Ticagrelor With Aspirin or Alone After Complex PCI: The TWILIGHT-COMPLEX Analysis

Brief Title: Ticagrelor Monotherapy After Complex PCI: The TWILIGHT-COMPLEX Analysis

George Dangas, MD, PhD[1], Usman Baber, MD, MS[1], Samin Sharma, MD[1], Gennaro Giustino, MD[1], Shamir Mehta, MD, MSc[2], David Cohen, MD, MSc[3], Dominick Angiolillo, MD, PhD[4], Samantha Sartori, PhD[1], Rishi Chandiramani, MD[1], Carlo Briguori, MD, PhD[5], Dariusz Dudek, MD, PhD[6,7], Javier Escaned, MD, PhD[8], Kurt Huber, MD[9], Timothy Collier, MSc[10], Ran Kornowski, MD[11], Vijay Kunadian, MBBS, MD[12], Upendra Kaul, MD[13], Keith Oldroyd, MBChB, MD (Hons)[14], Gennaro Sardella, MD[15], Richard Shlofmitz, MD[16], Bernhard Witzenbichler, MD[17], Han Ya-Ling, MD, PhD[18], Stuart Pocock, PhD[10], C. Michael Gibson, MD[19], Roxana Mehran, MD[1]

1. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, United States
2. Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
3. Kansas City, Missouri, United States
4. Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, United States
5. Mediterranea Cardiocentro, Naples, Italy
6. Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland
7. Maria Cecilia Hospital, GVM Care & Research, Cotignola (RA), Italy
8. Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain
9. 3rd Department of Medicine, Cardiology and Intensive Care Medicine, Wilhelminen Hospital, and Sigmund Freud University, Medical Faculty, Vienna, Austria
10. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom
11. Cardiology Department, Rabin Medical Center, Petach Tikva, Israel
12. 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
13. Batra Hospital and Medical Research Center, New Delhi, India
14. West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, United Kingdom
15. Department of Cardiology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy
16. St. Francis Hospital, Roslyn, New York, United States
17. Department of Cardiology and Pneumology, Helios Amper-Klinikum, Dachau, Germany
18. Department of Cardiology, General Hospital of Shenyang Military Region, Shenyang, Liaoning, China
19. Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States

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Corresponding author:
Roxana Mehran, MD
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
Tel: +1 (212) 659-9649; Fax: +1 (646) 537-8547

Email: roxana.mehran@mountsinai.org
Twitter: @Drroxmehran

Tweet: “Ticagrelor monotherapy reduces bleeding vs. ticagrelor plus aspirin, without increasing the risk of ischemic events in patients undergoing complex PCI”

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. To evaluate the effect of ticagrelor monotherapy versus ticagrelor plus aspirin in patients undergoing complex PCI from the randomized, double-blind, placebo-controlled TWILIGHT trial.

Methods. In the TWILIGHT trial, after 3 months of ticagrelor plus aspirin, event-free 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 BARC type 2, 3 or 5 bleeding (4.2% vs. 7.7%; hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0.38-0.76). BARC type 3 or 5 bleeding was also significantly reduced (1.1% vs. 2.6%; HR: 0.41; 95% CI: 0.21-0.80). There were no significant between-group differences in death, myocardial infarction or stroke (3.8% vs. 4.9%; HR: 0.77; 95% CI: 0.52-1.15), 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.

Clinical trial: (ClinicalTrials.gov Identifier: NCT02270242)

CONDENSED ABSTRACT: We conducted a post-hoc analysis from the large, randomized, double-blind, placebo-controlled TWILIGHT trial, examining the effect of ticagrelor monotherapy versus ticagrelor plus aspirin among patients who underwent complex percutaneous coronary intervention and initially completed 3 months of ticagrelor plus aspirin. Compared to continuing ticagrelor plus aspirin, ticagrelor plus placebo was associated with significantly lower rates of BARC type 2, 3 or 5 bleeding (4.2% vs. 7.7%; hazard ratio [HR]: 0.54; 95% confidence interval [CI]: 0.38-0.76). There were no significant differences between groups in death, myocardial infarction or stroke (3.8% vs. 4.9%; HR: 0.77; 95% CI: 0.52-1.15), nor in stent thrombosis.

