EuroIntervention

**Title:** **Safety and Efficacy of Ticagrelor Monotherapy According to Drug-Eluting Stent Type: The TWILIGHT-STENT Study.**

**Authors:** George Dangas, M.D, PhD; Usman Baber, M.D, MS; Samin Sharma, M.D; Gennaro Giustino, M.D; Samantha Sartori, PhD; Johny Nicolas, M.D; Ridhima Goel, M.D; Shamir Mehta, M.D, MSc; David Cohen, M.D, MSc; Dominick J. Angiolillo, M.D, PhD; Zhongjie Zhang, MPH; Anton Camaj, M.D; Davide Cao, M.D; Carlo Briguori, M.D, PhD; Dariusz Dudek, M.D, PhD; Javier Escaned, M.D, PhD; Kurt Huber, M.D; Timothy Collier, MSc; Ran Kornowski, M.D; Vijay Kunadian, MBBS, M.D; David J. Moliterno, M.D; E. Magnus Ohman, M.D; Giora Weisz, M.D; Robert Gil, M.D, PhD; Mitchell W. Krucoff, M.D; Upendra Kaul, M.D; Keith Oldroyd, MBChB, M.D; Gennaro Sardella, M.D; Richard Shlofmitz, M.D; Bernhard Witzenbichler, M.D; Adnan Kastrati, M.D; Ya-ling Han, M.D, PhD; Philippe Gabriel Steg, M.D; Stuart Pocock, PhD; C. Michael Gibson, M.D; Roxana Mehran, M.D

**DOI:** 10.4244/EIJ-D-21-00721

**Citation:** Dangas G, Baber U, Sharma S, Giustino G, Sartori S, Nicolas J, Goel R, Mehta S, Cohen D, Angiolillo DJ, Zhang Z, Camaj A, Cao D, Briguori C, Dudek D, Escaned J, Huber K, Collier T, Kornowski R, Kunadian V, Moliterno DJ Ohman EM, Weisz G, Gil R, Krucoff MW, Kaul U, Oldroyd K, Sardella G, Shlofmitz R, Witzenbichler B, Kastrati A, Han YL, Steg PG, Pocock S, Gibson CM, Mehran R. Safety and Efficacy of Ticagrelor Monotherapy According to Drug-Eluting Stent Type: The TWILIGHT-STENT Study. *EuroIntervention* 2020; Jaa-934 2020, doi: 10.4244/EIJ-D-21-00721

**Manuscript submission date:** 05 August 2021

**Revisions received:** 16 August 2021

**Accepted date:** 23 August 2021

**Online publication date:** 26 August 2021

**Safety and Efficacy of Ticagrelor Monotherapy According to Drug-Eluting Stent Type: The TWILIGHT-STENT Study**

**Running title:**
Ticagrelor Monotherapy According to Stent Type


**Authors:**
George Dangas, MD, PhD[1], Usman Baber, MD, MS[1,2], Samin Sharma, MD[1], Gennaro Giustino, MD[1], Samantha Sartori, PhD[1], Johny Nicolas, MD[1], Ridhima Goel, MD[1], Shamir Mehta, MD, MSc[3], David Cohen, MD, MSc[4], Dominick J. Angiolillo, MD, PhD[5], Zhongjie Zhang, MPH[1], Anton Camaj, MD[1], Davide Cao, MD[1], Carlo Briguori, MD, PhD[6], Dariusz Dudek, MD, PhD[7], Javier Escaned, MD, PhD[8], Kurt Huber, MD[9], Timothy Collier, MSc[10], Ran Kornowski, MD[11], Vijay Kunadian, MBBS, MD[12], David J. Moliterno, MD[13], E. Magnus Ohman, MD[14], Giora Weisz, MD[15], Robert Gil, MD, PhD[16], Mitchell W. Krucoff, MD[14], Upendra Kaul, MD[17], Keith Oldroyd, MBChB, MD[18], Gennaro Sardella, MD[19], Richard Shlofmitz, MD[20], Bernhard Witzenbichler, MD[21], Adnan Kastrati, MD[22], Ya-ling Han, MD, PhD[23], Philippe Gabriel Steg, MD[24] Stuart Pocock, PhD[10], C. Michael Gibson, MD[25], and Roxana Mehran, MD[1]

**Affiliations:**

1. The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA
2. Department of Cardiology, The University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104, USA
3. Population Health Research Institute, McMaster University and Hamilton Health Sciences, Hamilton, Ontario, Canada
4. St. Francis Hospital, Roslyn NY and Cardiovascular Research Foundation, New York, NY
5. Division of Cardiology, University of Florida College of Medicine, Jacksonville, FL, USA
6. Mediterranea Cardiocentro, Naples, Italy
7. Institute of Cardiology, Jagiellonian University Medical College, Krakow, Poland
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. University of Kentucky, Lexington, KY, USA
14. Duke University Medical Center-Duke Clinical Research Institute, Durham, NC, USA
15. New York Presbyterian Hospital, Columbia University Medical center, NY, USA
16. Center of Postgraduate Medical Education, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland
17. Batra Hospital and Medical Research Center, New Delhi, India
18. West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, United Kingdom

19. Department of Cardiology, Policlinico Umberto I, Sapienza University of Rome, Rome, Italy
20. St. Francis Hospital, Roslyn, NY, USA
21. Department of Cardiology and Pneumology, Helios Amper-Klinikum, Dachau, Germany
22. Department of Cardiology, Deutsches Herzzentrum Munchen, Lazarettstrabe 36, 80636 Munchen, Germany
23. Department of Cardiology, Shenyang North Hospital, Huanggu Qu, Shenyang Shi, Liaoning Sheng, China
24. Department of Cardiology, Groupe Hospitalier Bichat–Claude-Bernard, 46 Rue Henri Huchard, 75018 Paris, France
25. Division of Cardiovascular Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

**Funding:** Investigator-initiated grant from AstraZeneca

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

**ABSTRACT**

**Background**
In the TWILIGHT trial, ticagrelor monotherapy after a short course of dual antiplatelet therapy (DAPT) was shown to be a safe bleeding avoidance strategy in high-risk patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stent (DES).
**Aims**
To evaluate the effects of ticagrelor monotherapy after 3-month DAPT in patients undergoing PCI, according to DES type.
**Methods**
In the current subanalysis from TWILIGHT, patients were stratified into 3 groups based on DES type: durable polymer everolimus-eluting stents (DP-EES), durable polymer zotarolimus-eluting stents (DP-ZES), and biodegradable polymer DES (BP-DES). Bleeding and ischemic outcomes were assessed at 1 year after randomization.
**Results**
Out of 5,769 patients, 3,014 (52.2%) had DP-EES, 1,350 (23.4%) had DP-ZES and 1,405 (24.4%) had BP-DES. Compared with ticagrelor plus aspirin, ticagrelor monotherapy had significantly lower BARC type 2, 3 or 5 bleeding compared with DAPT; DP-EES (3.8% vs. 6.7%; HR:0.56, 95% CI:0.41-0.78), DP-ZES (4.6% vs. 6.9%; HR:0.66, 95% CI:0.42-1.04) and BP-DES (4.2% vs. 7.9%; HR:0.52, 95% CI:0.33-0.81; $p_{interaction}$=0.76). Ticagrelor monotherapy resulted in similar rates of death, MI, or stroke: DP-EES (4.2% vs. 4.3%; HR:0.97; 95% CI:0.68-1.37); DP-ZES (4.1% vs. 3.1%; HR:1.32; 95% CI:0.75-2.33); BP-DES (3.9% vs. 4.2%; HR:0.92; 95% CI:0.54-1.55; $p_{interaction}$=0.60). In both unadjusted and covariate-adjusted analyses, DES type was not associated with any differences in ischemic or bleeding complications.
**Conclusions**
As compared with ticagrelor plus aspirin, ticagrelor monotherapy after a short DAPT duration lowered bleeding complications without increasing the ischemic risk, irrespective of DES type. We observed no significant differences among DES-types.

**Keywords:** Adjunctive pharmacotherapy; Drug-eluting stent; Bleeding; Clinical trials

**CONDENSED ABSTRACT**

We investigated whether the benefits of ticagrelor monotherapy after a short course of DAPT in high-risk patients undergoing PCI, as shown in the TWILIGHT trial, are consistent across different DES types. Patients (n=5,769) were divided into 3 groups based on DES type: 1) durable polymer everolimus-eluting stents (n=3,014), durable polymer zotarolimus-eluting stents (n=1,350), and 3) biodegradable polymer DES (n=1,405). As compared with 12-month DAPT with ticagrelor plus aspirin, ticagrelor monotherapy after 3-month DAPT decreased bleeding without compromising ischemic protection across the 3 DES groups. No significant differences in clinical outcomes were observed among the 3 DES groups.

**LIST OF ABBREVIATIONS**

BARC = Bleeding Academic Research Consortium

CAD = Coronary Artery Disease

DAPT = Dual Antiplatelet Therapy

DES = Drug-Eluting Stent

GUSTO = Global Use of Strategies to Open Occluded Arteries

ISTH = International Society of Thrombosis or Hemostasis

MI = Myocardial Infarction

PCI = Percutaneous Coronary Intervention

ST = Stent Thrombosis

TIMI = Thrombolysis in Myocardial Infarction

## INTRODUCTION

Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$-receptor inhibitor constitutes the standard of care following percutaneous coronary intervention (PCI) with drug-eluting stents (DES) to prevent coronary thrombotic events[1]. First-generation DES, while more effective than bare metal stents at reducing rates of restenosis, were limited by late and very late thrombosis[2]. Iterations in DES technologies with refinements in stent design, drug, polymer and alloy as well as more potent $P2Y_{12}$-receptor inhibitors further improved the safety of PCI by reducing the incidence of early and late thrombotic complications[3, 4]. Prolonged DAPT, while effective in reducing long-term ischemic events, results in significantly higher rates of major bleeding complications which in turn are associated with increased risk of morbidity and mortality[5-9]. These observations led to a series of studies evaluating the safety and efficacy of abbreviated DAPT duration consisting of early $P2Y_{12}$-receptor inhibitor withdrawal following PCI with DES[10].

An emerging strategy of early aspirin withdrawal (i.e., 1-3 months post-PCI) with continuation of $P2Y_{12}$-receptor inhibitor has recently demonstrated to reduce bleeding risk while preserving ischemic protection[11]. Monotherapy with the potent $P2Y_{12}$-receptor inhibitor ticagrelor following 3 months of DAPT resulted in lower incidence of clinically relevant bleeding without increasing the risk of ischemic events compared to continuing DAPT up to 15 months post-PCI with DES[11]. Patients undergoing PCI with different stent types may have variable ischemic/bleeding risk profiles (i.e., due to large differences in strut thickness, polymer type, eluting drug, etc.) and thus may respond differently to this novel strategy. A prior sub-analysis from the TWILIGHT trial showed that the safety and efficacy of ticagrelor monotherapy in patients receiving the SYNERGY biodegradable polymer drug-eluting stents (BP-DES)[12]. A broader evaluation across various platforms of durable polymer drug-eluting stents (DP-DES) and BP-DES has not been performed. We therefore performed a post-hoc analysis of the Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) trial evaluating the safety and efficacy of a regimen of ticagrelor monotherapy versus ticagrelor plus aspirin in patients who initially completed 3 months of DAPT after a PCI with different types of new-generation DES.

## METHODS

**Study Design.** TWILIGHT was an international, multicenter, randomized, placebo-controlled trial conducted in 187 sites across 11 countries, as previously described[11, 13]. 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 [13]. For the present pre-specified analysis, only durable polymer everolimus-eluting stents (DP-EES), durable polymer zotarolimus-eluting stents (DP-ZES) and BP-DES were included (Supplementary Figure 1). Patients who underwent PCI with more than one stent type implanted or with bare-metal stent were excluded. A full list of the commercially approved DES types included in the analysis is provided in the appendix (**Supplementary Table 1**). 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 (including both oral and parenteral medications), 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.

