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Ticagrelor With or Without Aspirin After Complex Percutaneous Coronary Intervention

George Dangas, MD, PHD,[a] Usman Baber, MD, MS,[a] Samin Sharma, MD,[a] Gennaro Giustino, MD,[a] Shamir Mehta, MD, MSC,[b] David J. Cohen, MD, MSC,[c] Dominick J. Angiolillo, MD, PHD,[d] Samantha Sartori, PHD,[a] Rishi Chandiramani, MD,[a] Carlo Briguori, MD, PHD,[e] Dariusz Dudek, MD, PHD,[f,g] Javier Escaned, MD, PHD,[h] Kurt Huber, MD,[i] Timothy Collier, MSC,[j] Ran Kornowski, MD,[k] Vijay Kunadian, MBBS, MD,[l] Upendra Kaul, MD,[m] Keith Oldroyd, MBCHB, MD (HONS),[n] Gennaro Sardella, MD,[o] Richard Shlofmitz, MD,[p] Bernhard Witzenbichler, MD,[q] Han Ya-Ling, MD, PHD,[r] Stuart Pocock, PHD,[j] C. Michael Gibson, MD,[s] Roxana Mehran, MD[a]

ABSTRACT

BACKGROUND Whether a regimen of ticagrelor monotherapy attenuates bleeding complications without increasing ischemic risk in patients undergoing complex percutaneous coronary intervention (PCI) is unknown.

OBJECTIVES The purpose of this study was to evaluate the effect of ticagrelor monotherapy versus ticagrelor plus aspirin in patients undergoing complex PCI from the randomized, double-blind, placebo-controlled TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial.

METHODS In the TWILIGHT trial, after 3 months of ticagrelor plus aspirin, event-free and adherent patients remained on ticagrelor and were randomly assigned to receive aspirin or placebo for 1 year. Complex PCI was defined as any of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions. Bleeding and ischemic endpoints were evaluated at 1 year after randomization.

RESULTS Among 7,119 patients randomized in the main trial, complex PCI was performed in 2,342 patients. Compared to ticagrelor plus aspirin, ticagrelor plus placebo resulted in significantly lower rates of Bleeding Academic Research Consortium (BARC) type 2, 3, or 5 bleeding (4.2% vs. 7.7%; hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0.38 to 0.76). BARC type 3 or 5 bleeding was also significantly reduced (1.1% vs. 2.6%; HR: 0.41; 95% CI: 0.21 to 0.80). There were no significant between-group differences in death, myocardial infarction, or stroke (3.8% vs. 4.9%; HR: 0.77; 95% CI: 0.52 to 1.15), nor in stent thrombosis.

CONCLUSIONS Among patients undergoing complex PCI who initially completed 3 months of ticagrelor plus aspirin, continuation of ticagrelor monotherapy was associated with lower incidence of bleeding without increasing the risk of ischemic events compared to continuing ticagrelor plus aspirin. (Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention [TWILIGHT]; NCT02270242) (J Am Coll Cardiol 2020;75:2414–24)

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From [a]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [b]Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada; [c]University of Missouri-Kansas City, Kansas City, Missouri; [d]Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida; [e]Mediterranea Cardiocentro, Naples, Italy; [f]Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland; [g]Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy; [h]Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain; [i]3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, and Sigmund Freud University, Medical Faculty, Vienna, Austria; [j]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [k]Cardiology Department, Rabin Medical Center, Petach Tikva, Israel; [l]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University and Freeman Hospital, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; [m]Batra Hospital and Medical Research Center, New Delhi, India; [n]West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, United Kingdom; [o]Department of Cardiology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy; [p]St. Francis Hospital, Roslyn, New York; [q]Department of Cardiology and Pneumology, Helios Amper-Klinikum, Dachau, Germany; [r]Department of Cardiology, General Hospital of Shenyang Military Region, Shenyang, Liaoning, China; and the [s]Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts. Dr. Dangas has received research grants to his institution from AstraZeneca, Abbott, Boston Scientific,

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Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$-receptor inhibitor is required after percutaneous coronary intervention (PCI) to reduce the risk of coronary thrombotic events (1–5). Use of prolonged and/or more potent $P2Y_{12}$-receptor inhibitors lowers residual ischemic risk at the expense of increased bleeding (1–4,6). Patients who undergo complex PCI are at high risk of ischemic

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events (1,7–12). This risk has been shown to increase with increments of PCI complexity and may be reduced by extending DAPT using clopidogrel and aspirin versus aspirin alone (1,7,13). On the other hand, regardless of PCI complexity, extension of DAPT duration is associated with increased risk for major bleeding, which is in turn associated with increased morbidity, mortality, and health care cost (10,14–16). These observations underscore the need for antiplatelet treatment regimens that reduce the risk of bleeding while preserving efficacy in patients undergoing complex PCI.

Withdrawing aspirin and maintaining $P2Y_{12}$ inhibitor monotherapy after a brief period of DAPT (1 to 3 months) has emerged as a potential bleeding reduction strategy (17). In particular, monotherapy with the potent $P2Y_{12}$-receptor inhibitor ticagrelor after 3 months of DAPT was shown to be associated with a lower incidence of clinically relevant bleeding, without increasing the risk of ischemic events compared to continuing DAPT (18). Whether such an approach mitigates bleeding complications without increasing ischemic risk in patients who undergo complex PCI is unknown. Therefore we performed a post hoc analysis of the TWILIGHT (Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention) trial to evaluate the safety and efficacy of a regimen of ticagrelor monotherapy versus ticagrelor plus aspirin in patients who initially completed 3 months of DAPT after complex PCI.

ABBREVIATIONS AND ACRONYMS

BARC = Bleeding Academic Research Consortium

DAPT = dual antiplatelet therapy

MI = myocardial infarction

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

METHODS

STUDY DESIGN. TWILIGHT was a randomized, placebo-controlled trial conducted in 187 sites across 11 countries, as previously described (18,19). The Icahn School of Medicine at Mount Sinai designed and