Key words: Complex PCI; ticagrelor monotherapy; dual antiplatelet therapy; aspirin; bleeding

LIST OF ABBREVIATIONS

BARC = Bleeding Academic Research Consortium
DAPT = Dual Antiplatelet Therapy
DES = Drug-Eluting Stent
GUSTO = Global Use of Strategies to Open Occluded Arteries
ISTH = International Society of Thrombosis or Haemostasis
MI = Myocardial Infarction

PCI = Percutaneous Coronary Intervention
TIMI = Thrombolysis in Myocardial Infarction

INTRODUCTION

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 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 healthcare 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.

A strategy of withdrawing aspirin and maintaining $P2Y_{12}$ inhibitor monotherapy after a brief period of DAPT (1-3 months) has emerged 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. We therefore performed a post-hoc analysis of the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial in order 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.

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 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 one locally approved drug-eluting stent (DES) 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 one additional clinical feature and one 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 two 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, 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 one 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.

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, myocardial infarction, 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 non-adherence 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 myocardial infarction, 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 (GUSTO) moderate, severe, or life-threatening bleeding (26); or major bleeding as defined by the International Society on Thrombosis or Haemostasis (ISTH) (27). Other secondary endpoints included death from cardiovascular causes, myocardial infarction,

ischemic stroke, and definite or probable stent thrombosis. Myocardial infarction 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 (HR) and 95% confidence intervals were generated with Cox proportional-hazards models. The consistency of the treatment effect of ticagrelor monotherapy versus ticagrelor plus aspirin between the complex and non-complex 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%) patients respectively underwent complex PCI at the index hospitalization. Baseline characteristics for patients who underwent complex and non-complex 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 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 one 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%, respectively (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 non-complex 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: 0.38-0.76) (**Figure 2A**) and BARC type 3 or 5 bleeding (1.1% vs. 2.6%; absolute risk difference -1.5%; HR: 0.41; 95% CI: 0.21-0.80) (**Figure 2B**); 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 non-complex PCI groups **(Table 3)**.

Ischemic Outcomes

Ischemic event rates according to randomized treatment assignment in patients who underwent complex and non-complex 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: 0.52-1.15) and cardiovascular death, MI or ischemic stroke (3.6% vs. 4.8%; absolute risk difference -1.2%; HR: 0.75; 95% CI: 0.50-1.12).

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: 0.27-1.29). Rates of definite or probable stent thrombosis were 0.4% vs. 0.8%, respectively (absolute risk difference -0.4%; HR: 0.56; 95% CI: 0.19-1.67). There was no significant statistical interaction for the treatment effects on ischemic endpoints between the complex PCI and the non-complex 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 stratified according to progressive number of complex PCI criteria fulfilled are shown in **Figure 4B**.

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: (i) ticagrelor monotherapy resulted in significantly lower major bleeding complications compared with ticagrelor plus aspirin, which was consistent irrespective of PCI complexity and bleeding definition; (ii) ticagrelor monotherapy was not associated with increased risk of ischemic events compared to 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 DES (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 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 bleeding, including major and life-threatening 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 initial months of DAPT with ticagrelor plus aspirin) was not associated with increased risk compared to continuing ticagrelor plus aspirin; the confidence intervals of the composite ischemic endpoint excluded a 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 absence of aspirin, among high-risk lesion subsets. Notably, the TWILIGHT pharmacodynamic substudy indicated the two 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 the GLOBAL-LEADERS 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 the GLOBAL-LEADERS trial and the TWILIGHT trial are the larger sample size, lack of placebo blinding and lack of clinical event committee adjudication in the former.

The present study has several 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 non-complex 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 to continuing DAPT. This effect was consistent across the individual components of the complex PCI definition.

CLINICAL PERSPECTIVES

Competency in Medical Knowledge:

- Patients who undergo complex PCI are at high risk of ischemic events.
- Among patients who undergo complex PCI and after 3 months of dual antiplatelet therapy with ticagrelor plus aspirin, continuation of ticagrelor monotherapy resulted in lower rates of major bleeding complications without increasing ischemic risk compared to ticagrelor plus aspirin.

Competency in Patient Care:

- In patients undergoing PCI, after a short period of dual antiplatelet therapy with ticagrelor and aspirin, a regimen of ticagrelor monotherapy could be considered to lower the risk of bleeding complications irrespective of the complexity of PCI.

Translational Outlook:

- Further research is needed to establish optimal antithrombotic strategies with favorable risk-benefit trade-off between bleeding and ischemic complications among patients who undergo complex PCI.

