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# Safety and efficacy of ticagrelor monotherapy according to drug-eluting stent type: the TWILIGHT-STENT study

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**KEYWORDS**

- adjunctive pharmacotherapy
- bleeding
- clinical trials
- drug-eluting stent

## 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 stents (DES).

**Aims:** The aim of this study was to evaluate the effects of ticagrelor monotherapy after three-month DAPT in patients undergoing PCI, according to DES type.

**Methods:** In the current sub-analysis from TWILIGHT, patients were stratified into three 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 ischaemic outcomes were assessed at one year after randomisation.

**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 ischaemic or bleeding complications.

**Conclusions:** As compared with ticagrelor plus aspirin, ticagrelor monotherapy after a short DAPT duration lowered bleeding complications without increasing the ischaemic risk, irrespective of DES type. We observed no significant differences among DES types.

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## 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 Haemostasis |
| **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 ischaemic events, results in significantly higher rates of major bleeding complications which are in turn 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 been demonstrated to reduce bleeding risk while preserving ischaemic protection[11]. Monotherapy with the potent $P2Y_{12}$-receptor inhibitor ticagrelor following three months of DAPT resulted in a lower incidence of clinically relevant bleeding without increasing the risk of ischaemic events, compared to continuing DAPT up to 15 months post-PCI with DES[11]. Patients undergoing PCI with different stent types may have variable ischaemic/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 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 three months of DAPT after PCI with different types of new-generation DES.

## Methods

### STUDY DESIGN

TWILIGHT was an international, multicentre, randomised, 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 centres 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 DES and 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 ischaemic 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 or with a bare metal stent implanted were excluded. A full list of the commercially approved DES types included in the analysis is provided in **Supplementary Table 1**. The clinical criteria for high risk were: age ≥65 years, female sex, troponin-positive acute coronary syndrome (ACS), 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 (CAD), 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 three-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 ischaemic event (stroke, myocardial infarction, or coronary revascularisation) were eligible for randomisation 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 ischaemic risk, as reflected by the procedural/angiographic inclusion criteria of the study population[11,13]. Follow-up was performed by telephone at one month after randomisation and in person at

six and 12 months after randomisation. 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 a final telephone follow-up three months later.

### ENDPOINTS

The primary endpoint of the study was BARC type 2, 3 or 5 bleeding[15] between randomisation and the one-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, non-fatal myocardial infarction (MI) or non-fatal 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 Haemostasis (ISTH)[18]. Other secondary endpoints included death from cardiovascular causes, MI, ischaemic stroke, and definite or probable stent thrombosis (ST). MI was defined according to the third universal definition[19], and revascularisation 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 ischaemic 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$^2$), hypercholesterolaemia, peripheral arterial disease, previous PCI or coronary artery bypass graft surgery, multivessel CAD, indication for PCI (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, TX, USA). 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 three 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 three types of DES are reported in **Figure 1-Figure 3** and **Supplementary Table 4**; in both univariate analysis and multivariable analyses,

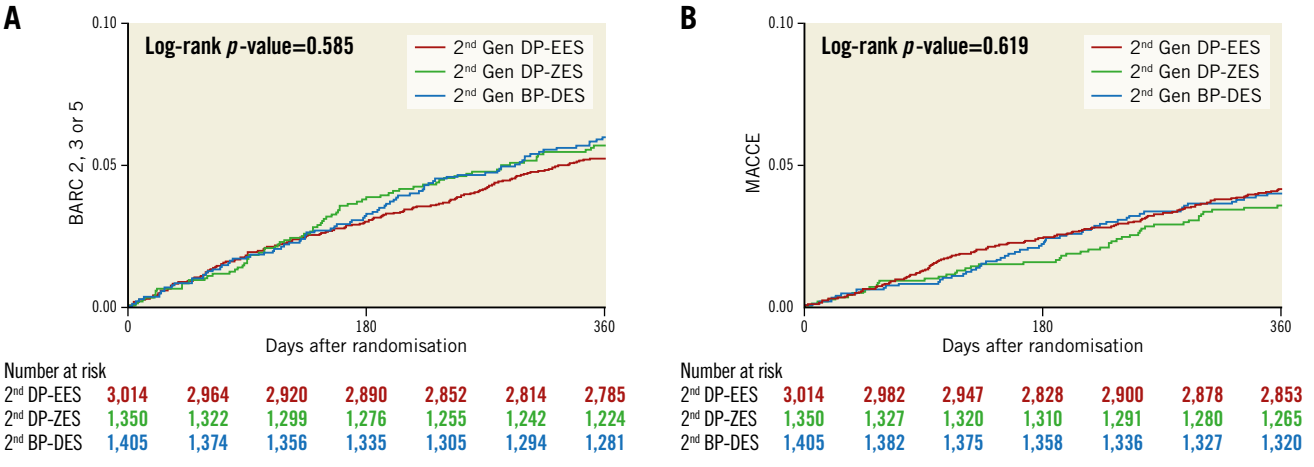



**Figure 1.** *Rates of (A) BARC 2, 3 or 5 bleeding and (B) MACCE among the three DES types evaluated. Kaplan-Meier estimates for BARC 2, 3 or 5 bleeding and target lesion failure at 12 months after randomisation (intention-to-treat population) by drug-eluting stent type in patients who underwent percutaneous coronary intervention. BARC: Bleeding Academic Research Consortium; BP-DES: biodegradable polymer drug-eluting stent; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; Gen: generation; MACCE: major adverse cardiac and cerebral events (all-cause death, myocardial infarction, or stroke)*