Medtronic, Bayer, and Daiichi-Sankyo; has received Advisory Board fees from Abbott, Boston Scientific, and Sanofi; has served as a consultant for Merck, CSL Behring, Bayer, Biosensors, and Daiichi-Sankyo; and has previously held stock in Medtronic. Dr. Baber has received honoraria from AstraZeneca, Boston Scientific, and Amgen; and has received a grant from AstraZeneca. Dr. Giustino has received consultant fees (Advisory Board) for Bristol-Myers Squibb/Pfizer. Dr. Mehta has received grant support from, served on an executive committee, and served as site investigator for AstraZeneca; and has received a research grant from Boston Scientific. Dr. Cohen has received grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, Abbott Vascular, and Boston Scientific; and has received grant support, paid to his institution, from AstraZeneca. Dr. Angiolillo has received grant support, consulting fees, and honoraria from Amgen, Aralez, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Janssen, Merck, and Sanofi; has received consulting fees and honoraria from Haemonetics, PhaseBio, PLx Pharma, Pfizer, and The Medicines Company; has received grant support and fees for review activities from CeloNova; has received fees for review activities from St. Jude Medical; and has received grant support from CSL Behring, Eisai, Gilead, Idorsia Pharmaceuticals, Matsutani Chemical Industry, Novartis, Osprey Medical, and RenalGuard Solutions. Dr. Escaned has received consulting fees and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic; and has received lecture fees from Abiomed, Terumo, and Biosensors. Dr. Huber has received lecture fees from AstraZeneca and Bayer. Dr. Kunadian has received consulting fees/honoraria from Bayer, Amgen, Daiichi-Sankyo, Abbott Vascular, and AstraZeneca; and has received a major institutional research grant from AstraZeneca. Dr. Oldroyd has received grant support and lecture fees from AstraZeneca; and has received lecture fees from Biosensors, Abbott Vascular, and GE. Dr. Gibson has received grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals; has received consulting fees from The Medicines Company, AstraZeneca, Eli Lilly, Gilead Sciences, Novo Nordisk, WebMD, UpToDate Cardiovascular Medicine, Amarin Pharma, Amgen, Boehringer Ingelheim, Chiesi, Merck, PharmaMar, Sanofi, Somahlution, Verreseon Corporation, Boston Scientific, Impact Bio, MedImmume, Medtelligence, MicroPort, PERT Consortium, and GE Healthcare; has held equity in nference; has served as chief executive officer of Baim Institute; and has received grant support, paid to Baim Institute, from Bristol-Myers Squibb. Dr. Mehran has received consulting fees from Abbott Vascular, Boston Scientific, Medscape/WebMD, Siemens Medical Solutions, Phillips/Volcano/Spectranetics, Roviant Sciences, Sanofi Italy, Bracco Group, Janssen, and AstraZeneca; has received grant support, paid to her institution, from Bayer, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Osprey Medical, PLC/RenalGuard, and Abbott Vascular; has received grant support and Advisory Board fees, paid to her institution, from Bristol-Myers Squibb; has received fees for serving on a Data and Safety Monitoring Board from Watermark Research Funding; has received advisory fees and lecture fees from Medintelligence (Janssen); and has received lecture fees from Bayer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Patrick W. Serruys, MD, PhD, served as Guest Associate Editor for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

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sponsored the trial, which was supported by an investigator-initiated grant from AstraZeneca. National regulatory agencies and institutional review boards or ethics committees of participating centers approved the trial protocol. An independent data and safety monitoring board provided external oversight to ensure the safety of the trial participants.

STUDY POPULATION. Patients who underwent successful PCI with at least 1 locally approved drug-eluting stent and in whom the treating clinician intended to discharge on a regimen of ticagrelor plus aspirin were eligible to participate. Patients also had to have at least 1 additional clinical feature and 1 angiographic feature associated with a high risk of ischemic or bleeding events (19). The clinical criteria for high risk were age ≥65 years, female sex, troponin-positive acute coronary syndrome, established vascular disease, diabetes mellitus that was being treated with medication, and chronic kidney disease. Angiographic criteria included multivessel coronary artery disease, a total stent length >30 mm, a thrombotic target lesion, a bifurcation lesion treated with 2 stents, an obstructive left main or proximal left anterior descending lesion, and a calcified target lesion treated with atherectomy. Key exclusion criteria included presentation with ST-segment elevation myocardial infarction (MI), cardiogenic shock, ongoing long-term treatment with oral anticoagulants, or contraindication to aspirin or ticagrelor.

Complex PCI was defined according to a modified version of previously published criteria, which have also been utilized in part in other clinical studies (1,20–22). These included PCI with at least 1 of the following characteristics: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion as target lesions (**Central Illustration**).

STUDY PROCEDURES. All enrolled patients received open-label ticagrelor (90 mg twice daily) and enteric-coated aspirin (81 to 100 mg daily) after the index PCI. At the 3-month follow-up visit, patients who remained adherent and had not sustained a major bleeding event (defined as a Bleeding Academic Research Consortium [BARC] type 3b or 5 bleed) or a major ischemic event (stroke, MI, or coronary revascularization) were eligible for randomization to either aspirin or matching placebo with continuation of open-label ticagrelor for an additional 12 months. Follow-up was performed by telephone at 1 month after randomization and in person at 6 and 12 months after randomization. Adherence was assessed with manual pill counts, and nonadherence was classified systematically, as described previously (23). After 12 months of protocol-mandated therapy, patients were switched to a standard-of-care antiplatelet regimen at the discretion of their treating physician, followed by final telephone follow-up 3 months later.