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Figure Legends

Figure 1. Prevalence of the individual qualifying variables within the complex PCI group. The definition of complex PCI required fulfillment of at least one 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 as target lesions. This figure shows the distribution of the qualifying characteristics within the complex PCI group (N=2,342). Total stent length >60mm was the most common characteristic in complex PCI patients while venous or arterial graft as target lesion was the least common.

Figure 2. Rates of (A) BARC 2, 3 or 5 bleeding and (B) BARC 3 or 5 bleeding at 12 months after randomization. Kaplan–Meier estimates and HRs for BARC 2, 3 or 5 bleeding and 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 non-complex 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 non-complex 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. 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 non-complex 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 non-complex PCI groups. CI = Confidence Interval; HR = Hazard Ratio; PCI = Percutaneous Coronary Intervention.

Figure 4. Risk of all-cause death, MI or stroke at 12 months after randomization (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. CI = Confidence Interval; CTO = chronic total occlusion; HR = Hazard Ratio; PCI = Percutaneous Coronary Intervention.

Central Illustration. Ticagrelor with or without aspirin after complex PCI. 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, as compared with ticagrelor plus aspirin, was associated with a 46% reduction in the incidence of BARC 2, 3 or 5 bleeding over one year. There was no significant difference in the one-year rate of all-cause death, MI or stroke between the two treatment arms. BARC = Bleeding Academic Research Consortium; CI = confidence interval; CTO = chronic total occlusion; DAPT = dual antiplatelet therapy; Def/prob = definite/probable; MI = myocardial infarction; PCI = percutaneous coronary intervention

Table 1. Baseline Clinical Characteristics in Patients With Complex and Non-Complex PCI in the randomized TWILIGHT trial.

	Complex PCI (2,342)	**Non-Complex PCI (4,777)**	**p-value**
Age, years	66.0 ± 10.4	64.7 ± 10.3	<0.0001
Female sex	498 (21.3%)	1200 (25.1%)	<0.0001
Body mass index, kg/m^2	28.1 ± 5.3	28.8 ± 5.7	<0.0001
Non-white race	803 (34.3%)	1393 (29.2%)	<0.0001
Enrolling region			<0.0001
Asian	630 (26.9%)	1008 (21.1%)	
Europe	796 (34.0%)	1713 (35.9%)	
North America	916 (39.1%)	2056 (43.0%)	
Hypertension	1667 (71.2%)	3487 (73.0%)	0.10
Hypercholesterolemia	1362 (58.2%)	2941 (61.6%)	0.006
Current smoker	483 (20.6%)	1065 (22.3%)	0.11
Diabetes mellitus	866 (37.0%)	1754 (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%)	1368 (28.6%)	0.96
Prior coronary artery bypass grafting	361 (15.4%)	349 (7.3%)	<0.0001
Prior percutaneous coronary intervention	971 (41.5%)	2027 (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%)	1355 (28.4%)	
Unstable angina	879 (37.6%)	1615 (33.8%)	
Non-ST-elevation myocardial infarction	609 (26.0%)	1511 (31.6%)	

Results reported as n (%) or mean ± standard deviation. *defined as an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area.

Table 2. Baseline Angiographic Characteristics in Patients Who Underwent Complex and Non-Complex PCI.

