT in patients with ACS (41, 42). However, the meta-analysis based on the TWILIGHT and TICO trials had a small proportion (14%) of STEMI, whereas the meta-analysis based on the TICO and T-PASS trials incorporated data from the initial DAPT phase after DES implantation in the primary analyses (41, 42). The current individual patient data meta-analysis overcomes these limitations by including only trials that exclusively enrolled patients with ACS, thus encompassing more than one third of those presenting with STEMI, and by only considering clinical events that occurred after DAPT was discontinued in the experimental group, thereby isolating the effect of de-escalation by discontinuation of aspirin and transitioning to ticagrelor monotherapy. Of note, although there has been a randomized clinical trial investigating the effects of de-escalating DAPT by discontinuation exclusively in patients with STEMI, aspirin was maintained instead of a P2Y12 inhibitor and failed to demonstrate safety in reducing major bleeding (43). In the current study, although not substantial, the rate of the primary ischemic end point was numerically higher in the ticagrelor monotherapy group compared with the standard DAPT group among patients with STEMI. Therefore, the current meta-analysis supporting the de-escalating DAPT to ticagrelor monotherapy as a viable antiplatelet therapy strategy in patients with ACS undergoing DES implantation is expected to promote further dedicated randomized clinical trials aimed at exploring the efficacy and safety of ticagrelor monotherapy, especially in patients with STEMI.

This study has several limitations. First, among the various possible de-escalation strategies, the current study focused only on the discontinuation of aspirin and maintenance of ticagrelor monotherapy. These results do not apply to other de-escalation strategies for modulating antiplatelet therapy, such as switching, reducing dose, and monotherapy with aspirin, clopidogrel, or prasugrel. Second, of the 3 trials included, 2 had open-label designs. Nonetheless, all trials implemented blinded central adjudication for clinical end points, and the results were consistent across the 3 trials, with minimal or no heterogeneity. Third, owing to the stringent eligibility criteria applied in the randomized clinical trials, patients at high risk for bleeding were excluded from the included trials, and thus might have been at lower risk than those seen in general clinical practice. Fourth, despite all trials being multicenter studies, most of patients were from Korea and China, which may reduce the generalizability of the results. Fifth, although the experimental group in the included trials consisted of ticagrelor monotherapy after 3 or less months of DAPT, the duration of DAPT period varied. Finally, the included trials had follow-up periods of only up to 12 months after PCI, warranting additional evidence to investigate longer-term effects. Therefore, our findings should be approached with caution and warrant further dedicated studies to determine the optimal strategy for de-escalating antiplatelet therapy, including the appropriate duration of DAPT and the choice of P2Y12 inhibitor to continue, in patients with ACS. Furthermore, additional research is needed to extend our findings to non-Asian patients.

In conclusion, in patients with ACS undergoing DES implantation, de-escalating DAPT to ticagrelor monotherapy was associated with a lower risk for major bleeding without an increased risk for ischemic events compared with continuing aspirin and ticagrelor, regardless of the type of ACS.