**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 (81 to 100 mg daily) or matching placebo with continuation of open-label ticagrelor (90 mg twice daily) for an additional 12 months. The choice of prolonged potent DAPT in the control group was justified by the heightened ischemic risk, as reflected by the procedural/angiographic inclusion criteria, of the studied population[11, 13]. 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 [14]. 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 [15] between randomization and 1-year follow-up (i.e. 15 months after the index procedure). The key secondary endpoint was major adverse cardiac and cerebrovascular events (MACCE) defined as a composite of death from any cause, nonfatal myocardial infarction (MI) or nonfatal stroke. Secondary bleeding endpoints included BARC type 3 or 5 bleeding [15]; Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding [16]; Global Use of Strategies to Open

Occluded Arteries (GUSTO) moderate, severe, or life-threatening bleeding [17]; or major bleeding as defined by the International Society on Thrombosis or Hemostasis (ISTH) [18]. Other secondary endpoints included death from cardiovascular causes, MI, ischemic stroke, and definite or probable ST. MI was defined according to the third universal definition [19], and revascularization and ST were classified according to the Academic Research Consortium [20]. The definitions of study endpoints are listed in Supplementary Table 2. 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 (CI) were generated using adjusted Cox proportional-hazards models for DES-type comparisons. Clinically relevant variables were included in the adjustment model: body mass index (kg/m$^2$), hypercholesterolemia, peripheral arterial disease, previous PCI or coronary artery bypass graft surgery, multivessel coronary artery disease (CAD), indication for PCI (acute coronary syndrome (ACS) versus stable CAD), total occlusion of target vessel, and total stent length. The consistency of the treatment effect of ticagrelor monotherapy versus ticagrelor plus aspirin between the different stent types (DP-EES, DP-ZES and BP-DES) 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 initially enrolled following PCI, of which 7,119 were randomly assigned 3 months later to receive ticagrelor plus placebo or ticagrelor plus aspirin. Of these 7,119 patients, 5,769 (81.0%) were included in this analysis. Of these, 3,014 (52.2%) received a DP-EES, 1,350 (23.4%) received a DP-ZES and 1,405 (24.4%) received a BP-DES. The study flow diagram is reported in Supplementary Figure 1. Baseline clinical and procedural characteristics for patients according to type of new-generation DES are reported in **Table 1;** similarly, baseline characteristics according to treatment arm within each stent type group are reported in Supplementary Table 3. Patients who underwent PCI with a BP-DES had fewer comorbidities and were more likely to present with an ACS. Overall outcomes according to the 3 types of DES are reported in **Figures 1-3** and **Supplementary Table 4**; in both univariate analysis and multivariable analyses, DES type was not associated with an increased risk of MACCE, TLF or major bleeding complications. One-year rates of stent thrombosis were <1% across all DES platforms.



**Bleeding Outcomes.** Bleeding event rates in patients according to randomized treatment assignment (ticagrelor plus placebo versus ticagrelor plus aspirin) and DES type are reported in **Table 2**. The reduction in bleeding rates of ticagrelor monotherapy was overall consistent across DES types. Ticagrelor monotherapy resulted in significantly lower rates of BARC type 2, 3 or 5 bleeding at 1 year after randomization consistently among patients treated with DP-EES (3.8% vs. 6.7%; absolute risk difference -2.9%; HR 0.56, 95% CI 0.41-0.78), DP-ZES (4.6% vs. 6.9%; absolute risk difference -2.3%; HR 0.66, 95% CI 0.42-1.04) and BP-DES (4.2% vs. 7.9%; absolute risk difference -3.7%; HR 0.52, 95% CI 0.33-0.81), without statistical interaction

($p_{\text{interaction}}$=0.76) **(Central Illustration).** These results were also consistent when other bleeding definitions were examined **(Table 2)**.

**Ischemic Outcomes.** Ischemic event rates in patients according to randomized group (ticagrelor plus placebo versus ticagrelor plus aspirin) and stent type are reported in **Table 2**. There were no significant differences in MACCE between ticagrelor monotherapy and ticagrelor plus aspirin consistently among patients treated with DP-EES (4.2% vs. 4.3%; absolute risk difference -0.1%; HR 0.97, 95% CI 0.68-1.37), DP-ZES (4.1% vs. 3.1%; absolute risk difference 1.0%; HR 1.32, 95% CI 0.75-2.33) and BP-DES (3.9% vs. 4.2%; absolute risk difference -0.3%; HR 0.92, 95% CI 0.54-1.55), without statistical interaction ($p_{\text{interaction}}$=0.597). Additionally, there were no significant differences among groups regarding the individual ischemic endpoints (**Central Illustration and Table 2**). The rates of DES thrombosis were <1% and not influenced by the randomized treatment assignment to ticagrelor monotherapy or DAPT.



## DISCUSSION

The key findings of the present, post-hoc analysis from the 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 stent type, include: (i) ticagrelor monotherapy as compared with ticagrelor plus aspirin resulted in significantly lower major bleeding complications, a finding that was consistent across new-generation DES types; and (ii) ticagrelor monotherapy compared to ticagrelor plus aspirin was not associated with increased risk of ischemic events irrespective of the type of new-generation DES; (iii) there were no significant differences in MACCEs across DES types in the overall population; notably, rates of DES thrombosis were uniformly low and not influenced by the randomized treatment assignment.

Iteration in DES technologies including improved drug release kinetics, polymer biocompatibility, and endothelialization patterns of new-generation DES significantly overcame the limitations observed with early-generation DES[4, 10]. In the era of first-generation DES, and extended period of DAPT (≥1 year) using aspirin and a $P2Y_{12}$-receptor inhibitor was considered necessary in order to reduce the risk of DES-related thrombotic events[10]. While extended DAPT has been shown to reduce the risk of DES-related and non-DES-related ischemic events, it may also result in higher risk of hemorrhagic complications which are strongly associated with increased risk of morbidity, mortality and healthcare costs[21-23]. New-generation DES platforms have been associated with lower risk of DES-related thrombotic events compared to first-generation DESs therefore obviating the need for mandatory prolonged DAPT[10, 24]. In a previous large meta-analysis of randomized controlled trials investigating the efficacy and safety of longer vs. shorter DAPT, the risk for ST was significantly higher using short-term DAPT in patients who received a first-generation DES (OR 3.94, 95% CI 2.20-7.05) compared with those who received a new-generation DES (OR 1.54, 95% CI 0.96-2.47; $p_{\text{interaction}}$=0.008)[10].

In the current analysis from the TWILIGHT trial we extended prior knowledge by evaluating the safety and efficacy of a strategy of abbreviated DAPT using aspirin and ticagrelor followed by ticagrelor monotherapy among high-risk patients undergoing PCI with different types of new-generation DESs. Overall, DP-EES, DP-ZES and BP-DES were associated with very low rates of late DES thrombosis (between 3 and 15 months post-PCI). Among randomized patients, a strategy of ticagrelor monotherapy did not result in increased rates of MACCE nor stent thrombosis irrespective of the type of DES implanted compared to continuing DAPT. The bleeding-avoidance benefits of ticagrelor monotherapy versus DAPT were not influenced by the type of DES. These findings are overall consistent with the main results of the TWILIGHT trial as well as with prior trials evaluating a strategy of $P2Y_{12}$-receptor monotherapy following abbreviated DAPT using clopidogrel[11]. For example, in the Short and Optimal Duration of Dual Antiplatelet Therapy After Everolimus-Eluting Cobalt Chromium Stent (STOPDAPT 2) trial in which 3,009 patients who underwent PCI with a cobalt-chromium EES and randomized to 1 month of DAPT followed by clopidogrel monotherapy versus 12 months of DAPT with aspirin and clopidogrel, the former regimen resulted in lower rates of bleeding complications and similar rates of ischemic events compared with 1-year DAPT[25]. In the GLOBAL LEADERS trial, a randomized, open-label superiority trial of all-comers undergoing PCI with a bioresorbable polymer biolimus A9-eluting DES (N=15,968), tested aspirin plus ticagrelor for 1 month followed by 23 months of ticagrelor monotherapy also resulted in similar rates of ischemic events compared to 12 months of DAPT (aspirin plus clopidogrel in those with stable CAD or 12 months of aspirin plus ticagrelor in those with ACS) followed by 12 months of aspirin monotherapy[26]. Hence, the totality of evidence supports the efficacy and safety of a strategy of P2Y12-receptor monotherapy followed an initial short period of DAPT when using a latest-generation DES after PCI in patients with high-risk clinical or anatomic characteristics[27]. Furthermore, P2Y12-receptor monotherapy has recently gained attention within the context of chronic maintenance therapy (i.e., beyond one year) after PCI. Indeed, the recently published HOST-EXAM randomized trial revealed a significant decrease in net adverse events (composite of all-cause death, MI, stroke, and BARC bleeding type 3 or greater) with clopidogrel versus aspirin monotherapy at 24-month follow-up among patients who were maintained on DAPT and remained event free for 6 to 18 months following PCI [28]. Whether ticagrelor monotherapy could similarly extend its benefits beyond the period tested in our trial warrants further investigation[11].

Improvements in DES design continue to strive for biocompatibility; allowing enthothelialization after the implantation-induced arterial trauma is a key process in coronary devices adherence to the arterial wall[29]. Strut material, thickness and metallic mesh configuration, polymer type and properties as well as drug type, dose and elution kinetics are all important. Notably, the TWILIGHT-pharmacodynamic study supported the rationale for safety of aspirin withdrawal, and the present study concurs that aspirin can be withdrawn rather safely after an initial 3 month DAPT treatment after the index PCI, irrespective of DES type[30].

**LIMITATIONS**

Our findings should be considered in the light of the following limitations. First, as a subgroup analysis from a RCT, the current findings can only be considered hypothesis-generating and should be further tested in adequately powered studies for individual stent types. Second, the 3 DES groups were not individually powered to draw definitive conclusions on the effect of ticagrelor monotherapy versus DAPT within each DES type; for the same reason, we could not perform landmark analyses assessing the time dependent effect of ticagrelor monotherapy according to stent type. Nonetheless, the magnitude and direction of the effects were largely consistent with the overall trial findings. Third, due to absence of statistical correction for multiple comparisons, the chance findings related to multiple testing should be considered by the readers. Fourth, these results are not generalizable to all patients who undergo PCI due to the inclusion and exclusion criteria of our trial. 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 across different new-generation DES types are generalizable to a regimen of clopidogrel or prasugrel monotherapy remains unknown. Finally, treatment with a specific type of DES was not randomly assigned. Therefore, these comparisons can be subject to residual confounding despite multivariable adjustment.

**CONCLUSIONS**

In conclusion, among high-risk patients who underwent PCI a regimen of ticagrelor monotherapy (after an initial 3 months of DAPT with ticagrelor plus aspirin) resulted in significantly lower clinically relevant bleeding without increasing the risk of ischemic events compared to continuing DAPT regardless of the type of new-generation DES implanted. There were no significant differences in the rates of MACCE among types of DES between 3 and 15 months. Rates of stent thrombosis were low (<1%) and not influenced by the randomized assignment to ticagrelor monotherapy or DAPT.

**IMPACT ON DAILY PRACTICE**

Owing to significant advances in DES technologies and antithrombotic therapies, initiation of ticagrelor monotherapy after 3-month DAPT reduced bleeding without increasing ischemic events as compared with 12-month DAPT across different DES types. Further studies are warranted to investigate whether shorter DAPT durations (i.e., <3 months) with ticagrelor monotherapy is a safe bleeding avoidance strategy in patients receiving different types of newer-generation DES.