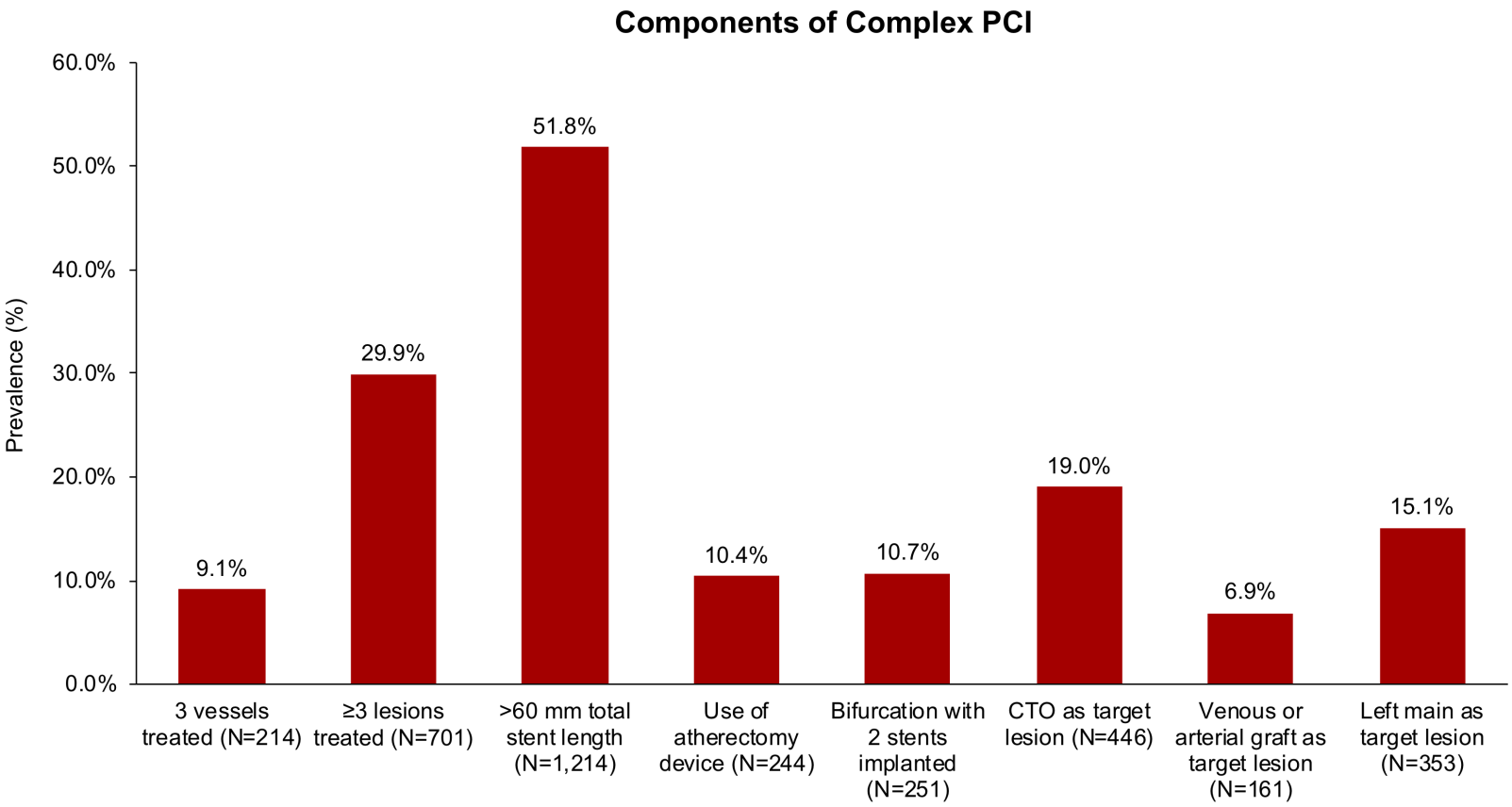
	Complex PCI (2,342)	**Non-Complex PCI (4,777)**	**p-value**
Multivessel coronary artery disease	1734 (74.0%)	2732 (57.2%)	<0.0001
Number of vessels treated	1.6 ± 0.7	1.2 ± 0.4	<0.0001
Vessel treated			
Left main	353 (15.1%)	0 (0.0%)	<0.0001
Left anterior descending	1429 (61.0%)	2574 (53.9%)	<0.0001
Left circumflex	874 (37.3%)	1423 (29.8%)	<0.0001
Right coronary artery	996 (42.5%)	1504 (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

Results reported as n (%) or mean ± standard deviation.

Table 3. Bleeding and Ischemic Events 1 Year after Randomization according to PCI complexity and treatment group.