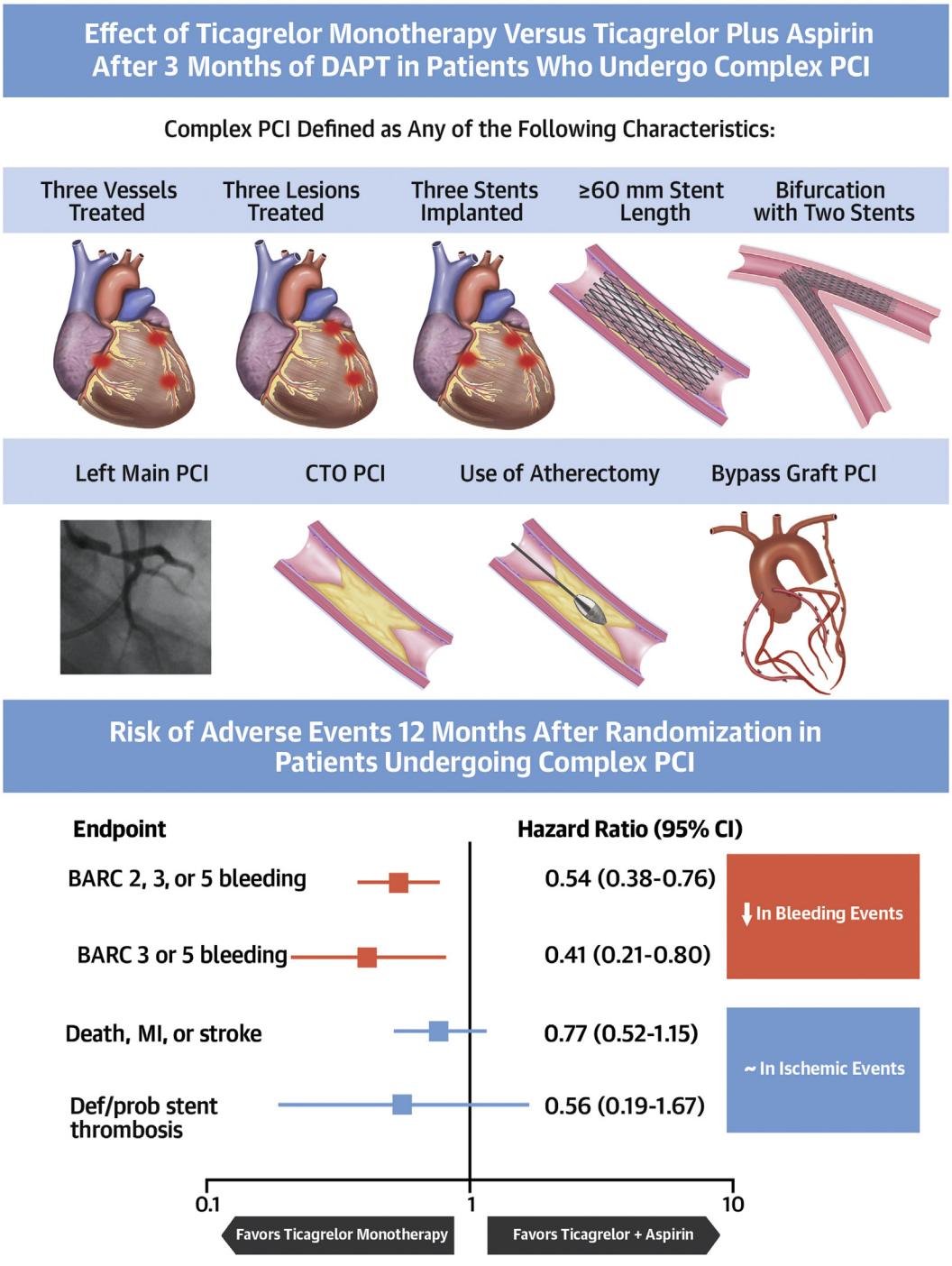
ENDPOINTS. The primary endpoint of the study was BARC type 2, 3, or 5 bleeding (24) between randomization and 1-year follow-up (i.e., 15 months after the index procedure). The key secondary endpoint was death from any cause, nonfatal MI, or nonfatal stroke. Secondary bleeding endpoints included BARC type 3 or 5 bleeding (24); Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding (25); Global Use of Strategies to Open Occluded Arteries moderate, severe, or life-threatening bleeding (26); or major bleeding as defined by the International Society on Thrombosis or Haemostasis (27). Other secondary endpoints included death from cardiovascular causes, MI, ischemic stroke, and definite or probable stent thrombosis. MI was defined according to the Third Universal Definition (28), and revascularization and stent thrombosis were classified according to the Academic Research Consortium (29). All clinical events were adjudicated by an external independent committee, the members of which were unaware of the treatment group assignments.

STATISTICAL ANALYSIS. Analyses were performed in the intention-to-treat population for bleeding endpoints and in the per-protocol population for ischemic endpoints. Baseline characteristics were compared using chi-square or Student's *t*-test for categorical or continuous variables, respectively. The cumulative incidence of the primary and secondary endpoints was estimated by the Kaplan-Meier method. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated with Cox proportional-hazards models. The consistency of the treatment effect of ticagrelor monotherapy versus ticagrelor plus aspirin between the complex and noncomplex PCI subgroups was evaluated with formal interaction testing. All analyses were performed using Stata version 16.0 (College Station, Texas). A p value <0.05 indicates statistical significance.

RESULTS

A total of 9,006 patients were enrolled after PCI, and 7,119 were randomly assigned 3 months later to receive ticagrelor plus placebo or ticagrelor plus aspirin. Of the enrolled and randomized patients, 2,956 (32.8%) and 2,342 (32.9%), respectively, underwent complex PCI at the index hospitalization. Baseline characteristics for patients who underwent complex and noncomplex PCI are reported in **Table 1**. Patients who underwent complex PCI were more commonly enrolled in Asia and had more comorbidities. Regarding baseline angiography (**Table 2**), patients who underwent complex PCI had greater extent and

CENTRAL ILLUSTRATION **Ticagrelor With or Without Aspirin After Complex Percutaneous Coronary Intervention**



Dangas, G. et al. J Am Coll Cardiol. 2020;75(19):2414–24.

Complex PCI was defined as any of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents implanted, atherectomy device use, left main PCI, surgical bypass graft or chronic total occlusion as target lesions. Following 3 months of adherence to DAPT post-PCI and in the absence of major bleeding or ischemic events, this post hoc analysis from the TWILIGHT trial assessing clinical outcomes in patients who underwent complex PCI (n = 2,342) showed that ticagrelor monotherapy, compared with ticagrelor plus aspirin, was associated with a 46% reduction in the incidence of BARC 2, 3, or 5 bleeding over 1 year. There was no significant difference in the 1-year rate of all-cause death, MI, or stroke between the 2 treatment arms. CI = confidence interval; CTO =chronic total occlusion; DAPT = dual antiplatelet therapy; MI = myocardial infarction; PCI = percutaneous coronary intervention.

TABLE 1 Baseline Clinical Characteristics in Patients With Complex and Noncomplex PCI in the Randomized TWILIGHT Trial

	Complex PCI (n = 2,342)	Noncomplex PCI (n = 4,777)	p Value
Age, yrs	66.0 ± 10.4	64.7 ± 10.3	<0.0001
Female	498 (21.3)	1,200 (25.1)	<0.0001
Body mass index, kg/m^2	28.1 ± 5.3	28.8 ± 5.7	<0.0001
Nonwhite race	803 (34.3)	1,393 (29.2)	<0.0001
Enrolling region			<0.0001
Asian	630 (26.9)	1,008 (21.1)	
Europe	796 (34.0)	1,713 (35.9)	
North America	916 (39.1)	2,056 (43.0)	
Hypertension	1,667 (71.2)	3,487 (73.0)	0.10
Hypercholesterolemia	1,362 (58.2)	2,941 (61.6)	0.006
Current smoker	483 (20.6)	1,065 (22.3)	0.11
Diabetes mellitus	866 (37.0)	1,754 (36.7)	0.83
Insulin-treated	254 (29.3)	455 (25.9)	0.07
Chronic kidney disease*	405 (18.1)	740 (16.1)	0.04
Anemia	479 (21.4)	850 (18.5)	0.004
Peripheral artery disease	184 (7.9)	305 (6.4)	0.02
Prior myocardial infarction	672 (28.7)	1,368 (28.6)	0.96
Prior coronary artery bypass grafting	361 (15.4)	349 (7.3)	<0.0001
Prior percutaneous coronary intervention	971 (41.5)	2,027 (42.4)	0.44
Prior major bleeding event	23 (1.0)	40 (0.8)	0.54
Indication for percutaneous coronary intervention			<0.0001
Asymptomatic	162 (6.9)	295 (6.2)	
Stable angina	691 (29.5)	1,355 (28.4)	
Unstable angina	879 (37.6)	1,615 (33.8)	
Non-ST-segment elevation myocardial infarction	609 (26.0)	1,511 (31.6)	

Values are mean ± SD or n (%). *Defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 of body surface area.
PCI = percutaneous coronary intervention.