**FUNDING**
Funded by AstraZeneca; TWILIGHT ClinicalTrials.gov number, NCT02270242)

**DISCLOSURES**

**Dr. Dangas** reports receiving consulting fees and advisory board fees from AstraZeneca, consulting fees from Biosensors, and previously holding stock in Medtronic. **Dr. Baber** reports speaker honoraria from AstraZeneca and Boston Scientific. **Dr. Sharma** has received consulting fees or honoraria from Abbott, Boston Scientific, Abiomed, and Cardiovascular Systems, Inc. **Dr. Mehta** has received research grants to the institution from AstraZeneca, Abbott, Boston Scientific, and Sanofi; and has received honoraria for consultancy from AstraZeneca, Bayer, Biosensors, and Sanofi. **Dr. Cohen** reports receiving grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, and Abbott Vascular, and Boston Scientific. **Dr. Angiolillo** has received payment as an individual for: a) Consulting fee or honorarium from Abbott, Amgen, Aralez, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, PhaseBio, PLx Pharma, Pfizer, Sanofi, and The Medicines Company; b) Participation in review activities from CeloNova and St. Jude Medical. Institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and the Scott R. MacKenzie Foundation. **Dr. Escaned** reports receiving consulting fees and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic, and lecture fees from Abiomed, Terumo, and Biosensors. **Dr. Huber** reports receiving lecture fees from AstraZeneca and Bayer. **Dr. Kunadian** has received personal fees/honoraria from Bayer, Astra Zeneca, Abbott, Amgen, Daichii Sankyo. **Dr. Moliterno** reports grants from AstraZeneca, during the conduct of the study. **Dr. Ohman** reports research grants from Abiomed and Chiesi, and consulting fees from AstraZeneca, Cara Therapeutics, Faculty Connection, Imbria, Impulse Medical, Janssen Pharmaceuticals, Milestone Pharmaceuticals, Xylocor, and Zoll Medical. **Dr. Weisz** reports receiving grant support and advisory board fees from and holding equity in Corindus, advisory board fees from and holding equity in Filterlex, serving on an advisory board for and holding options in Trisol, and receiving grant support from Abbott, CSI, and RenalGuard. **Dr. Krucoff** reports reports grants and/or personal fees from Abbott Vascular, Biosensors, Boston Scientific, Celonova, Medtronic, OrbusNeich, Terumo. **Dr. Oldroyd** reports receiving grant support and lecture fees from AstraZeneca; and is employed by Biosensors. **Dr. Sardella** reports receiving consulting fees from Abbott, Shockwave, Boston Scientific, and Balmed, and payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events Abbott, Alvimedica, Shockwave, Medtronic, Biosensors. **Dr. Steg** reports receiving research grants from Amarin, Bayer, Sanofi, and Servier, compensation for work in clinical trials from Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Idorsia, Novartis, Pfizer, Sanofi, Servier, receiving fees for consulting or speaking from Amgen, BMS/Myokardia, Novo-Nordisk, Regeneron and being a Senior Associate Editor at Circulation. **Dr. Gibson** reports receiving grant support and consulting fees from Angel Medical, Bayer, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson, and Portola Pharmaceuticals, consulting fees from the Medicines Company, 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, holding equity in nference, serving as chief executive officer of Baim Institute, and receiving grant support, paid to Baim Institute, from Bristol-Myers Squibb. **Dr. Mehran** reports institutional research grants from Abbott, Abiomed, Applied Therapeutics, Arena, AstraZeneca, Bayer, Biosensors, Boston Scientific, Bristol-Myers Squibb, CardiaWave, CellAegis, CERC, Chiesi, Concept Medical, CSL Behring, DSI, Insel Gruppe AG, Medtronic, Novartis Pharmaceuticals, OrbusNeich, Philips, Transverse Medical, Zoll; personal fees from ACC, Boston Scientific, California Institute for Regenerative Medicine (CIRM), Cine-Med Research, Janssen, WebMD, SCAI; consulting fees paid to the institution from Abbott, Abiomed, AM-Pharma, Alleviant Medical, Bayer, Beth Israel Deaconess, CardiaWave, CeloNova, Chiesi, Concept Medical, DSI, Duke University, Idorsia Pharmaceuticals, Medtronic, Novartis, Philips; Equity <1% in Applied Therapeutics, Elixir Medical, STEL, CONTROLRAD (spouse); Scientific Advisory Board for AMA, Biosensors (spouse).

The other authors have nothing to disclose.

## REFERENCES

1. 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**(23 Pt A):2915-2931.

2. Galløe AM, Kelbæk H, Thuesen L, Hansen HS, Ravkilde J, Hansen PR, Christiansen EH, Abildgaard U, Stephansen G, Lassen JF, Engstrøm T, Jensen JS, Jeppesen JL, Bligaard N. 10-Year Clinical Outcome After Randomization to Treatment by Sirolimus- or Paclitaxel-Eluting Coronary Stents. J Am Coll Cardiol 2017;**69**(6):616-624.

3. Giustino G, Harari R, Baber U, Sartori S, Stone GW, Leon MB, Windecker S, Serruys PW, Kastrati A, Von Birgelen C, Kimura T, Stefanini GG, Dangas GD, Wijns W, Steg PG, Morice MC, Camenzind E, Weisz G, Smits PC, Sorrentino S, Sharma M, Farhan S, Faggioni M, Kandzari D, Galatius S, Jeger RV, Valgimigli M, Itchhaporia D, Mehta L, Kim HS, Chieffo A, Mehran R. Long-term Safety and Efficacy of New-Generation Drug-Eluting Stents in Women With Acute Myocardial Infarction: From the Women in Innovation and Drug-Eluting Stents (WIN-DES) Collaboration. JAMA Cardiol 2017;**2**(8):855-862.

4. Madhavan MV, Kirtane AJ, Redfors B, Genereux P, Ben-Yehuda O, Palmerini T, Benedetto U, Biondi-Zoccai G, Smits PC, von Birgelen C, Mehran R, McAndrew T, Serruys PW, Leon MB, Pocock SJ, Stone GW. Stent-Related Adverse Events >1 Year After Percutaneous Coronary Intervention. J Am Coll Cardiol 2020;**75**(6):590-604.

5. Généreux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol 2015;**66**(9):1036-45.

6. Baber U, Dangas G, Chandrasekhar J, Sartori S, Steg PG, Cohen DJ, Giustino G, Ariti C, Witzenbichler B, Henry TD, Kini AS, Krucoff MW, Gibson CM, Chieffo A, Moliterno DJ, Weisz G, Colombo A, Pocock S, Mehran R. Time-Dependent Associations Between Actionable Bleeding, Coronary Thrombotic Events, and Mortality Following Percutaneous Coronary Intervention: Results From the PARIS Registry. JACC Cardiovasc Interv 2016;**9**(13):1349-57.

7. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, Spertus JA, Steg PG, Cutlip DE, Rinaldi MJ, Camenzind E, Wijns W, Apruzzese PK, Song Y, Massaro JM, Mauri L. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. Jama 2016;**315**(16):1735-49.

8. Costa F, van Klaveren D, James S, Heg D, Räber L, Feres F, Pilgrim T, Hong MK, Kim HS, Colombo A, Steg PG, Zanchin T, Palmerini T, Wallentin L, Bhatt DL, Stone GW, Windecker S, Steyerberg EW, Valgimigli M. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;**389**(10073):1025-1034.

9. Valgimigli M, Costa F, Lokhnygina Y, Clare RM, Wallentin L, Moliterno DJ, Armstrong PW, White HD, Held C, Aylward PE, Van de Werf F, Harrington RA, Mahaffey KW, Tricoci P. Trade-off of myocardial infarction vs. bleeding types on mortality after acute coronary syndrome: lessons from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) randomized trial. Eur Heart J 2017;**38**(11):804-810.

10. Giustino G, Baber U, Sartori S, Mehran R, Mastoris I, Kini AS, Sharma SK, Pocock SJ, Dangas GD. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a

systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol 2015;**65**(13):1298-1310.

11. Mehran R, Baber U, Sharma SK, Cohen DJ, Angiolillo DJ, Briguori C, Cha JY, Collier T, Dangas G, Dudek D, Džavík V, Escaned J, Gil R, Gurbel P, Hamm CW, Henry T, Huber K, Kastrati A, Kaul U, Kornowski R, Krucoff M, Kunadian V, Marx SO, Mehta SR, Moliterno D, Ohman EM, Oldroyd K, Sardella G, Sartori S, Shlofmitz R, Steg PG, Weisz G, Witzenbichler B, Han YL, Pocock S, Gibson CM. Ticagrelor with or without Aspirin in High-Risk Patients after PCI. N Engl J Med 2019;**381**(21):2032-2042.

12. Baber U, Chandiramani R, Mehta SR, Sartori S, Zhang Z, Claessen BE, Briguori C, Sharma S, Dangas G, Mehran R. Safety and efficacy of the bioabsorbable polymer everolimus-eluting stent versus durable polymer drug-eluting stents in high-risk patients undergoing PCI: TWILIGHT-SYNERGY. Catheterization and Cardiovascular Interventions 2021;**97**(1):63-71.

13. Baber U, Dangas G, Cohen DJ, Gibson CM, Mehta SR, Angiolillo DJ, Pocock SJ, Krucoff MW, Kastrati A, Ohman EM, Steg PG, Badimon J, Zafar MU, Chandrasekhar J, Sartori S, Aquino M, Mehran R. Ticagrelor with aspirin or alone in high-risk patients after coronary intervention: Rationale and design of the TWILIGHT study. Am Heart J 2016;**182**:125-134.

14. Mehran R, Baber U, Steg PG, Ariti C, Weisz G, Witzenbichler B, Henry TD, Kini AS, Stuckey T, Cohen DJ, Berger PB, Iakovou I, Dangas G, Waksman R, Antoniucci D, Sartori S, Krucoff MW, Hermiller JB, Shawl F, Gibson CM, Chieffo A, Alu M, Moliterno DJ, Colombo A, Pocock S. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (PARIS): 2 year results from a prospective observational study. Lancet 2013;**382**(9906):1714-22.

15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;**123**(23):2736-2747.

16. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT. 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. Annals of internal medicine 1991;**115**(4):256-265.

17. Investigators G. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. New England Journal of Medicine 1993;**329**(10):673-682.

18. Kaatz S, Ahmad D, Spyropoulos A, Schulman S, Anticoagulation SoCo. 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. Journal of Thrombosis and Haemostasis 2015;**13**(11):2119-2126.

19. Bax JJ, Baumgartner H, Ceconi C, Dean V, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J. Third universal definition of myocardial infarction. Journal of the American College of Cardiology 2012;**60**(16):1581-1598.

20. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Gabriel Steg P, Morel M-al, Mauri L, Vranckx P. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;**115**(17):2344-2351.

21. Sorrentino S, Sartori S, Baber U, Claessen BE, Giustino G, Chandrasekhar J, Chandiramani R, Cohen DJ, Henry TD, Guedeney P, Ariti C, Dangas G, Gibson CM, Krucoff

MW, Moliterno DJ, Colombo A, Vogel B, Chieffo A, Kini AS, Witzenbichler B, Weisz G, Steg PG, Pocock S, Urban P, Mehran R. Bleeding Risk, Dual Antiplatelet Therapy Cessation, and Adverse Events After Percutaneous Coronary Intervention: The PARIS Registry. Circ Cardiovasc Interv 2020;**13**(4):e008226.

22. Sorrentino S, Baber U, Claessen BE, Camaj A, Vogel B, Sartori S, Guedeney P, Chandrasekhar J, Farhan S, Barman N, Sweeny J, Giustino G, Dangas G, Kini A, Sharma S, Mehran R. Determinants of Significant Out-Of-Hospital Bleeding in Patients Undergoing Percutaneous Coronary Intervention. Thromb Haemost 2018;**118**(11):1997-2005.

23. Genereux P, Giustino G, Witzenbichler B, Weisz G, Stuckey TD, Rinaldi MJ, Neumann FJ, Metzger DC, Henry TD, Cox DA, Duffy PL, Mazzaferri E, Yadav M, Francese DP, Palmerini T, Kirtane AJ, Litherland C, Mehran R, Stone GW. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol 2015;**66**(9):1036-45.

24. Palmerini T, Sangiorgi D, Valgimigli M, Biondi-Zoccai G, Feres F, Abizaid A, Costa RA, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Mariani A, Della Riva D, Genereux P, Leon MB, Bhatt DL, Bendetto U, Rapezzi C, Stone GW. Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation: an individual patient data pairwise and network meta-analysis. J Am Coll Cardiol 2015;**65**(11):1092-102.

25. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T, Ohya M, Suwa S, Takagi K, Nanasato M, Hata Y, Yagi M, Suematsu N, Yokomatsu T, Takamisawa I, Doi M, Noda T, Okayama H, Seino Y, Tada T, Sakamoto H, Hibi K, Abe M, Kawai K, Nakao K, Ando K, Tanabe K, Ikari Y, Hanaoka KI, Morino Y, Kozuma K, Kadota K, Furukawa Y, Nakagawa Y, Kimura T, Investigators S-. Effect of 1-Month Dual Antiplatelet Therapy Followed by

Clopidogrel vs 12-Month Dual Antiplatelet Therapy on Cardiovascular and Bleeding Events in Patients Receiving PCI: The STOPDAPT-2 Randomized Clinical Trial. JAMA 2019;**321**(24):2414-2427.

26. Vranckx P, Valgimigli M, Jüni P, Hamm C, Steg PG, Heg D, van Es GA, McFadden EP, Onuma Y, van Meijeren C, Chichareon P, Benit E, Möllmann H, Janssens L, Ferrario M, Moschovitis A, Zurakowski A, Dominici M, Van Geuns RJ, Huber K, Slagboom T, Serruys PW, Windecker S. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;**392**(10151):940-949.

27. Dangas G, Baber U, Sharma S, Giustino G, Mehta S, Cohen DJ, Angiolillo DJ, Sartori S, Chandiramani R, Briguori C, Dudek D, Escaned J, Huber K, Collier T, Kornowski R, Kunadian V, Kaul U, Oldroyd K, Sardella G, Shlofmitz R, Witzenbichler B, Ya-Ling H, Pocock S, Gibson CM, Mehran R. Ticagrelor With or Without Aspirin After Complex PCI. J Am Coll Cardiol 2020;**75**(19):2414-2424.

28. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, Rha SW, Bae JW, Lee NH, Hur SH, Yoon J, Park TH, Kim BS, Lim SW, Cho YH, Jeon DW, Kim SH, Han JK, Shin ES, Kim HS. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;**397**(10293):2487-2496.

29. Torii S, Jinnouchi H, Sakamoto A, Kutyna M, Cornelissen A, Kuntz S, Guo L, Mori H, Harari E, Paek KH, Fernandez R, Chahal D, Romero ME, Kolodgie FD, Gupta A, Virmani R,

Finn AV. Drug-eluting coronary stents: insights from preclinical and pathology studies. Nat Rev Cardiol 2020;**17**(1):37-51.

30. Baber U, Zafar MU, Dangas G, Escolar G, Angiolillo DJ, Sharma SK, Kini AS, Sartori S, Joyce L, Vogel B, Farhan S, Gurbel P, Gibson CM, Fuster V, Mehran R, Badimon JJ. Ticagrelor With or Without Aspirin After PCI: The TWILIGHT Platelet Substudy. J Am Coll Cardiol 2020;**75**(6):578-586.

## FIGURE LEGENDS

**Figure 1.** Rates of (**A)** BARC 2, 3 or 5 bleeding and (**B) MACCE** among the 3 DES types evaluated.

Kaplan–Meier estimates for BARC 2, 3 or 5 bleeding and Target Lesion Failure at 12 months after randomization (intention-to-treat population) by drug-eluting stent type in patients who underwent percutaneous coronary intervention.

BARC = Bleeding Academic Research Consortium; MACCE = major adverse cardiac and cerebral events (all-cause death, myocardial infarction, or stroke); Gen = Generation; DP-EES = Durable Polymer Everolimus-Eluting Stent; DP-ZES = Durable Polymer Zotarlimus-Eluting Stent; BP-DES = Biodegradable Polymer Drug-Eluting Stent.

**Figure 2.** Rates of target lesion failure among the 3 DES types evaluated.

Kaplan–Meier estimates for target lesion failure at 12 months after randomization (intention-to-treat population) by drug-eluting stent type in patients who underwent percutaneous coronary intervention.

Gen = Generation; DP-EES = Durable Polymer Everolimus-Eluting Stent; DP-ZES = Durable Polymer Zotarlimus-Eluting Stent; BP-DES = Biodegradable Polymer Drug-Eluting Stent.

**Figure 3.** Rates of BARC 3 or 5 bleeding among the 3 DES types evaluated.

Kaplan–Meier estimates for BARC 3 or 5 bleeding at 12 months after randomization by drug-eluting stent type in patients who underwent percutaneous coronary intervention.

BARC = Bleeding Academic Research Consortium; Gen = Generation; DP-EES = Durable Polymer Everolimus-Eluting Stent; DP-ZES = Durable Polymer Zotarlimus-Eluting Stent; BP-DES = Biodegradable Polymer Drug-Eluting Stent.

**Central Illustration.** Bleeding and Ischemic Effects of Ticagrelor Monotherapy Versus Ticargelor Plus After 3 Months of DAPT in Patients Undergoing PCI with second-generation DES.

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 n=5,769 patients who underwent PCI with a second-generation DES showed that ticagrelor monotherapy, compared with ticagrelor plus aspirin, was associated with a reduction in BARC 2, 3, or 5 bleeding over 1 year consistently across the 3 studied DES types. There was no significant difference in the 1-year rate of all-cause death, MI, or stroke between the 2 treatment arms; this was also consistent across the 3 DES types.

ASA = Aspirin; BARC = Bleeding Academic Research Consortium; Gen = Generation; DP-EES = Durable Polymer Everolimus-Eluting Stent; DP-ZES = Durable Polymer Zotarlimus-Eluting Stent; BP-DES = Biodegradable Polymer Drug-Eluting Stent; MACCE = Major Adverse Cardiac and Cerebrovascular Events, a composite of death, myocardial infarction or stroke.

**Table 1.** Baseline clinical and procedural characteristics.

| | New-Generation Drug-Eluting Stent | | | |
|---|---|---|---|---|
| | DP-EES N=3014 (52.2%) | DP-ZES N=1350 (23.4%) | BP-DES N=1405 (24.4%) | P-value |
| Age, years | 65.3±10.3 | 65.3±10.2 | 65.2±10.3 | 0.96 |
| Female sex | 696 (23.1%) | 321 (23.8%) | 342 (24.3%) | 0.65 |
| BMI, kg/m$^2$ | 29.3±5.9 | 29.2±5.6 | 28.4±5.2 | <.001 |
| Diabetes | 1107 (36.7%) | 526 (39.0%) | 504 (35.9%) | 0.21 |
| Diabetes treated with insulin | 304 (27.5%) | 144 (27.4%) | 138 (27.4%) | 0.99 |
| Chronic kidney disease | 509 (17.6%) | 242 (18.4%) | 241 (18.1%) | 0.78 |
| Anemia | 572 (19.8%) | 259 (19.7%) | 247 (18.6%) | 0.67 |
| Current smoker | 617 (20.5%) | 287 (21.3%) | 317 (22.6%) | 0.28 |
| Hypercholesterolemia | 2076 (68.9%) | 965 (71.5%) | 814 (57.9%) | <.001 |
| Hypertension | 2273 (75.4%) | 1002 (74.2%) | 1014 (72.2%) | 0.07 |
| Peripheral arterial disease | 207 (6.9%) | 138 (10.2%) | 87 (6.2%) | <.001 |
| Previous MI | 953 (31.6%) | 394 (29.2%) | 414 (29.5%) | 0.17 |
| Previous PCI | 1333 (44.2%) | 644 (47.7%) | 604 (43.0%) | 0.03 |
| Previous CABG | 368 (12.2%) | 156 (11.6%) | 140 (10.0%) | 0.09 |
| Multivessel CAD | 1786 (59.3%) | 876 (64.9%) | 844 (60.1%) | 0.002 |
| Previous major bleed | 28 (0.9%) | 10 (0.7%) | 11 (0.8%) | 0.78 |
| Indication for PCI | | | | <.001 |
| ACS | 1880 (62.4%) | 785 (58.2%) | 937 (66.7%) | |
| Stable CAD | 1134 (37.6%) | 564 (41.8%) | 468 (33.3%) | |
| Target vessel | | | | |
| Left Main | 124 (4.1%) | 57 (4.2%) | 61 (4.3%) | 0.94 |
| LAD | 1619 (53.7%) | 714 (52.9%) | 802 (57.1%) | 0.05 |
| LCX | 949 (31.5%) | 434 (32.1%) | 410 (29.2%) | 0.19 |
| RCA | 996 (33.0%) | 455 (33.7%) | 500 (35.6%) | 0.25 |
| Number of vessels treated | 1.2±0.5 | 1.2±0.5 | 1.3±0.5 | 0.04 |
| Number of lesions treated | 1.5±0.7 | 1.5±0.7 | 1.5±0.7 | 0.69 |
| Lesion morphology† | | | | |
| Moderate/severe calcification | 412 (13.7%) | 206 (15.3%) | 199 (14.2%) | 0.38 |
| Bifurcation | 343 (11.4%) | 134 (9.9%) | 174 (12.4%) | 0.12 |
| Total occlusion | 155 (5.1%) | 42 (3.1%) | 113 (8.0%) | <.001 |
| Thrombotic | 403 (13.4%) | 136 (10.1%) | 125 (8.9%) | <.001 |
| Total stent length, mm‡ | 36.2±21.6 | 36.0±21.5 | 39.2±23.9 | <.001 |

| New-Generation Drug-Eluting Stent | | | | |
|---|---|---|---|---|
| | **DP-EES N=3014 (52.2%)** | **DP-ZES N=1350 (23.4%)** | **BP-DES N=1405 (24.4%)** | **P-value** |
| Minimum stent diameter, mm | 2.9±0.5 | 2.9±0.5 | 2.9±0.5 | 0.38 |

DP-EES: durable polymer everolimus-eluting stent; DP-ZES: zotarolimus-eluting stent; BP-DES: biodegradable polymer drug-eluting stent; BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

†Lesion morphology assessed by operators

‡Stent length calculated as the addition of individual stent lengths per lesion

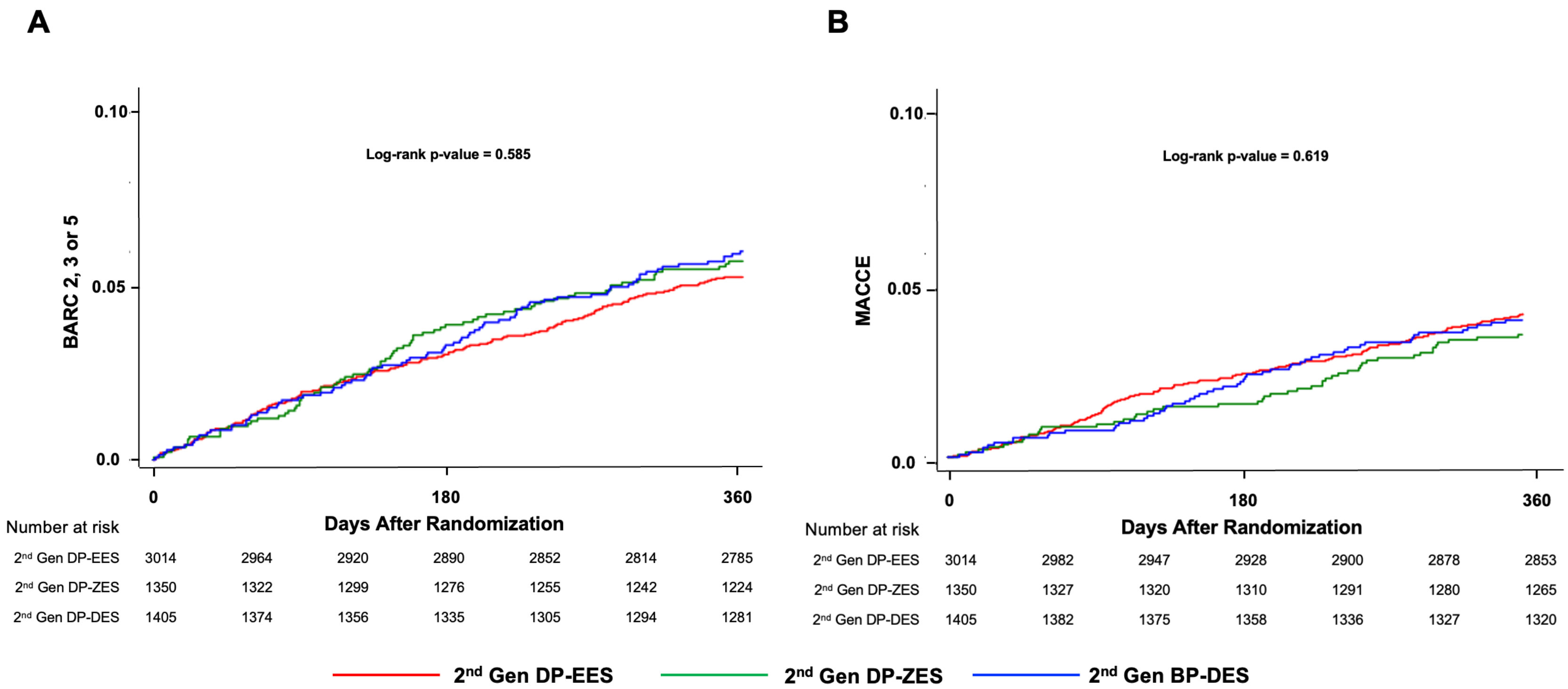
**Table 2.** Bleeding and Ischemic Events Within Each Stent Subgroup 1 Year After Randomization.