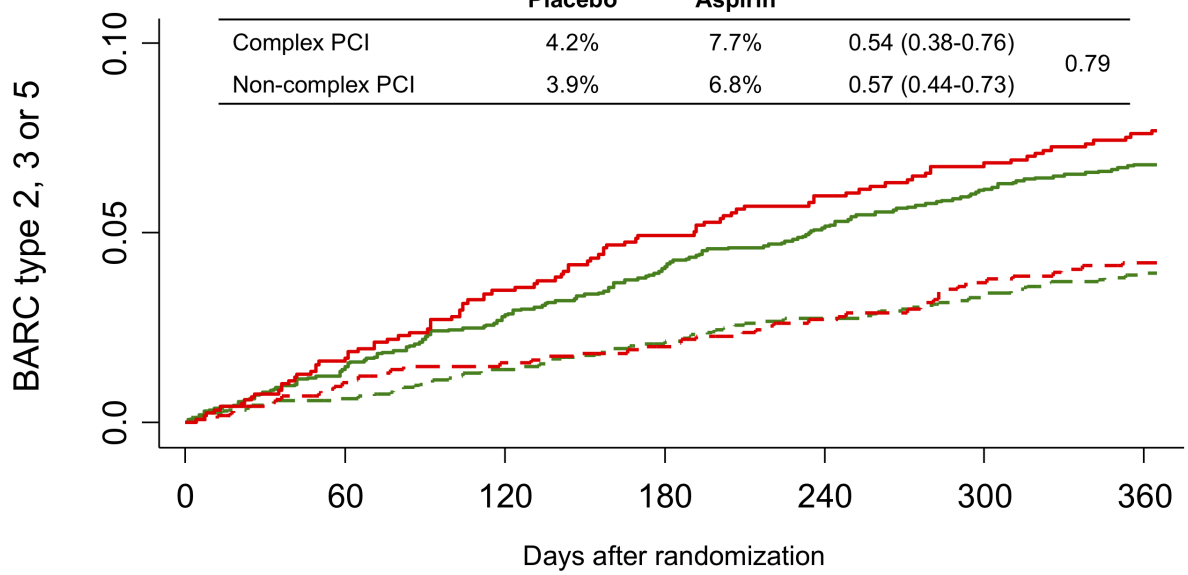
	Complex PCI (N=2,342)			Non-Complex PCI (N=4,777)			
	Ticagrelor plus Placebo (N=1,158)	Ticagrelor plus Aspirin (N=1,184)	Hazard Ratio (95% CI)	Ticagrelor plus Placebo (N=2,397)	Ticagrelor plus Aspirin (N=2,380)	Hazard Ratio (95% CI)	$p_{interaction}$
Bleeding endpoints*							
BARC type 2, 3 or 5	48 (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). 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; TIMI = Thrombolysis in Myocardial Infarction. * bleeding outcomes analyzed by intention-to-treat. ^ ischemic outcomes analyzed per-protocol.
[#] indicates significant differences between complex and non-complex PCI patients


Components of Complex PCI
Prevalence (%)
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
9.1%
29.9%
51.8%
10.4%
10.7%
19.0%
6.9%
15.1%
3 vessels treated (N=214)
≥3 lesions treated (N=701)
>60 mm total stent length (N=1,214)
Use of atherectomy device (N=244)
Bifurcation with 2 stents implanted (N=251)
CTO as target lesion (N=446)
Venous or arterial graft as target lesion (N=161)
Left main as target lesion (N=353)

A

	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	4.2%	7.7%	0.54 (0.38-0.76)	0.79
Non-complex PCI	3.9%	6.8%	0.57 (0.44-0.73)	