TABLE 2 Baseline Angiographic Characteristics in Patients Who Underwent Complex and Noncomplex PCI

	Complex PCI (n = 2,342)	Noncomplex PCI (n = 4,777)	p Value
Multivessel coronary artery disease	1,734 (74.0)	2,732 (57.2)	<0.0001
Number of vessels treated	1.6 ± 0.7	1.2 ± 0.4	<0.0001
Vessel treated			
Left main	353 (15.1)	0 (0.0)	<0.0001
Left anterior descending	1,429 (61.0)	2,574 (53.9)	<0.0001
Left circumflex	874 (37.3)	1,423 (29.8)	<0.0001
Right coronary artery	996 (42.5)	1,504 (31.5)	<0.0001
Venous or arterial bypass graft	161 (6.9)	0 (0.0)	<0.0001
Total stent length, mm	59.6 ± 29.4	30.2 ± 13.1	<0.0001
Minimal stent diameter, mm	2.8 ± 0.5	2.9 ± 0.5	<0.0001
Number of lesions treated	2.1 ± 0.9	1.3 ± 0.4	<0.0001
Lesion morphology			
Moderate to severe calcification	506 (21.6)	481 (10.1)	<0.0001
Bifurcation	502 (21.4)	364 (7.6)	<0.0001
Total Occlusion	446 (19.0)	0 (0.0)	<0.0001

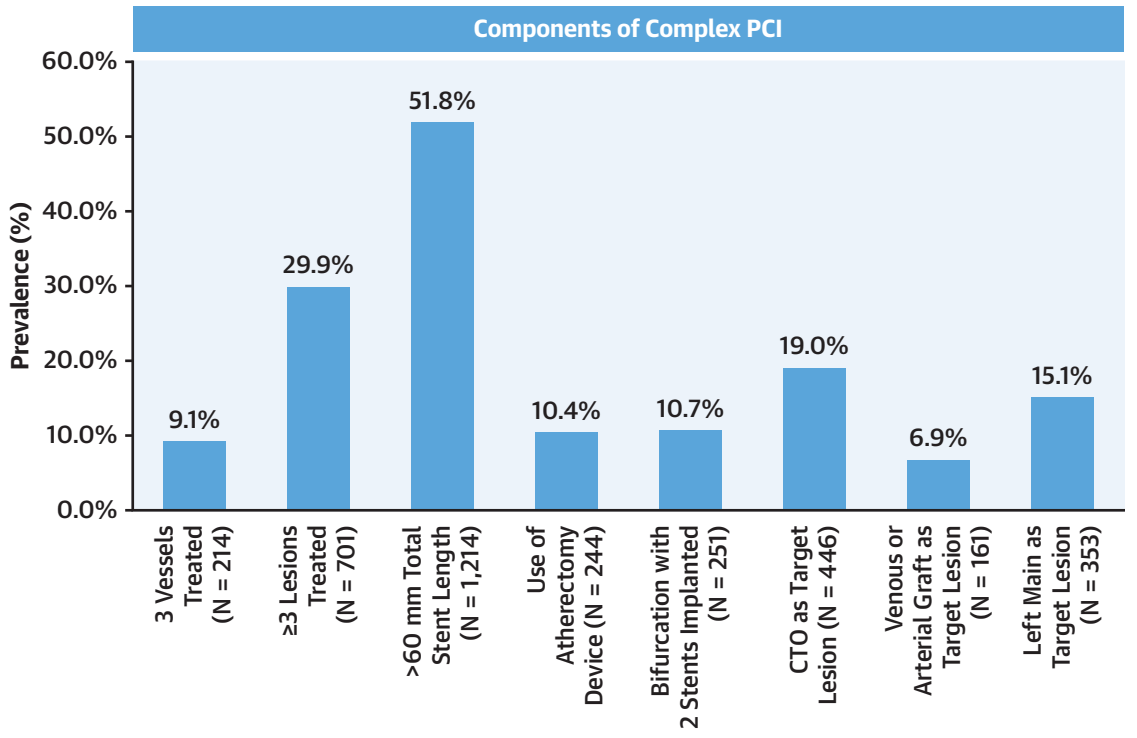
Values are n (%) or mean ± SD.
Abbreviation as in Table 1.

complexity of coronary artery disease. The prevalence of each component of the complex PCI definition is reported in Figure 1. Within the complex PCI cohort, rates of permanent ticagrelor discontinuation at 1 year were 13.0% and 13.6% among those randomized to ticagrelor plus placebo versus ticagrelor plus aspirin, respectively (p = 0.69). Respective results for blinded study drug discontinuation were 18.4% and 18.2% (p = 0.88).

BLEEDING OUTCOMES. Bleeding event rates according to the randomized assignment to ticagrelor plus placebo versus ticagrelor plus aspirin in patients who underwent complex and noncomplex PCI are reported in Table 3. Among patients who underwent complex PCI, ticagrelor plus placebo resulted in lower rates of the primary endpoint of BARC type 2, 3, or 5 bleeding (4.2% vs. 7.7%; absolute risk difference: −3.5%; HR: 0.54; 95% CI: 0.38 to 0.76) (Figure 2A) and BARC type 3 or 5 bleeding (1.1% vs. 2.6%; absolute risk difference: −1.5%; HR: 0.41; 95% CI: 0.21 to 0.80) (Figure 2B) (Central Illustration); the bleeding benefits of ticagrelor monotherapy were consistent across alternative bleeding scales (Table 3). There was no evidence of significant statistical interaction for the treatment effects on bleeding endpoints between the complex PCI and the noncomplex PCI groups (Table 3).

ISCHEMIC OUTCOMES. Ischemic event rates according to randomized treatment assignment in patients who underwent complex and noncomplex PCI are reported in Table 3 and Figure 3. Among patients who underwent complex PCI, there were no significant differences between the ticagrelor plus placebo versus ticagrelor plus aspirin groups in terms of death, MI, or stroke (3.8% vs. 4.9%; absolute risk difference: −1.1%; HR: 0.77; 95% CI: 0.52 to 1.15) and cardiovascular death, MI, or ischemic stroke (3.6% vs. 4.8%; absolute risk difference: −1.2%; HR: 0.75; 95% CI: 0.50 to 1.12). There were no significant differences in all-cause death between groups (0.9% vs. 1.5%; absolute risk difference: −0.6%; HR: 0.59; 95% CI: 0.27 to 1.29). Rates of definite or probable stent thrombosis were 0.4% versus 0.8%, respectively (absolute risk difference: −0.4%; HR: 0.56; 95% CI: 0.19 to 1.67) (Central Illustration). There was no significant statistical interaction for the treatment effects on ischemic endpoints between the complex PCI and the noncomplex PCI groups. The effect of ticagrelor monotherapy versus ticagrelor plus aspirin for the endpoint of death, MI, or stroke was consistent across the components of the complex PCI definition (Figure 4A); results were stratified according to progressive number of complex PCI criteria fulfilled are shown in Figure 4B.