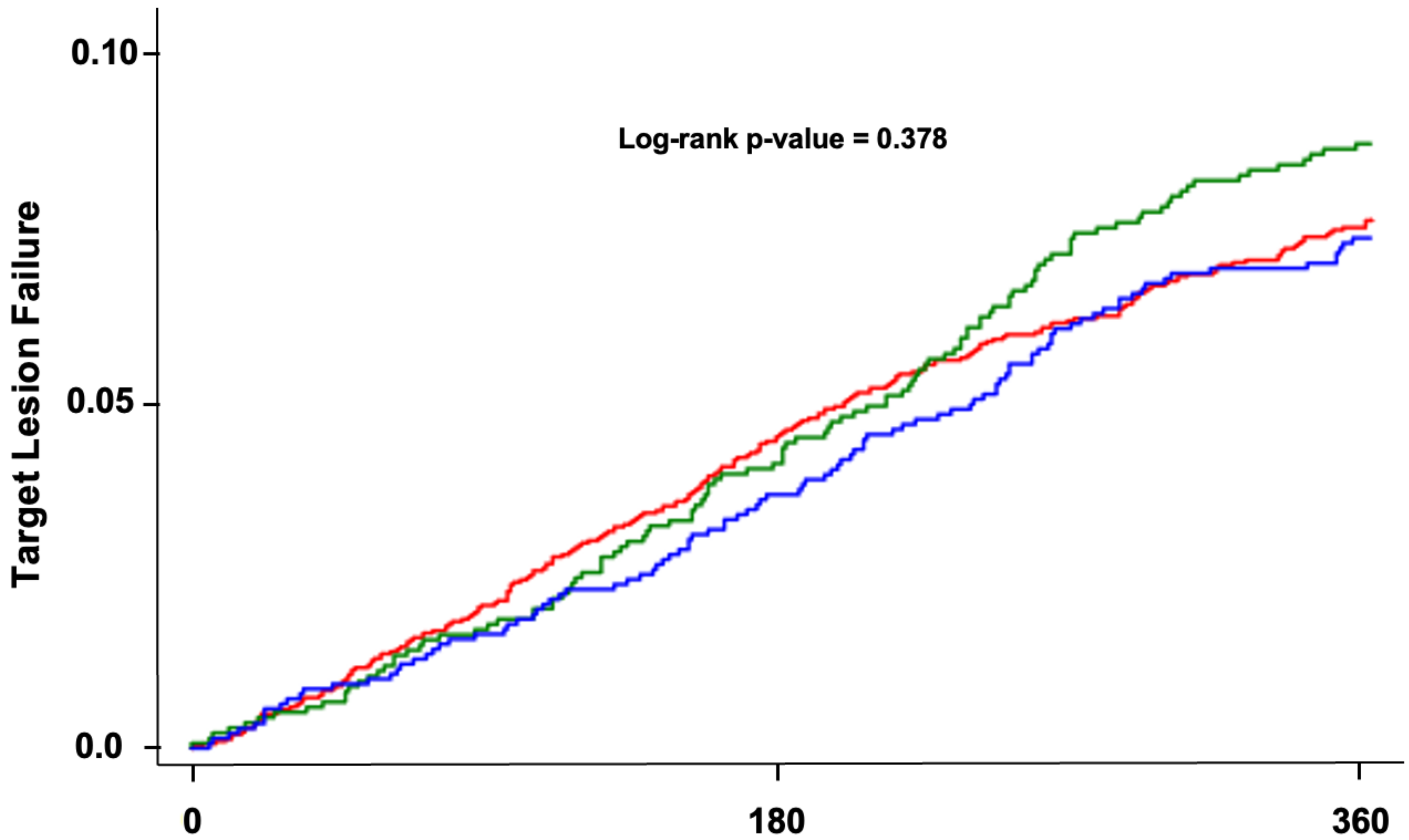
| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Tica+ placebo (N=1525)** | **Tica+ Aspirin (N=1489)** | **Hazard ratio (95% CI)** | **Tica+ placebo (N=669)** | **Tica+ Aspirin (N=681)** | **Hazard ratio (95% CI)** | **Tica+ placebo (N=705)** | **Tica+ Aspirin (N=700)** | **Hazard ratio (95% CI)** | **Interaction p-value†** |
| | no. of events (%) | | | no. of events (%) | | | no. of events (%) | | | |
| **Bleeding Endpoints** | | | | | | | | | | |
| BARC 2, 3, or 5 | 58 (3.8%) | 99 (6.7%) | 0.56 (0.41 - 0.78) | 30 (4.6%) | 46 (6.9%) | 0.66 (0.42 - 1.04) | 29 (4.2%) | 54 (7.9%) | 0.52 (0.33 - 0.81) | 0.76 |
| BARC 3 or 5 | 10 (0.7%) | 25 (1.7%) | 0.39 (0.19 - 0.81) | 8 (1.2%) | 12 (1.8%) | 0.68 (0.28 - 1.66) | 8 (1.2%) | 17 (2.5%) | 0.46 (0.20 - 1.07) | 0.64 |
| TIMI major | 4 (0.3%) | 11 (0.7%) | 0.35 (0.11 - 1.11) | 7 (1.1%) | 5 (0.7%) | 1.43 (0.45 - 4.51) | 4 (0.6%) | 7 (1.0%) | 0.57 (0.17 - 1.93) | 0.22 |
| GUSTO moderate or severe | 6 (0.4%) | 16 (1.1%) | 0.37 (0.14 - 0.93) | 7 (1.1%) | 8 (1.2%) | 0.89 (0.32 - 2.46) | 8 (1.2%) | 10 (1.4%) | 0.79 (0.31 - 2.00) | 0.36 |
| ISTH major | 11 (0.7%) | 27 (1.8%) | 0.40 (0.20 - 0.80) | 9 (1.4%) | 12 (1.8%) | 0.76 (0.32 - 1.81) | 10 (1.4%) | 18 (2.6%) | 0.55 (0.25 - 1.18) | 0.51 |
| **Ischemic Endpoints** | | | | | | | | | | |
| MACCE | 63 (4.2%) | 64 (4.3%) | 0.97 (0.68 - 1.37) | 27 (4.1%) | 21 (3.1%) | 1.32 (0.75 - 2.33) | 27 (3.9%) | 29 (4.2%) | 0.92 (0.54 - 1.55) | 0.60 |
| Target lesion failure | 112 (7.4%) | 117 (7.9%) | 0.94 (0.72 - 1.22) | 65 (9.9%) | 51 (7.6%) | 1.31 (0.91 - 1.89) | 54 (7.8%) | 48 (7.0%) | 1.13 (0.76 - 1.66) | 0.33 |
| Cardiovascular death | 10 (0.7%) | 20 (1.4%) | 0.49 (0.23 - 1.04) | 8 (1.2%) | 5 (0.7%) | 1.64 (0.54 - 5.00) | 6 (0.9%) | 7 (1.0%) | 0.85 (0.29 - 2.52) | 0.20 |
| MI | 47 (3.1%) | 44 (3.0%) | 1.05 (0.69 - 1.58) | 19 (2.9%) | 16 (2.4%) | 1.22 (0.62 - 2.36) | 17 (2.4%) | 20 (2.9%) | 0.84 (0.44 - 1.60) | 0.73 |
| Ischemic stroke | 7 (0.5%) | 1 (0.1%) | 6.85 (0.84 - 55.7) | 2 (0.3%) | 1 (0.2%) | 2.05 (0.19 - 22.6) | 2 (0.3%) | 4 (0.6%) | 0.49 (0.09 - 2.70) | 0.10 |
| Target vessel revascularization | 57 (3.8%) | 54 (3.7%) | 1.03 (0.71 - 1.50) | 30 (4.6%) | 25 (3.7%) | 1.23 (0.72 - 2.09) | 30 (4.3%) | 28 (4.1%) | 1.07 (0.64 - 1.78) | 0.87 |
| Stent thrombosis (definite/probable) | 5 (0.3%) | 9 (0.6%) | 0.54 (0.18 - 1.62) | 5 (0.8%) | 3 (0.4%) | 1.71 (0.41 - 7.14) | 3 (0.4%) | 6 (0.9%) | 0.49 (0.12 - 1.98) | 0.37 |

| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Tica+ placebo (N=1525)** | **Tica+ Aspirin (N=1489)** | **Hazard ratio (95% CI)** | **Tica+ placebo (N=669)** | **Tica+ Aspirin (N=681)** | **Hazard ratio (95% CI)** | **Tica+ placebo (N=705)** | **Tica+ Aspirin (N=700)** | **Hazard ratio (95% CI)** | **Interaction p-value†** |
| NACE | 70 (4.6%) | 83 (5.6%) | 0.82 (0.60 - 1.13) | 33 (5.0%) | 31 (4.6%) | 1.09 (0.67 - 1.77) | 35 (5.0%) | 44 (6.4%) | 0.78 (0.50 - 1.22) | 0.57 |

DP-EES: durable polymer everolimus-eluting stent; DP-ZES: zotarolimus-eluting stent; BP-DES: biodegradable polymer drug-eluting stent;
CI: confidence interval, MI: myocardial infarction, Target lesion failure: cardiac death/target vessel MI/clinically indicated revascularization/definite or probable stent thrombosis, BARC: Bleeding Academic Research Consortium
MACCE: death/MI/stroke, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis, NACE: death/MI/stroke/BARC 3 or 5
†P-value is for the test of interaction between randomized treatment assignment and stent type
The percentages mentioned above represent K-M rates at 1 year after randomization

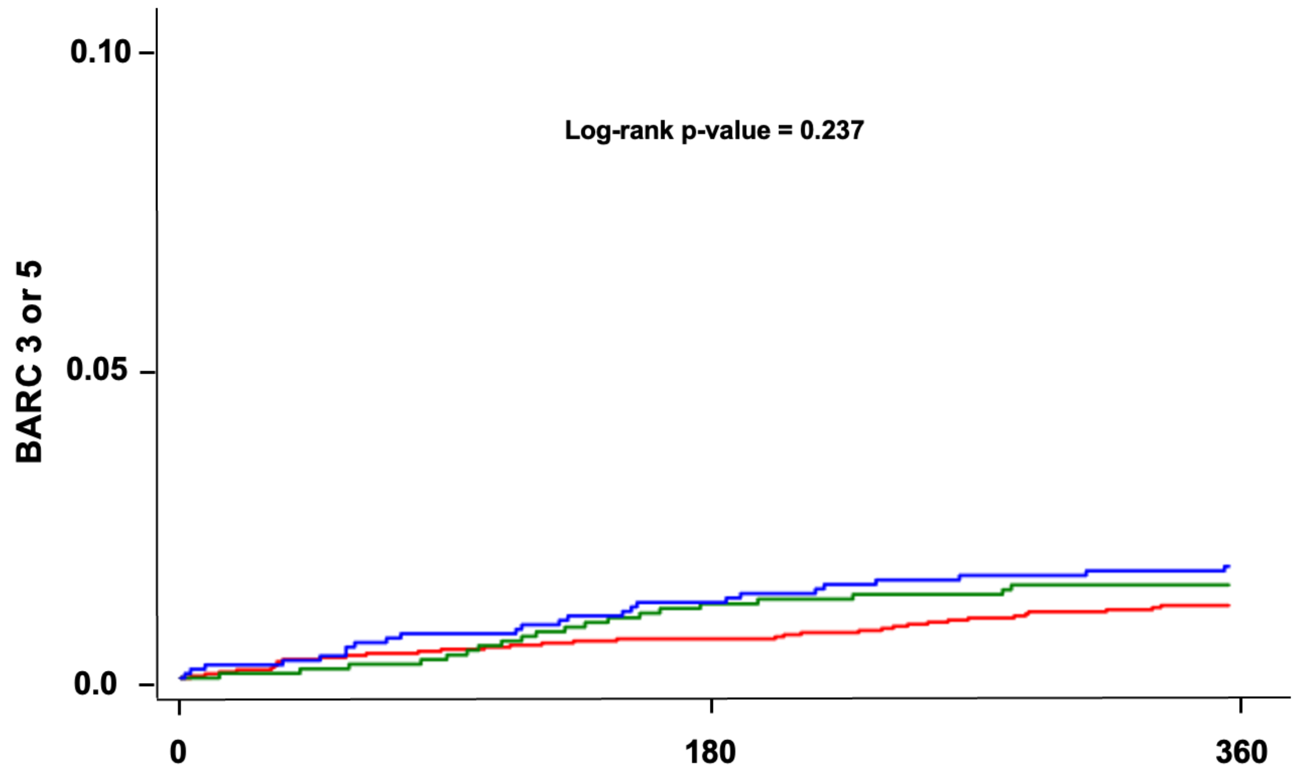
Hazard ratio comparing ticagrelor+placebo versus ticagrelor+aspirin