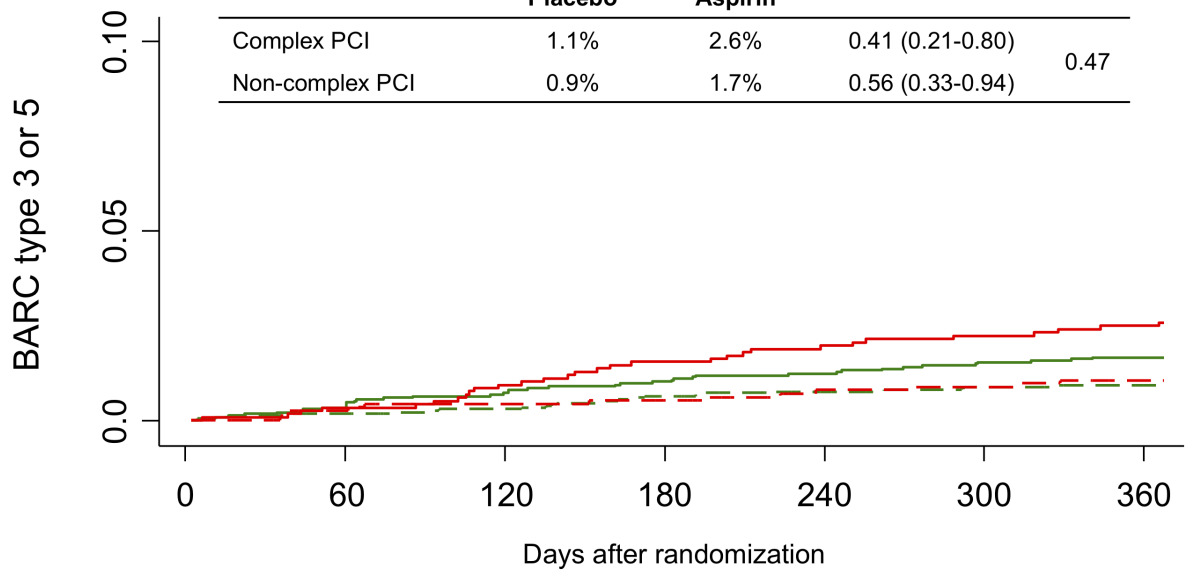
Number at risk

Ticagrelor + Aspirin - Non-Complex	2380	2331	2291	2256	2216	2184	2154
Ticagrelor + Placebo - Non-Complex	2397	2365	2340	2314	2282	2263	2244
Ticagrelor + Aspirin - Complex	1184	1157	1130	1107	1090	1077	1061
Ticagrelor + Placebo - Complex	1158	1133	1123	1115	1098	1086	1077

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

B

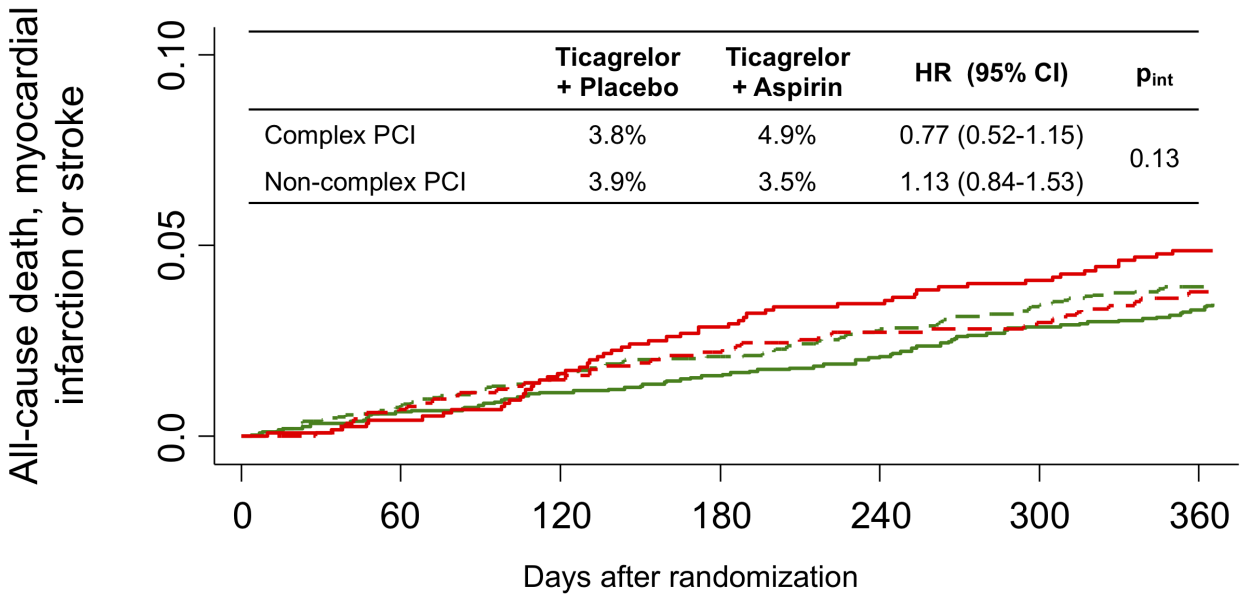
	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	1.1%	2.6%	0.41 (0.21-0.80)	0.47
Non-complex PCI	0.9%	1.7%	0.56 (0.33-0.94)	



Number at risk

Ticagrelor + Aspirin - Non-Complex	2380	2353	2338	2328	2307	2290	2273
Ticagrelor + Placebo - Non-Complex	2397	2376	2366	2347	2328	2320	2313
Ticagrelor + Aspirin - Complex	1184	1172	1159	1146	1136	1129	1120
Ticagrelor + Placebo - Complex	1158	1140	1135	1131	1118	1116	1110

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



	Ticagrelor + Placebo	Ticagrelor + Aspirin	HR (95% CI)	p_{int}
Complex PCI	3.8%	4.9%	0.77 (0.52-1.15)	0.13
Non-complex PCI	3.9%	3.5%	1.13 (0.84-1.53)	

Number at risk

Ticagrelor + Aspirin - Non-Complex	2356	2327	2314	2300	2275	2256	2238
Ticagrelor + Placebo - Non-Complex	2372	2342	2321	2302	2276	2260	2246
Ticagrelor + Aspirin - Complex	1159	1147	1132	1118	1107	1099	1085
Ticagrelor + Placebo - Complex	1152	1133	1123	1114	1099	1096	1084