FIGURE 1 Prevalence of the Individual Qualifying Variables Within the Complex PCI Group



The definition of complex percutaneous coronary intervention (PCI) required fulfillment of at least 1 of the following: 3 vessels treated, ≥3 lesions treated, total stent length >60 mm, bifurcation with 2 stents, use of any atherectomy device, left main as target vessel, surgical bypass graft or chronic total occlusion (CTO) as target lesions. This figure shows the distribution of the qualifying characteristics within the complex PCI group (n = 2,342). Total stent length >60 mm was the most common characteristic in complex PCI patients, whereas venous or arterial graft as target lesion was the least common.

TABLE 3 Bleeding and Ischemic Events 1 Year After Randomization According to PCI Complexity and Treatment Group

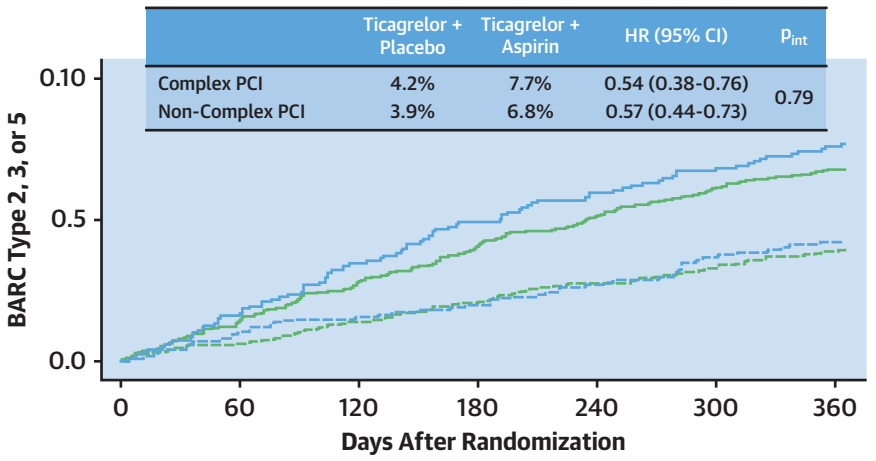
	Complex PCI (n = 2,342)			Noncomplex PCI (n = 4,777)			
	Ticagrelor Plus Placebo (n = 1,158)	Ticagrelor Plus Aspirin (n = 1,184)	Hazard Ratio (95% CI)	Ticagrelor Plus Placebo (n = 2,397)	Ticagrelor Plus Aspirin (n = 2,380)	Hazard Ratio (95% CI)	p Value for Interaction
Bleeding endpoints*							
BARC type 2, 3, or 5	48 (4.2)	90 (7.7)	0.54 (0.38–0.76)	93 (3.9)	160 (6.8)	0.57 (0.44–0.73)	0.79
BARC type 3 or 5	12 (1.1)	30 (2.6)	0.41 (0.21–0.80)	22 (0.9)	39 (1.7)	0.56 (0.33–0.94)	0.47
TIMI minor or major	48 (4.2)	90 (7.7)	0.54 (0.38–0.76)	93 (3.9)	160 (6.8)	0.57 (0.44–0.73)	0.79
GUSTO moderate or severe	10 (0.9)	20 (1.7)	0.51 (0.24–1.09)	16 (0.7)	29 (1.2)	0.55 (0.30–1.01)	0.89
ISTH major	13 (1.1)	32 (2.7)	0.41 (0.22–0.79)	26 (1.1)	40 (1.7)	0.64 (0.39–1.05)	0.29
Ischemic endpoints†							
Death, MI, or stroke	43 (3.8)	56 (4.9)	0.77 (0.52–1.15)	92 (3.9)	81 (3.5)	1.13 (0.84–1.53)	0.13
Cardiovascular death, MI, or ischemic stroke	41 (3.6)	55 (4.8)	0.75 (0.50–1.12)	85 (3.6)	75 (3.2)	1.13 (0.83–1.54)	0.12
All-cause death	10 (0.9)	17 (1.5)	0.59 (0.27–1.29)	24 (1.0)	28 (1.2)	0.85 (0.49–1.47)	0.45
Cardiovascular death	9 (0.8)	17 (1.5)	0.53 (0.24–1.20)	17 (0.7)	20 (0.9)	0.84 (0.44–1.61)	0.39
Myocardial infarction	33 (2.9)	40 (3.5)	0.83 (0.52–1.32)	62 (2.6)	55 (2.4)	1.12 (0.78–1.61)	0.32
Ischemic stroke‡	1 (0.1)	2 (0.2)	0.50 (0.05–5.56)	15 (0.6)	6 (0.3)	2.49 (0.97–6.42)	0.23
Def/prob stent thrombosis	5 (0.4)	9 (0.8)	0.56 (0.19–1.67)	9 (0.4)	10 (0.4)	0.89 (0.36–2.20)	0.52
Definite stent thrombosis	5 (0.4)	9 (0.8)	0.56 (0.19–1.67)	8 (0.3)	9 (0.4)	0.88 (0.34–2.29)	0.54

Events reported as n (Kaplan-Meier estimate), unless otherwise indicated. *Bleeding outcomes analyzed by intention-to-treat. †Ischemic outcomes analyzed per-protocol. ‡Indicates significant differences between complex and noncomplex PCI patients.

BARC = Bleeding Academic Research Consortium; Def/prob = definite/probable; GUSTO = Global Strategies for Opening Occluded Coronary Arteries; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

FIGURE 2 Rates of BARC 2, 3, or 5 Bleeding and BARC 3 or 5 Bleeding at 12 Months After Randomization

A

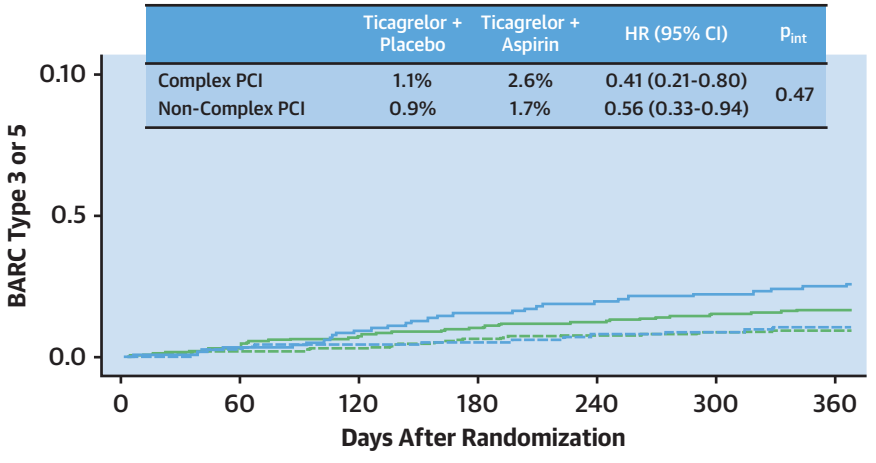


Number at Risk

Ticagrelor + Aspirin - Non-Complex	2,380	2,331	2,291	2,256	2,216	2,184	2,154
Ticagrelor + Placebo - Non-Complex	2,397	2,365	2,340	2,314	2,282	2,263	2,244
Ticagrelor + Aspirin - Complex	1,184	1,157	1,130	1,107	1,090	1,077	1,061
Ticagrelor + Placebo - Complex	1,158	1,133	1,123	1,115	1,098	1,086	1,077