A
B
BARC 2, 3 or 5
MACCE
0.10
0.05
0.0
Log-rank p-value = 0.585
Log-rank p-value = 0.619
0
180
360
Days After Randomization
Number at risk
2nd Gen DP-EES 3014 2964 2920 2890 2852 2814 2785
2nd Gen DP-ZES 1350 1322 1299 1276 1255 1242 1224
2nd Gen DP-DES 1405 1374 1356 1335 1305 1294 1281
2nd Gen DP-EES 3014 2982 2947 2928 2900 2878 2853
2nd Gen DP-ZES 1350 1327 1320 1310 1291 1280 1265
2nd Gen DP-DES 1405 1382 1375 1358 1336 1327 1320
2nd Gen DP-EES
2nd Gen DP-ZES
2nd Gen BP-DES



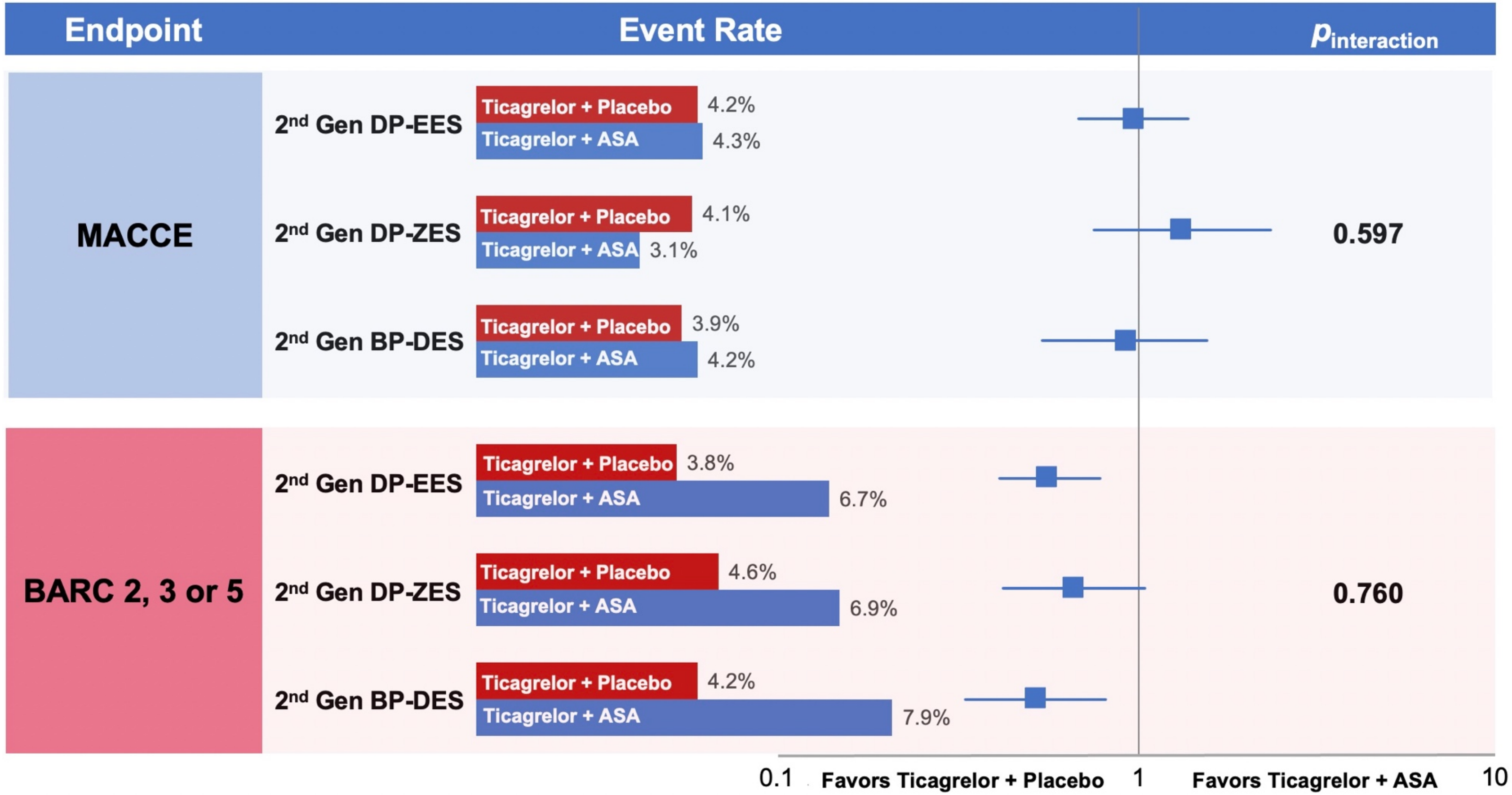

Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2nd Gen DP-EES | 3014 | 2961 | 2912 | 2862 | 2812 | 2780 | 2745 |
| 2nd Gen DP-ZES | 1350 | 1323 | 1303 | 1277 | 1242 | 1217 | 1197 |
| 2nd Gen DP-DES | 1405 | 1377 | 1359 | 1336 | 1308 | 1283 | 1272 |




| Number at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2nd Gen DP-EES | 3014 | 2987 | 2970 | 2959 | 2938 | 2920 | 2904 |
| 2nd Gen DP-ZES | 1350 | 1333 | 1322 | 1311 | 1296 | 1289 | 1278 |
| 2nd Gen DP-DES | 1405 | 1383 | 1375 | 1362 | 1345 | 1341 | 1337 |

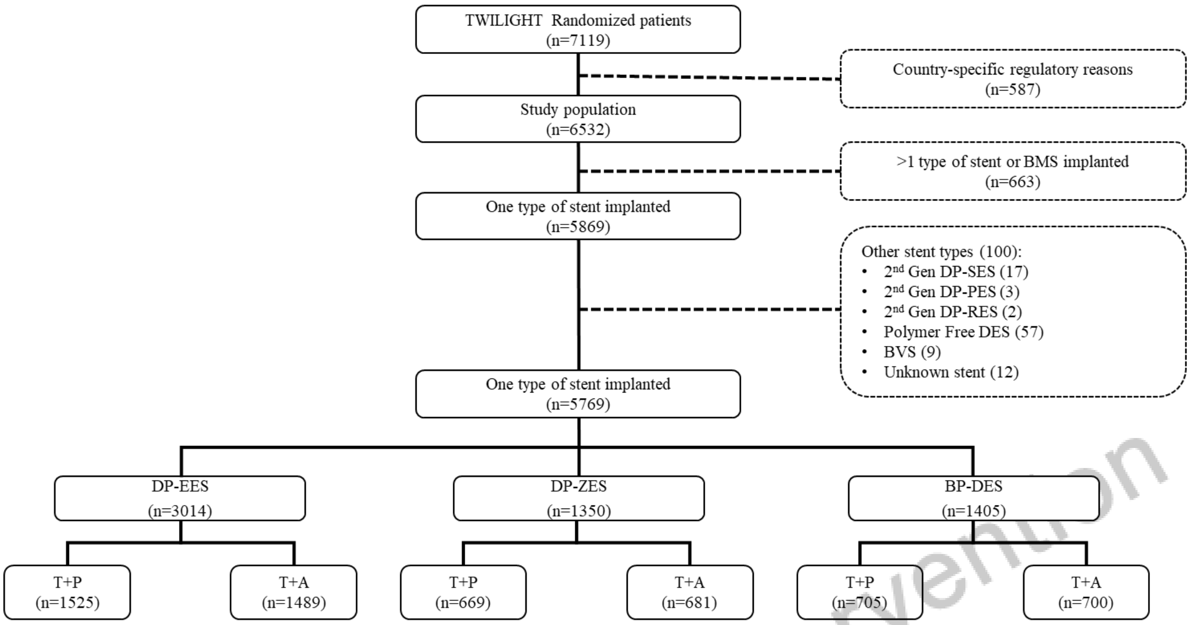
2nd Gen DP-EES — 2nd Gen DP-ZES — 2nd Gen BP-DES


Endpoint
Event Rate
pinteraction
MACCE
2nd Gen DP-EES
Ticagrelor + Placebo 4.2%
Ticagrelor + ASA 4.3%
2nd Gen DP-ZES
Ticagrelor + Placebo 4.1%
Ticagrelor + ASA 3.1%
0.597
2nd Gen BP-DES
Ticagrelor + Placebo 3.9%
Ticagrelor + ASA 4.2%
BARC 2, 3 or 5
2nd Gen DP-EES
Ticagrelor + Placebo 3.8%
Ticagrelor + ASA 6.7%
2nd Gen DP-ZES
Ticagrelor + Placebo 4.6%
Ticagrelor + ASA 6.9%
0.760
2nd Gen BP-DES
Ticagrelor + Placebo 4.2%
Ticagrelor + ASA 7.9%
0.1
Favors Ticagrelor + Placebo
1
Favors Ticagrelor + ASA
10

## Safety and Efficacy of Ticagrelor Monotherapy According to Drug-Eluting Stent Type: The TWILIGHT-STENT Analysis

### Appendix

**Supplemental Figure 1.** Study Flow Diagram




BP-DES: biodegradable polymer drug eluting stents; BVS: bioresorbable vascular scaffold; DP-EES: durable polymer everolimus eluting stents; DP-PES: durable polymer paclitaxel eluting stents; DP-RES: durable polymer ridaforolimus eluting stents; DP-SES: durable polymer sirolimus eluting stents; DP-ZES: durable polymer zotarolimus eluting stents; PF-DES: polymer-free drug eluting stents; T+A: ticagrelor + aspirin therapy; T+P: ticagrelor + placebo therapy.

**Supplemental Table 1.** Types of Drug-Eluting Stents

| DES Type | Specifications |
|---|---|
| Included DES types in the present analysis (n=5769 patients) | |
| DP-EES | Promus Premier, Promus Element, Xience Alpine, Xience Xpedition, Xience prime II, Xience pro |
| DP-ZES | Onyx, Endeavor |
| BP DES | Orsiro, Ultimaster, Alex, Abluminus, Tetriflex, Suprflex, Yukon choice flex, Yukon choice elite, Biomime, Metafor, MiStent, Destiny, Firehawk, Eucatech/eucalimus, Bioss LIM C, Xlimus, Buma, Tivoli, Helios, Noya, Prolim, Cordimax, Gureater; Synergy, Tetrilimus, Biomatrix Flex, Biomatrix Alpha, Axxess |
| Excluded DES Types from the present analysis (n=100 patients) | |
| DP SES | Firebird, Partner/Lepu, Xposition, Angiolite, Firebird 2 |
| DP PES | Active |
| DP RES | Elunir |
| POLYMER FREE | Biofreedom, Cre8, Coroflex ISR, Amazonia, Pronova, Carbo stent |
| BVS | ABSORB, Biotronik Magmaris |

DP-EES: durable polymer everolimus-eluting stent; DP-ZES: zotarolimus-eluting stent; BP-DES: biodegradable polymer drug-eluting stent; DP-SES: durable polymer sirolimus-eluting stent; DP-PES: durable polymer paclitaxel-eluting stent; DP-RES: durable polymer ridaforolimus-eluting stent; BVS: bioresorbable vascular scaffolds.