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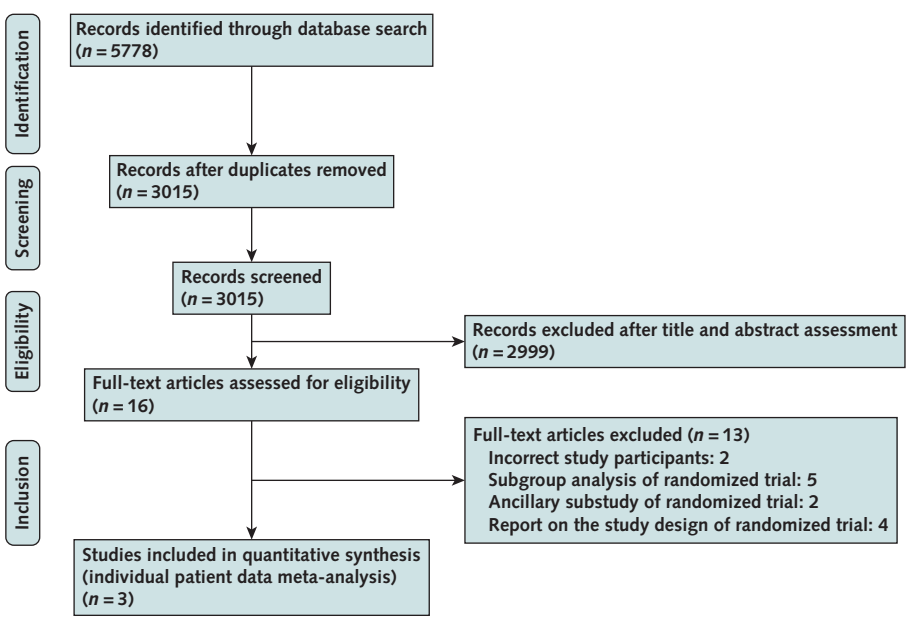
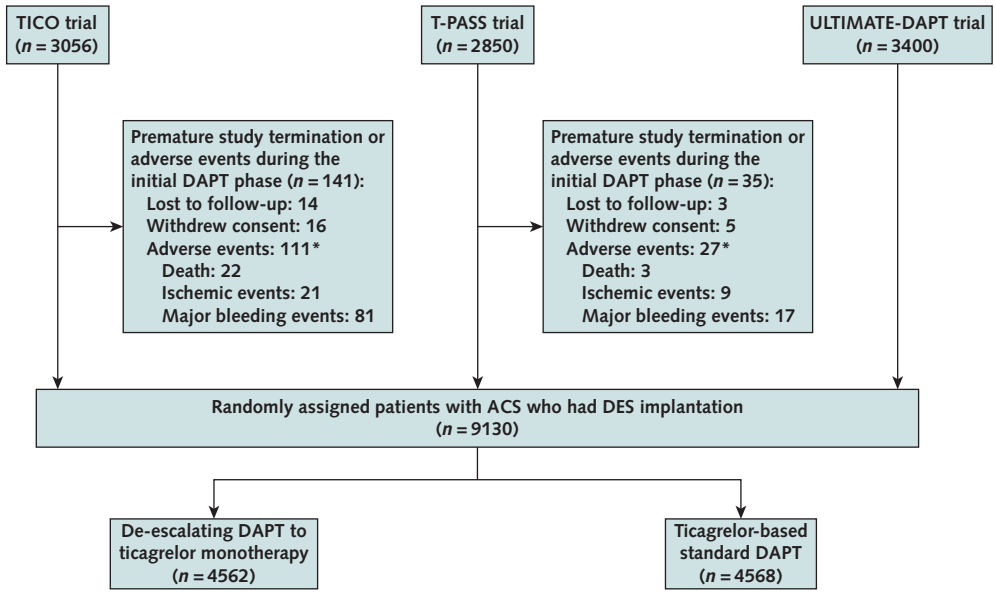
Appendix Figure 1. PRISMA flow diagram.



PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses.

Appendix Figure 2. Study flow of participants.



In this individual patient data meta-analysis of the TICO, T-PASS, and ULTIMATE-DAPT trials, patients who neither prematurely terminated their participation nor experienced adverse events during the initial DAPT phase after DES implantation (before the time point at which each trial mandated transition from DAPT to ticagrelor monotherapy in the experimental group) were included. A total of 9130 patients were analyzed, among which 4562 (50.0%) and 4568 (50.0%) patients were included in the de-escalating DAPT to ticagrelor monotherapy group and the ticagrelor-based standard DAPT group. ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; TICO = Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-Eluting Stent for Acute Coronary Syndrome; T-PASS = Ticagrelor Monotherapy in Patients Treated With New-Generation Drug-Eluting Stents for Acute Coronary Syndrome; ULTIMATE-DAPT = Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes.

* The events are not mutually exclusive. Ischemic events include non-procedural myocardial infarction, stroke, stent thrombosis, or target-vessel revascularization, and major bleeding events include BARC types 3 or 5 bleeding.