Ticagrelor + Aspirin – Complex PCI
Ticagrelor + Aspirin – Non-Complex PCI
Ticagrelor + Placebo – Complex PCI
Ticagrelor + Placebo – Non-Complex PCI

B



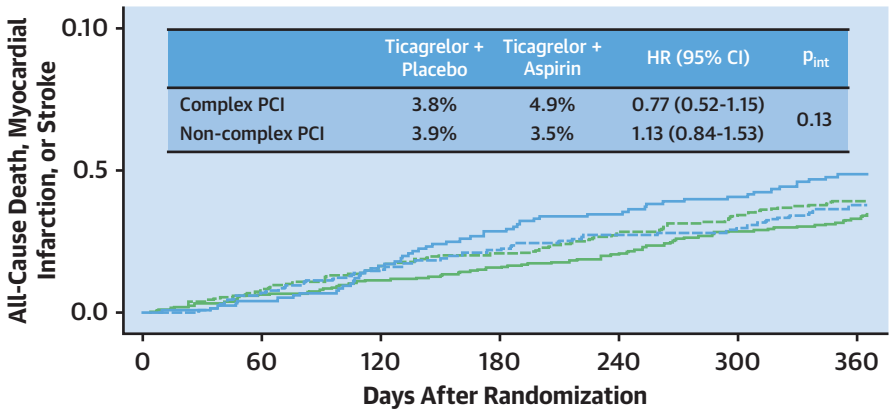
Number at Risk

Ticagrelor + Aspirin - Non-Complex	2,380	2,353	2,338	2,328	2,307	2,290	2,273
Ticagrelor + Placebo - Non-Complex	2,397	2,376	2,366	2,347	2,328	2,320	2,313
Ticagrelor + Aspirin - Complex	1,184	1,172	1,159	1,146	1,136	1,129	1,120
Ticagrelor + Placebo - Complex	1,158	1,140	1,135	1,131	1,118	1,116	1,110

Ticagrelor + Aspirin – Complex PCI
Ticagrelor + Aspirin – Non-Complex PCI
Ticagrelor + Placebo – Complex PCI
Ticagrelor + Placebo – Non-Complex PCI

Kaplan-Meier estimates and HRs for **(A)** BARC 2, 3, or 5 bleeding and **(B)** BARC 3 or 5 bleeding at 12 months after randomization (intention-to-treat population) comparing ticagrelor plus placebo versus ticagrelor plus aspirin in patients who underwent complex and noncomplex PCI. The interaction p values show no evidence of significant statistical interaction for the treatment effects on bleeding endpoints between the complex PCI and the noncomplex PCI groups. BARC = Bleeding Academic Research Consortium; CI = confidence interval; HR = hazard ratio; PCI = percutaneous coronary intervention.

FIGURE 3 Rates of All-Cause Death, Myocardial Infarction, or Stroke at 12 Months After Randomization



Number at Risk

Ticagrelor + Aspirin - Non-Complex	2,356	2,327	2,314	2,300	2,275	2,256	2,238
Ticagrelor + Placebo - Non-Complex	2,372	2,342	2,321	2,302	2,276	2,260	2,246
Ticagrelor + Aspirin - Complex	1,159	1,147	1,132	1,118	1,107	1,099	1,085
Ticagrelor + Placebo - Complex	1,152	1,133	1,123	1,114	1,099	1,096	1,084

Ticagrelor + Aspirin – Complex PCI
Ticagrelor + Placebo – Complex PCI
Ticagrelor + Aspirin – Non-Complex PCI
Ticagrelor + Placebo – Non-Complex PCI

Kaplan-Meier estimates and HRs for all-cause death, myocardial infarction, or stroke at 12 months after randomization (per-protocol population) comparing ticagrelor plus placebo versus ticagrelor plus aspirin in patients who underwent complex and noncomplex PCI. The interaction p values show no evidence of significant statistical interaction for the treatment effects on ischemic endpoints between the complex PCI and the noncomplex PCI groups. Abbreviations as in Figure 2.

DISCUSSION

The main findings of the present analysis from the international, multicenter, placebo-controlled TWILIGHT trial, in which we examined the effect of aspirin withdrawal on a background of potent $P2Y_{12}$-receptor inhibition with ticagrelor after 3 months of DAPT according to PCI complexity, are as follows: 1) ticagrelor monotherapy resulted in significantly lower major bleeding complications compared with ticagrelor plus aspirin, which was consistent irrespective of PCI complexity and bleeding definition; and 2) ticagrelor monotherapy was not associated with increased risk of ischemic events compared with ticagrelor plus aspirin among patients who underwent complex PCI; moreover, there were no signals of increased risk of ischemic events, including stent thrombosis, using ticagrelor monotherapy among the individual high-risk features of the complex PCI definition.

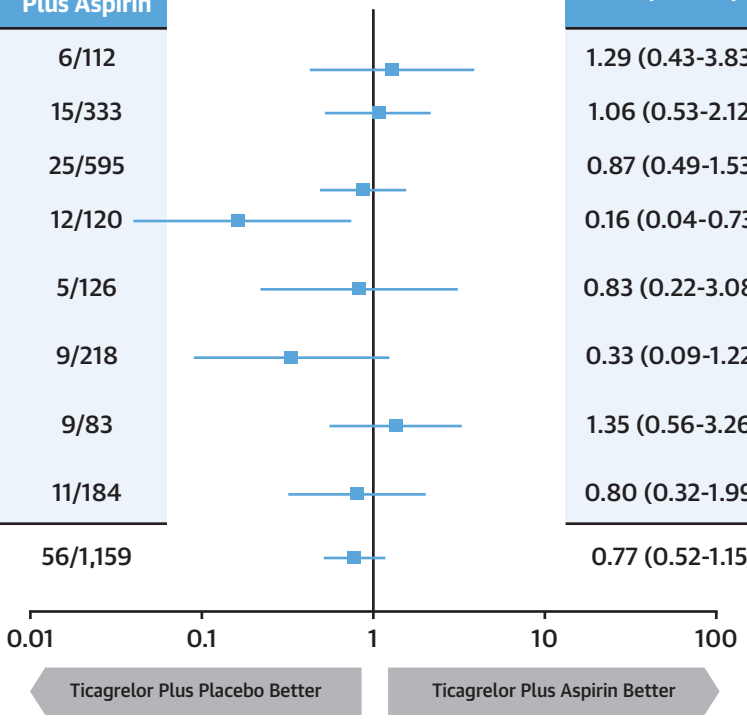
The TWILIGHT trial examined the hypothesis whether, after an initial 3-month course of DAPT with aspirin plus the potent $P2Y_{12}$-receptor inhibitor ticagrelor, withdrawal of aspirin could be associated with a reduction in bleeding complications without increasing ischemic risk (18). By design, the TWILIGHT trial enrolled high-risk patients, based on both clinical and angiographic criteria. Over the last few years, PCI complexity has been emphasized as an ischemic risk factor for clinical decision-making regarding DAPT duration (1,7,9,13,20). In particular, in a patient-level pooled analysis of 6 randomized controlled trials investigating different DAPT durations after PCI in over 9,000 patients, use of ≥12 months of DAPT (with aspirin and clopidogrel) was associated with significantly lower risk of major adverse cardiac events compared with 3 or 6 months of DAPT followed by aspirin alone among patients who underwent complex PCI with mostly new-generation drug-eluting stents (1). The benefit of prolonged DAPT in these patients was not influenced by the type of clinical presentation and increased with greater procedural complexity. However, the anti-ischemic benefit of prolonging DAPT was counterbalanced by increased risk for major bleeding (1).