**Supplementary Table 3.** Definitions of Study Endpoints

**BARC Bleeding Definitions**

| Type | Definition |
|---|---|
| **0** | No evidence of bleeding. |
| **1** | Bleeding that is not actionable and patient does not have unscheduled studies, hospitalization or treatment by a health care professional |
| **2** | Any clinically overt sign of hemorrhage that is actionable but does not meet criteria for type 3, 4 or 5 bleeding. It must meet at least one of the following criteria:<br>• requiring medical or percutaneous intervention guided by a health care profession, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection<br>• leading to hospitalization or an increased level of care<br>• prompting evaluation defined as an unscheduled visit to a healthcare professional resulting in diagnostic testing (laboratory or imaging) |
| **3** | Clinical, laboratory and/or imaging evidence of bleeding with specific healthcare provider responses, as listed below: |
| **3a** | Any transfusion with overt bleeding<br>• Overt bleeding plus hemoglobin (Hb) drop ≥3 to <5g/dL (provided Hb drop is related to bleeding) |
| **3b** | Overt bleeding plus Hb drop ≥5g/dL* (Hb drop is related to bleed)<br>• Cardiac tamponade<br>• Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)<br>• Bleeding requiring intravenous vasoactive drugs |
| **3c** | Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal). Subcategories: confirmed by autopsy, imaging or lumbar puncture<br>• Intraocular bleed compromising vision |
| **4** | CABG – Related Bleeding<br>• Perioperative intracranial bleeding within 48 hours<br>• Reoperation following closure of sternotomy for the purpose of controlling bleeding<br>• Transfusion of ≥5 units of whole blood or packed red blood cells within a 48 hour period<br>• Chest tube output ≥2L within a 24 hour period |
| **5** | Fatal Bleeding. Bleeding directly causes death with no other explainable cause. Categorized further as either definite or probable. |

| Type | Definition |
|---|---|
| **5a** | Probable fatal bleeding is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging. |
| **5b** | Definite fatal bleeding is bleeding that is directly observed (either by clinical specimen – blood, emesis, stool, etc. – or by imaging) or confirmed on autopsy. |

**TIMI Bleeding Definitions**

| Type | Definition |
|---|---|
| Non-CABG related bleeding | |
| | • Major Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI)<br>• Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit<br>• Fatal bleeding (bleeding that directly results in death within 7 days)<br>**Life threatening** bleeding is a TIMI major bleeding event that meets any of the following criteria:<br>• Symptomatic intracranial hemorrhage<br>• Fatal bleeding<br>• Leads to hypotension requiring inotropic agents<br>• Requires surgical intervention for ongoing bleeding<br>• Necessitates transfusion of 4 or more units of whole blood or packed red blood cells over a 48-hour period<br>Minor:<br>• Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or ≥10% decrease in hematocrit<br>• No observed blood loss: ≥4 g/dL decrease in the hemoglobin concentration or ≥12% decrease in hematocrit<br>• Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major bleeding event:<br>o Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug)<br>o Leading to or prolonging hospitalization<br>o Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging)<br>Minimal<br>• Any overt bleeding event that does not meet the criteria above<br>• Any clinically overt sign of hemorrhage (including imaging) associated with a <3 g/dL decrease in hemoglobin concentration or <9% decrease in hematocrit<br>Bleeding in the setting of CABG<br>• Fatal bleeding (bleeding that directly results in death)<br>• Perioperative intracranial bleeding |

| Type | Definition |
|---|---|
| | • Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding<br>• Transfusion of ≥5 U PRBCs or whole blood within a 48-h period; cell saver transfusion will not be counted in calculations of blood products.<br>• Chest tube output >2 L within a 24-h period |

**GUSTO Bleeding Definitions**

| Type | Definition |
|---|---|
| **Severe or life-threatening** | Intracerebral bleeding or bleeding resulting in substantial hemodynamic compromise requiring treatment |
| **Moderate** | Any bleeding not meeting the requirements for severe / life-threatening bleeding that requires transfusion |
| **Minor** | Other bleeding not requiring transfusion or causing hemodynamic compromise |

**ISTH Bleeding Definitions**

The ISTH classification of major bleeding in non-surgical patients includes any one of the following:

- Fatal bleeding,
- Symptomatic bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,
- Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

**Major Adverse Cardiovascular Events**

*Classification of Death*

| | |
|---|---|
| Cardiac death | Any death due to proximate cardiac cause (eg, MI, low-output failure, fatal arrhythmia), unwitnessed death and death of unknown cause, all procedure-related deaths including those related to concomitant treatment, will be classified as cardiac death. |
| Vascular death | Death caused by noncoronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes. |
| Noncardiovascular death | Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide or trauma. |

*Myocardial Infarction*

Myocardial infarction is defined according to the third universal definition and includes:[6]

- Type 1: spontaneous MI

- Type 2: MI secondary to an ischemic imbalance
- Type 3: MI resulting in death when biomarker values are unavailable
- Type 4a. MI related to PCI
- Type 4b: MI related to stent thrombosis
- Type 5: MI related to CABG

Any one of the following criteria meets the diagnosis of MI:

- Detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile URL and with at least one of the following:
    - Symptoms of ischemia
    - (Presumed) new significant ST-T wave changes or new LBBB
    - Development of pathological Q waves
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
    - Identification of an intracoronary thrombus by angiography or autopsy
- Cardiac death with symptoms suggestive of MI and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased
- PCI related MI is arbitrarily defined by elevation of cardiac biomarkers
    - (>5 x 99th percentile URL) in patients with normal baseline values or
    - > 20% if the baseline values are elevated and are stable or falling

In addition, one of the following is required:

- Symptoms suggestive of ischemia
- New ischemic ECG changes
- Angiographic findings consistent with a procedural complication OR
- Imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality

- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL
- CABG related MI is arbitrarily defined by elevation of cardiac biomarkers >10 x 99th percentile URL in patients with normal baseline values, AND one of the following:
    - New pathological Q waves or new LBBB
    - Angiographic documented new graft or new native coronary artery occlusion, or
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*Stroke*

Stroke is defined as an acute symptomatic episode of neurological dysfunction, more than 24 hours in duration in the absence of therapeutic intervention or death, due to cerebral, spinal or retinal tissue injury as evidenced by neuroimaging or lumbar puncture. It includes the following subclassifications:

- Ischemic stroke: infarction due to prolonged ischemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion.
- Hemorrhagic stroke: caused by a non-traumatic intraparenchymal, intraventricular or subarachnoid hemorrhage
- Undetermined: stroke with insufficient information to determine ischemic or hemorrhagic cause

- Transient ischemic attack (TIA) is a transient episode of neurological dysfunction (< 24 hours) caused by temporary cerebral, spinal or retinal ischemia with no evidence of acute infarction on neuroimaging.

*Stent thrombosis*

Stent thrombosis is classified according to the level of certainty and timing following PCI.[5]

- Definite stent thrombosis: is highly specific and requires angiographic or pathological confirmation of stent thrombosis in or within 5 mm of the stent in the setting of at least one of the following criteria with a 48-hour time window
  - Acute ischemic symptoms at rest
  - New ischemic ECG changes
  - Typical rise and fall in cardiac biomarkers
- Probable stent thrombosis includes
  - Any unexplained death within the first 30 days following PCI
  - Any MI at any time following PCI that is related to documented acute ischemia in the territory of the implanted stent, in the absence of angiographic/pathological confirmation of stent thrombosis and no other obvious cause
- Possible stent thrombosis
  - Any unexplained death after the first 30 days following PCI until the end of trial follow-up

**Timing of Stent Thrombosis**

| | |
|---|---|
| Acute | 0-24 hours following PCI |
| Subacute | >24 hours to 30 days following |
| PCI Late | >30 days to 1 year following PCI |
| Very late | >1 year following PCI |

**Clinically Driven Revascularization**

Clinically driven revascularization includes repeat PCI or CABG for recurrent or persistent symptomatic ischemia and can be defined according to the relationship to the index PCI (target lesion)[5]:

- Target lesion revascularization, at the previously stented segment
- Non-target lesion, target vessel revascularization, of the previously treated vessel or its side branches AND
- Non-target vessel lesion revascularization, of a vessel other than the previously treated vessel

**Other Definitions**

*Coronary Artery Disease (CAD)*

Multivessel (CAD), defined as significant disease in at least 2 major epicardial vessels or significant left main disease plus one major epicardial vessel. Significant coronary artery disease is defined as angiographic stenosis of at least 70% in a major epicardial vessel or at least 50% in the left main trunk. For intermediate stenosis in major epicardial vessels (50%-70%), an invasive hemodynamic assessment using fractional flow reserve (FFR) with values less than or equal to 0.8 will be considered significant. For intermediate left main lesions, a minimal lumen area by intravascular ultrasound (IVUS) less than 6.0 $mm^2$ will be considered significant.

*Successful PCI*

PCI is considered successful for lesions treated with stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 10% and the final TIMI flow grade is 3. PCI is considered successful for lesions treated without stent implantation if the residual diameter stenosis based on visual estimation is less than or equal to 30% and the final TIMI flow grade is 3.

**Supplementary Table 3.** Baseline Clinical and Procedural Characteristics Within Each Stent Group.

| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Tica+ placebo (N=1525)** | **Tica+ Aspirin (N=1489)** | **p-value** | **Tica+ placebo (N=669)** | **Tica+ Aspirin (N=681)** | **p-value** | **Tica+ placebo (N=705)** | **Tica+ Aspirin (N=700)** | **p-value** |
| Age, years | 64.0±10.0 | 63.8±10.2 | 0.656 | 64.3±9.9 | 64.1±10.3 | 0.720 | 63.9±10.3 | 64.4±10.0 | 0.303 |
| Female sex | 359 (23.5%) | 337 (22.6%) | 0.554 | 154 (23.0%) | 167 (24.5%) | 0.517 | 175 (24.8%) | 167 (23.9%) | 0.673 |
| BMI, $kg/m^2$ | 29.3±5.8 | 29.2±6.0 | 0.620 | 29.2±5.9 | 29.2±5.4 | 0.894 | 28.4±5.2 | 28.4±5.3 | 0.924 |
| Diabetes | 567 (37.2%) | 540 (36.3%) | 0.603 | 272 (40.7%) | 254 (37.3%) | 0.206 | 247 (35.0%) | 257 (36.7%) | 0.512 |
| Diabetes treated with insulin | 146 (25.7%) | 158 (29.3%) | 0.191 | 71 (26.1%) | 73 (28.7%) | 0.498 | 64 (25.9%) | 74 (28.8%) | 0.468 |
| Chronic kidney disease | 233 (15.9%) | 257 (17.9%) | 0.147 | 123 (18.8%) | 115 (17.4%) | 0.507 | 125 (18.8%) | 110 (16.4%) | 0.254 |
| Anemia | 295 (20.2%) | 277 (19.3%) | 0.536 | 129 (19.8%) | 130 (19.7%) | 0.968 | 121 (18.2%) | 126 (19.0%) | 0.695 |
| Current smoker | 290 (19.0%) | 327 (22.0%) | 0.043 | 138 (20.6%) | 149 (21.9%) | 0.574 | 144 (20.5%) | 173 (24.7%) | 0.056 |
| Hypercholesterolemia | 1051 (68.9%) | 1025 (68.8%) | 0.962 | 488 (72.9%) | 477 (70.0%) | 0.238 | 405 (57.4%) | 409 (58.4%) | 0.709 |
| Hypertension | 1142 (74.9%) | 1131 (76.0%) | 0.474 | 501 (74.9%) | 501 (73.6%) | 0.579 | 514 (72.9%) | 500 (71.4%) | 0.536 |
| Peripheral arterial disease | 97 (6.4%) | 110 (7.4%) | 0.265 | 78 (11.7%) | 60 (8.8%) | 0.084 | 43 (6.1%) | 44 (6.3%) | 0.885 |

| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Tica+ placebo (N=1525)** | **Tica+ Aspirin (N=1489)** | **p-value** | **Tica+ placebo (N=669)** | **Tica+ Aspirin (N=681)** | **p-value** | **Tica+ placebo (N=705)** | **Tica+ Aspirin (N=700)** | **p-value** |
| Previous MI | 485 (31.8%) | 468 (31.4%) | 0.826 | 202 (30.2%) | 192 (28.2%) | 0.419 | 206 (29.2%) | 208 (29.7%) | 0.839 |
| Previous PCI | 672 (44.1%) | 661 (44.4%) | 0.857 | 326 (48.7%) | 318 (46.7%) | 0.455 | 303 (43.0%) | 301 (43.0%) | 0.994 |
| Previous CABG | 198 (13.0%) | 170 (11.4%) | 0.189 | 87 (13.0%) | 69 (10.1%) | 0.097 | 57 (8.1%) | 83 (11.9%) | 0.018 |

| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tica+ placebo (N=1525) | Tica+ Aspirin (N=1489) | p-value | Tica+ placebo (N=669) | Tica+ Aspirin (N=681) | p-value | Tica+ placebo (N=705) | Tica+ Aspirin (N=700) | p-value |
| Multivessel CAD | 926 (60.7%) | 860 (57.8%) | 0.098 | 462 (69.1%) | 414 (60.8%) | 0.001 | 424 (60.1%) | 420 (60.0%) | 0.957 |
| Previous major bleed | 13 (0.9%) | 15 (1.0%) | 0.658 | 7 (1.0%) | 3 (0.4%) | 0.221 | 5 (0.7%) | 6 (0.9%) | 0.753 |
| Indication for PCI | | | 0.300 | | | 0.009 | | | 0.003 |
| ACS | 965 (63.3%) | 915 (61.5%) | | 365 (54.6%) | 420 (61.7%) | | 444 (63.0%) | 493 (70.4%) | |
| Stable CAD | 560 (36.7%) | 574 (38.5%) | | 303 (45.4%) | 261 (38.3%) | | 261 (37.0%) | 207 (29.6%) | |
| Target vessel | | | | | | | | | |
| Left Main | 57 (3.7%) | 67 (4.5%) | 0.292 | 27 (4.0%) | 30 (4.4%) | 0.736 | 34 (4.8%) | 27 (3.9%) | 0.375 |
| LAD | 811 (53.2%) | 808 (54.3%) | 0.551 | 358 (53.5%) | 356 (52.3%) | 0.649 | 412 (58.4%) | 390 (55.7%) | 0.302 |
| LCX | 480 (31.5%) | 469 (31.5%) | 0.990 | 228 (34.1%) | 206 (30.2%) | 0.132 | 206 (29.2%) | 204 (29.1%) | 0.975 |
| RCA | 513 (33.6%) | 483 (32.4%) | 0.483 | 221 (33.0%) | 234 (34.4%) | 0.606 | 239 (33.9%) | 261 (37.3%) | 0.185 |
| Number of vessels treated | 1.2±0.5 | 1.2±0.5 | 0.663 | 1.2±0.5 | 1.2±0.5 | 0.151 | 1.3±0.5 | 1.3±0.5 | 0.885 |
| Number of lesions treated | 1.5±0.7 | 1.5±0.7 | 0.879 | 1.5±0.7 | 1.4±0.7 | 0.016 | 1.5±0.7 | 1.5±0.7 | 0.613 |
| Lesion morphology† | | | | | | | | | |

| | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tica+ placebo (N=1525) | Tica+ Aspirin (N=1489) | p-value | Tica+ placebo (N=669) | Tica+ Aspirin (N=681) | p-value | Tica+ placebo (N=705) | Tica+ Aspirin (N=700) | p-value |
| Moderate/severe calcification | 214 (14.0%) | 198 (13.3%) | 0.557 | 105 (15.7%) | 101 (14.8%) | 0.659 | 99 (14.0%) | 100 (14.3%) | 0.896 |
| Bifurcation | 174 (11.4%) | 169 (11.3%) | 0.959 | 67 (10.0%) | 67 (9.8%) | 0.914 | 90 (12.8%) | 84 (12.0%) | 0.663 |
| Total occlusion | 85 (5.6%) | 70 (4.7%) | 0.278 | 21 (3.1%) | 21 (3.1%) | 0.953 | 55 (7.8%) | 58 (8.3%) | 0.739 |
| Thrombotic | 197 (12.9%) | 206 (13.8%) | 0.460 | 59 (8.8%) | 77 (11.3%) | 0.129 | 64 (9.1%) | 61 (8.7%) | 0.811 |
| Total stent length, mm‡ | 36.6±21.4 | 35.9±21.7 | 0.388 | 36.3±21.1 | 35.6±21.9 | 0.552 | 39.3±24.2 | 39.2±23.6 | 0.970 |
| Minimum stent diameter, mm | 2.9±0.5 | 2.9±0.5 | 0.610 | 2.8±0.5 | 2.9±0.5 | 0.285 | 2.9±0.5 | 2.9±0.5 | 0.776 |

BMI: body mass index, MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, CAD: coronary artery disease, ACS: Acute coronary syndrome, CAD: coronary artery disease, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery

†Lesion morphology assessed by operators

‡Stent length calculated as the addition of individual stent lengths per lesion.

**Supplemental Table 4.** Outcomes Associated With DES Types 1-Year After Randomization

| | Event (%) | Hazard ratio (95% CI) | p-value | Adjusted Hazard ratio (95% CI)† | p-value | Interaction p-value‡ |
|---|---|---|---|---|---|---|
| **Target lesion failure** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 229 (7.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 116 (8.7%) | 1.14 (0.91 - 1.43) | 0.247 | 1.07 (0.86 - 1.34) | 0.532 | 0.368 |
| 2nd Gen BP-DES (n=1405) | 102 (7.4%) | 0.96 (0.76 - 1.21) | 0.717 | 1.03 (0.82 - 1.31) | 0.784 | |
| **BARC 2, 3, or 5** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 157 (5.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 76 (5.7%) | 1.09 (0.83 - 1.44) | 0.532 | 1.09 (0.83 - 1.43) | 0.555 | 0.772 |
| 2nd Gen BP-DES (n=1405) | 83 (6.0%) | 1.14 (0.88 - 1.49) | 0.324 | 1.17 (0.89 - 1.52) | 0.264 | |
| **MACCE** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 127 (4.2%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 48 (3.6%) | 0.85 (0.61 - 1.18) | 0.328 | 0.79 (0.56 - 1.10) | 0.164 | 0.685 |
| 2nd Gen BP-DES (n=1405) | 56 (4.0%) | 0.95 (0.69 - 1.30) | 0.756 | 0.99 (0.72 - 1.36) | 0.961 | |
| **Cardiovascular death** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 30 (1.0%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 13 (1.0%) | 0.97 (0.51 - 1.87) | 0.939 | 0.91 (0.47 - 1.76) | 0.789 | 0.168 |
| 2nd Gen BP-DES (n=1405) | 13 (0.9%) | 0.94 (0.49 - 1.79) | 0.841 | 1.00 (0.52 - 1.94) | 0.994 | |
| **Myocardial infarction** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 91 (3.0%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 35 (2.6%) | 0.86 (0.58 - 1.27) | 0.454 | 0.80 (0.54 - 1.19) | 0.278 | 0.833 |
| 2nd Gen BP-DES (n=1405) | 37 (2.7%) | 0.88 (0.60 - 1.28) | 0.498 | 0.93 (0.63 - 1.37) | 0.728 | |
| **Ischemic stroke** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 8 (0.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 3 (0.2%) | 0.84 (0.22 - 3.18) | 0.802 | 0.82 (0.22 - 3.10) | 0.767 | 0.104 |
| 2nd Gen BP-DES (n=1405) | 6 (0.4%) | 1.62 (0.56 - 4.67) | 0.371 | 1.56 (0.53 - 4.53) | 0.417 | |
| **Target vessel revascularization** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 111 (3.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 55 (4.2%) | 1.11 (0.80 - 1.54) | 0.520 | 1.06 (0.77 - 1.47) | 0.714 | 0.918 |
| 2nd Gen BP-DES (n=1405) | 58 (4.2%) | 1.13 (0.82 - 1.55) | 0.463 | 1.18 (0.86 - 1.63) | 0.301 | |
| **Stent thrombosis (definite/probable)** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 14 (0.5%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 8 (0.6%) | 1.29 (0.54 - 3.07) | 0.570 | 1.26 (0.52 - 3.01) | 0.608 | 0.395 |
| 2nd Gen BP-DES (n=1405) | 9 (0.7%) | 1.39 (0.60 - 3.21) | 0.442 | 1.51 (0.65 - 3.52) | 0.336 | |

| | Event (%) | Hazard ratio (95% CI) | p-value | Adjusted Hazard ratio (95% CI)† | p-value | Interaction p-value‡ |
|---|---|---|---|---|---|---|
| **BARC 3 or 5 bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 35 (1.2%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 20 (1.5%) | 1.29 (0.74 - 2.23) | 0.369 | 1.20 (0.69 - 2.08) | 0.517 | 0.705 |
| 2nd Gen BP-DES (n=1405) | 25 (1.8%) | 1.55 (0.93 - 2.58) | 0.096 | 1.56 (0.93 - 2.62) | 0.093 | |
| **TIMI major bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 15 (0.5%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 12 (0.9%) | 1.80 (0.84 - 3.85) | 0.129 | 1.74 (0.81 - 3.73) | 0.156 | 0.238 |
| 2nd Gen BP-DES (n=1405) | 11 (0.8%) | 1.58 (0.73 - 3.45) | 0.247 | 1.60 (0.73 - 3.51) | 0.242 | |
| **GUSTO moderate or severe bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 22 (0.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 15 (1.1%) | 1.53 (0.80 - 2.96) | 0.201 | 1.41 (0.73 - 2.74) | 0.303 | 0.406 |
| 2nd Gen BP-DES (n=1405) | 18 (1.3%) | 1.77 (0.95 - 3.30) | 0.072 | 1.81 (0.96 - 3.39) | 0.066 | |
| **ISTH major bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 38 (1.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 21 (1.6%) | 1.24 (0.73 - 2.12) | 0.423 | 1.15 (0.68 - 1.97) | 0.599 | 0.578 |
| 2nd Gen BP-DES (n=1405) | 28 (2.0%) | 1.60 (0.98 - 2.60) | 0.060 | 1.59 (0.97 - 2.61) | 0.065 | |
| **NACE** | | | | | | |
| 2nd Gen DP-EES (n=3014) | 153 (5.1%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1350) | 64 (4.8%) | 0.94 (0.70 - 1.26) | 0.674 | 0.87 (0.65 - 1.17) | 0.368 | 0.675 |
| 2nd Gen BP-DES (n=1405) | 79 (5.7%) | 1.12 (0.85 - 1.47) | 0.417 | 1.16 (0.88 - 1.53) | 0.280 | |

DP-EES: durable polymer everolimus-eluting stent; DP-ZES: zotarolimus-eluting stent; BP-DES: biodegradable polymer drug-eluting stent; CI: confidence interval, MI: myocardial infarction, Target lesion failure: cardiac death/target vessel MI/clinically indicated revascularization/definite or probable stent thrombosis, BARC: Bleeding Academic Research Consortium, MACCE: death/MI/stroke, TIMI: Thrombolysis in Myocardial Infarction, GUSTO: Global Utilization of Streptokinase
and TPA for Occluded Arteries, ISTH: International Society on Thrombosis and Hemostasis, NACE: death/MI/stroke/BARC 3 or 5 bleeding events

†Model adjusted for body mass index (kg/m$^2$), hypercholesterolemia, peripheral arterial disease, previous PCI or CABG, multivessel CAD, indication for PCI, total occlusion of target vessel, total stent length (mm)

‡P-value is from the interaction test between randomized treatment assignment and stent type with model adjustment

The percentages mentioned above represent K-M rates at 1 year after randomization