Ticagrelor + Aspirin – Complex PCI

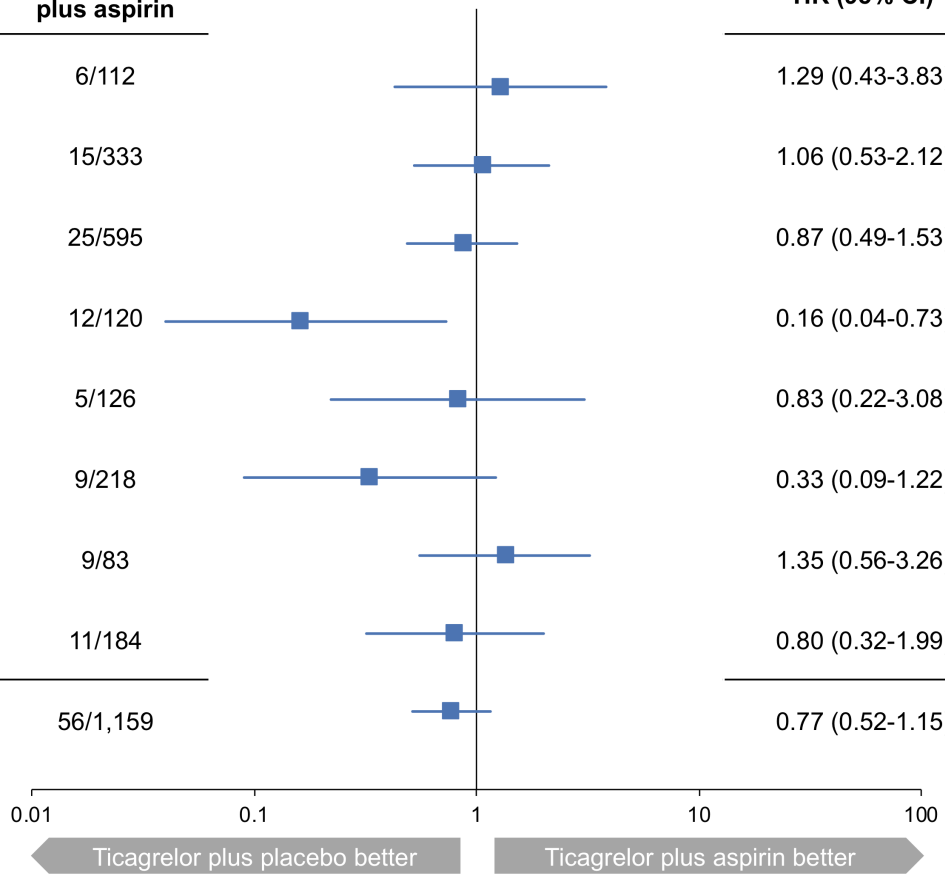
Ticagrelor + Aspirin – Non-complex PCI

Ticagrelor + Placebo – Complex PCI

Ticagrelor + Placebo – Non-complex PCI

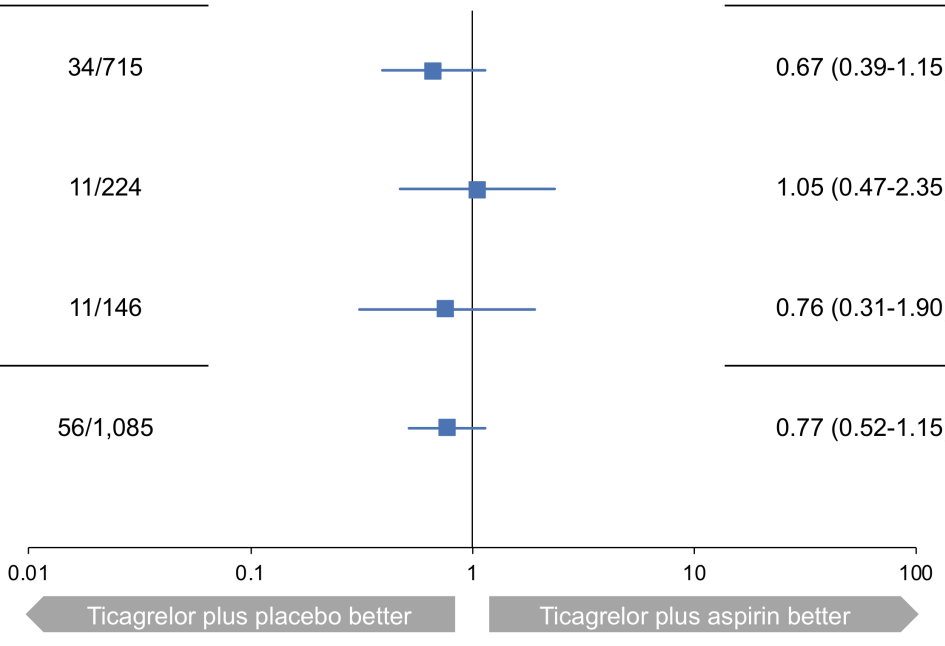
A

	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

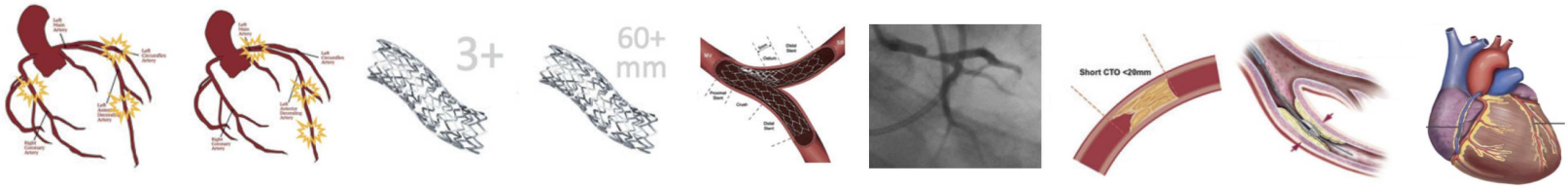
	Ticagrelor plus placebo	Ticagrelor plus aspirin	HR (95% CI)
1 Complex PCI criterion	22/694	34/715	0.67 (0.39-1.15)
2 Complex PCI criteria	13/252	11/224	1.05 (0.47-2.35)
≥3 Complex PCI criteria	8/138	11/146	0.76 (0.31-1.90)
Overall	43/1,084	56/1,085	0.77 (0.52-1.15)