In the current study, we examined the effect of ticagrelor monotherapy versus ticagrelor plus aspirin in patients with complex PCI. Patients who undergo complex PCI have more extensive coronary artery disease and higher burden of comorbidities, which

FIGURE 4 Risk of All-Cause Death, MI, or Stroke at 12 Months After Randomization

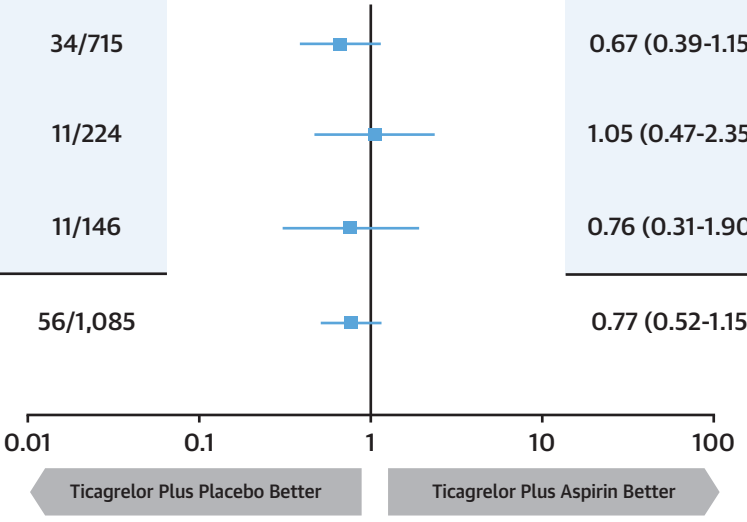
A

	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin	HR (95% CI)
3 vessels treated	7/101	6/112	1.29 (0.43-3.83)
≥3 lesions treated	17/359	15/333	1.06 (0.53-2.12)
>60 mm total stent length	22/609	25/595	0.87 (0.49-1.53)
Use of atherectomy device	2/119	12/120	0.16 (0.04-0.73)
Bifurcation with 2 stents implanted	4/123	5/126	0.83 (0.22-3.08)
CTO as target lesion	3/220	9/218	0.33 (0.09-1.22)
Venous or arterial graft as target lesion	11/76	9/83	1.35 (0.56-3.26)
Left main as target lesion	8/165	11/184	0.80 (0.32-1.99)
Overall	43/1,152	56/1,159	0.77 (0.52-1.15)



B

	Ticagrelor Plus Placebo	Ticagrelor Plus Aspirin	HR (95% CI)
1 Complex PCI criterion	22/694	34/715	0.67 (0.39-1.15)
2 Complex PCI criteria	13/252	11/224	1.05 (0.47-2.35)
≥3 Complex PCI criteria	8/138	11/146	0.76 (0.31-1.90)
Overall	43/1,084	56/1,085	0.77 (0.52-1.15)



Risk **(A)** across the individual components of the complex PCI definition and **(B)** stratified by number of complex PCI criteria fulfilled. The effect of ticagrelor monotherapy versus ticagrelor plus aspirin for the endpoint of death, MI, or stroke was consistent across the components of the complex PCI definition as well as when stratified according to progressive number of complex PCI criteria fulfilled. Abbreviations as in Figure 2.

are associated with increased ischemic and bleeding risk (11,30). Implementation of antithrombotic strategies associated with a favorable benefit-risk ratio in this patient population is important. In the present study, we extended the previously introduced definition of complex PCI (1) to also include other procedural features, available in the TWILIGHT database, that have been shown to be associated with increased ischemic risk and are commonly performed in real-world practice (12,31–33). Consistent with the results of the main TWILIGHT trial, a regimen of ticagrelor monotherapy was associated with a significant and sustained reduction in clinically relevant and major bleeding, irrespective of PCI complexity. This effect was consistent across alternative bleeding definitions.

In terms of ischemic endpoints, we observed that among patients who underwent complex PCI, a regimen of ticagrelor monotherapy (after 3 months of DAPT with ticagrelor plus aspirin) was not associated with increased risk compared with continuing ticagrelor plus aspirin; the CIs of the composite ischemic endpoint included a modest 15% possible relative risk increase with use of placebo instead of aspirin; there was no signal of excess stent thrombosis. Moreover, there were no significant differences between ticagrelor monotherapy and ticagrelor plus aspirin for each of the components of the implemented complex PCI definition. These findings provide reassurance regarding the anti-ischemic efficacy of ticagrelor, even in the absence of aspirin, among high-risk lesion subsets. Notably, the TWILIGHT pharmacodynamic substudy indicated the 2 randomized treatment regimens had similar overall thrombus formation under dynamic flow conditions in an ex vivo model, as well as similar thrombosis biomarkers except for the COX-1–mediated pathways, which were more active in the absence of aspirin (34).

Our findings are in line with a recent secondary analysis from a large randomized trial that examined the efficacy and safety of an experimental antiplatelet strategy consisting of 23 months of ticagrelor monotherapy following 1 month of DAPT versus a standard antiplatelet strategy consisting of 12 months of aspirin monotherapy following 12 months of DAPT according to PCI complexity using the previously mentioned definition (1,13,20). The experimental strategy of adopting ticagrelor monotherapy reduced the risk of death or MI and the composite of all-cause mortality, any stroke, any MI, or any revascularization in patients who underwent complex PCI. Differences between that randomized trial and the TWILIGHT trial are the larger sample size, lack of placebo blinding, and lack of clinical event committee adjudication in the former.

STUDY LIMITATIONS. First, as this was a post hoc analysis, randomization was not stratified by complex PCI status and we did not account for multiplicity thereby increasing the chance for a type 1 error. Therefore, the current findings should be considered hypothesis-generating. Second, the complex PCI and the noncomplex PCI groups were not individually powered to draw definite conclusions on the effect of a regimen of ticagrelor monotherapy on the bleeding and ischemic endpoints. However, the magnitude and direction of the effect were largely consistent with the overall trial findings. Third, these results are not generalizable to all patients who undergo PCI due to the inclusion and exclusion criteria of our trial. Finally, the observed treatment effects are applicable only to patients who tolerated an initial 3 months of DAPT with ticagrelor plus aspirin without any major adverse events. Whether these findings within a complex PCI cohort are generalizable to a regimen of clopidogrel or prasugrel monotherapy remains unknown.

CONCLUSIONS

Among patients who underwent complex PCI as defined by a combination of high-risk angiographic and procedural features, a regimen of ticagrelor monotherapy (after an initial 3 months of DAPT with ticagrelor plus aspirin) was associated with significantly lower clinically relevant bleeding without increasing the risk of ischemic events compared with continuing DAPT. This effect was consistent across the individual components of the complex PCI definition.

ADDRESS FOR CORRESPONDENCE: Dr. Roxana Mehran, Center for Interventional Cardiovascular Research and Clinical Trials, The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1030, New York, New York 10029-6574. E-mail: roxana.mehran@mountsinai.org. Twitter: @Drroxmehran.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Among patients undergoing anatomically complex PCI, initiation of ticagrelor monotherapy after 3 months of DAPT with ticagrelor plus aspirin resulted in less major bleeding without increasing ischemic risk compared to continuing DAPT.

TRANSLATIONAL OUTLOOK: Further research is needed to establish the optimum type and duration of antithrombotic therapy for patients undergoing complex PCI.

REFERENCES

1. Giustino G, Chieffo A, Palmerini T, et al. Efficacy and safety of dual antiplatelet therapy after Complex PCI. J Am Coll Cardiol 2016;68:1851–64.

2. Colombo A, Chieffo A, Frasheri A, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. J Am Coll Cardiol 2014;64:2086–97.

3. Mehran R, Giustino G, Baber U. DAPT duration after DES: what is the "mandatory" duration? J Am Coll Cardiol 2015;65:1103–6.

4. Piccolo R, Giustino G, Mehran R, Windecker S. Stable coronary artery disease: revascularisation and invasive strategies. Lancet 2015;386:702–13.

5. Capodanno D, Alfonso F, Levine GN, Valgimigli M, Angiolillo DJ. ACC/AHA versus ESC guidelines on dual antiplatelet therapy: JACC guideline comparison. J Am Coll Cardiol 2018;72:2915–31.

6. Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155–66.

7. Giustino G, Baber U, Aquino M, et al. Safety and efficacy of new-generation drug-eluting stents in women undergoing complex percutaneous coronary artery revascularization: from the WIN-DES Collaborative patient-level pooled analysis. J Am Coll Cardiol Intv 2016;9:674–84.

8. Chen H, Power D, Giustino G. Optimal duration of dual antiplatelet therapy after PCI: integrating procedural complexity, bleeding risk and the acuteness of clinical presentation. Expert Rev Cardiovasc Ther 2018;16:735–48.

9. Genereux P, Giustino G, Redfors B, et al. Impact of percutaneous coronary intervention extent, complexity and platelet reactivity on outcomes after drug-eluting stent implantation. Int J Cardiol 2018;268:61–7.

10. Giustino G, Mehran R. Navigating the complexity of percutaneous coronary intervention in patients at high risk for bleeding. EuroIntervention 2018;14:e383–5.

11. Kirtane AJ, Doshi D, Leon MB, et al. Treatment of higher-risk patients with an indication for revascularization: evolution within the field of contemporary percutaneous coronary intervention. Circulation 2016;134:422–31.

12. Giustino G, Mastoris I, Baber U, et al. Correlates and impact of coronary artery calcifications in women undergoing percutaneous coronary intervention with drug-eluting stents: from the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration. J Am Coll Cardiol Intv 2016;9:1890–901.

13. Serruys PW, Takahashi K, Chichareon P, et al. Impact of long-term ticagrelor monotherapy following 1-month dual antiplatelet therapy in patients who underwent complex percutaneous coronary intervention: insights from the Global Leaders trial. Eur Heart J 2019;40:2595–604.

14. Genereux P, Giustino G, Witzenbichler B, et al. Incidence, predictors, and impact of post-discharge bleeding after percutaneous coronary intervention. J Am Coll Cardiol 2015;66:1036–45.

15. Baber U, Dangas G, Chandrasekhar J, et al. Time-dependent associations between actionable bleeding, coronary thrombotic events, and mortality following percutaneous coronary intervention: results from the PARIS Registry. J Am Coll Cardiol Intv 2016;9:1349–57.

16. Baber U, Mehran R, Giustino G, et al. Coronary thrombosis and major bleeding after PCI with drug-eluting stents: risk scores from PARIS. J Am Coll Cardiol 2016;67:2224–34.

17. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. Nat Rev Cardiol 2018;15:480–96.

18. Mehran R, Baber U, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032–42.

19. Baber U, Dangas G, Cohen DJ, et al. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: rationale and design of the TWILIGHT study. Am Heart J 2016;182:125–34.

20. Valgimigli M, Bueno H, Byrne RA, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. Eur J Cardiothorac Surg 2018;53:34–78.

21. Lipiecki J, Brunel P, Morice M-C, et al. Biolimus A9 polymer-free coated stents in high bleeding risk patients undergoing complex PCI: evidence from the LEADERS FREE randomised clinical trial. EuroIntervention 2018;14:e418–25.

22. Azzalini L, Poletti E, Lombardo F, et al. Risk of contrast-induced nephropathy in patients undergoing complex percutaneous coronary intervention. Int J Cardiol 2019;290:59–63.

23. Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;382:1714–22.

24. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

25. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI), phase II trial. Ann Intern Med 1991;115:256–65.

26. Investigators GUSTO. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.

27. Kaatz S, Ahmad D, Spyropoulos A, Schulman S, Subcommittee on Control of Anticoagulation. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 2015;13:2119–26.

28. Bax JJ, Baumgartner H, Ceconi C, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012;60:1581–98.

29. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

30. Baber U. Defining PCI complexity in the contemporary DES era: clarity or confusion? Int J Cardiol 2018;268:94–5.

31. Genereux P, Redfors B, Witzenbichler B, et al. Angiographic predictors of 2-year stent thrombosis in patients receiving drug-eluting stents: insights from the ADAPT-DES study. Catheter Cardiovasc Interv 2017;89:26–35.

32. Redfors B, Genereux P, Witzenbichler B, et al. Percutaneous coronary intervention of saphenous vein graft. Circ Cardiovasc Interv 2017;10:e004953.

33. Genereux P, Madhavan MV, Mintz GS, et al. Ischemic outcomes after coronary intervention of calcified vessels in acute coronary syndromes. Pooled analysis from the HORIZONS-AMI (Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction) and ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) TRIALS. J Am Coll Cardiol 2014;63:1845–54.

34. Baber U, Zafar MU, Dangas G, et al. Ticagrelor with or without aspirin after PCI: the TWILIGHT platelet substudy. J Am Coll Cardiol 2020;75:578–86.

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