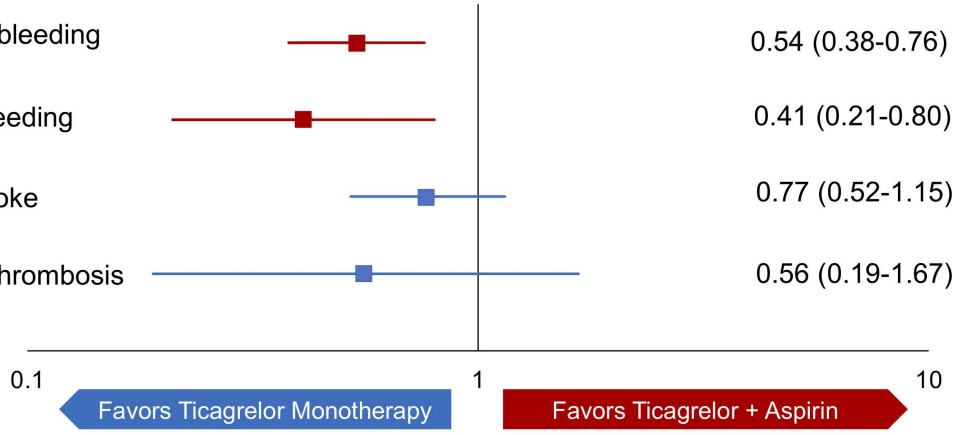
Effect of Ticagrelor Monotherapy Versus Ticagrelor Plus Aspirin After Three Months of DAPT in Patients who Undergo Complex PCI

Complex PCI defined as any of the following characteristics:

3 vessels treated | 3 lesions treated | 3 stents implanted | ≥60 mm stent length | Bifurcation with 2 stents | Left main PCI | CTO PCI | Use of atherectomy | Bypass graft PCI



Endpoint	Hazard Ratio (95% CI)
BARC 2, 3 or 5 bleeding	0.54 (0.38-0.76)
BARC 3 or 5 bleeding	0.41 (0.21-0.80)
Death, MI or stroke	0.77 (0.52-1.15)
Def/prob stent thrombosis	0.56 (0.19-1.67)



↓ in bleeding events

≈ in ischemic events