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

| New-generation drug-eluting stent | | DP-EES N=3,014 (52.2%) | DP-ZES N=1,350 (23.4%) | BP-DES N=1,405 (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 | <0.001 |
| Diabetes | | 1,107 (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 |
| Anaemia | | 572 (19.8%) | 259 (19.7%) | 247 (18.6%) | 0.67 |
| Current smoker | | 617 (20.5%) | 287 (21.3%) | 317 (22.6%) | 0.28 |
| Hypercholesterolaemia | | 2,076 (68.9%) | 965 (71.5%) | 814 (57.9%) | <0.001 |
| Hypertension | | 2,273 (75.4%) | 1,002 (74.2%) | 1,014 (72.2%) | 0.07 |
| Peripheral arterial disease | | 207 (6.9%) | 138 (10.2%) | 87 (6.2%) | <0.001 |
| Previous MI | | 953 (31.6%) | 394 (29.2%) | 414 (29.5%) | 0.17 |
| Previous PCI | | 1,333 (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 | | 1,786 (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 | ACS | 1,880 (62.4%) | 785 (58.2%) | 937 (66.7%) | <0.001 |
| | Stable CAD | 1,134 (37.6%) | 564 (41.8%) | 468 (33.3%) | |
| Target vessel | Left main | 124 (4.1%) | 57 (4.2%) | 61 (4.3%) | 0.94 |
| | LAD | 1,619 (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%) | <0.001 |
| | Thrombotic | 403 (13.4%) | 136 (10.1%) | 125 (8.9%) | <0.001 |
| Total stent length, mm# | | 36.2±21.6 | 36.0±21.5 | 39.2±23.9 | <0.001 |
| Minimum stent diameter, mm | | 2.9±0.5 | 2.9±0.5 | 2.9±0.5 | 0.38 |

*Lesion morphology assessed by operators. #Stent length calculated as the addition of individual stent lengths per lesion. ACS: acute coronary syndrome; BMI: body mass index; BP-DES: biodegradable polymer drug-eluting stent; CABG: coronary artery bypass graft; CAD: coronary artery disease; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; LAD: left anterior descending; LCx: left circumflex; MI: myocardial infarction; PCI: percutaneous coronary intervention; RCA: right coronary artery

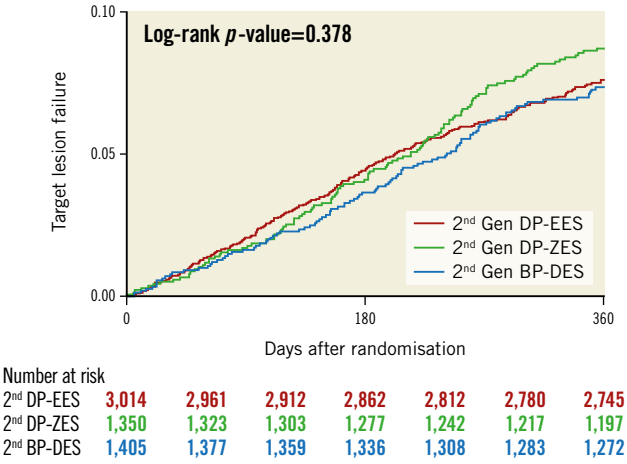
DES type was not associated with an increased risk of MACCE, target lesion failure (TLF) or major bleeding complications. One-year rates of stent thrombosis were <1% across all DES platforms.

## BLEEDING OUTCOMES

Bleeding event rates in patients according to randomised treatment assignment (ticagrelor plus placebo versus ticagrelor plus aspirin) and DES type are reported in **Table 2**. Overall, the reduction in bleeding rates of ticagrelor monotherapy was consistent across DES types. Ticagrelor monotherapy consistently resulted in significantly lower rates of BARC type 2, 3 or 5 bleeding at one year after randomisation 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 ($p_{interaction}$=0.76) **(Central illustration)**. These results were also consistent when other bleeding definitions were examined **(Table 2)**.

## ISCHAEMIC OUTCOMES

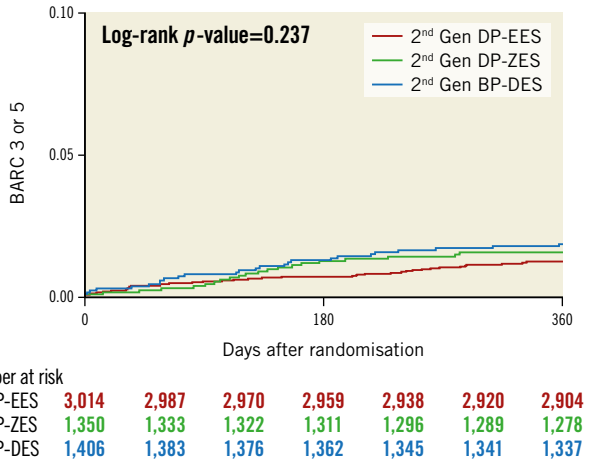
Ischaemic event rates in patients according to randomised group (ticagrelor plus placebo versus ticagrelor plus aspirin) and stent type are reported in **Table 2**. There were no significant differences




Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2nd DP-EES | 3,014 | 2,961 | 2,912 | 2,862 | 2,812 | 2,780 | 2,745 |
| 2nd DP-ZES | 1,350 | 1,323 | 1,303 | 1,277 | 1,242 | 1,217 | 1,197 |
| 2nd BP-DES | 1,405 | 1,377 | 1,359 | 1,336 | 1,308 | 1,283 | 1,272 |

**Figure 2.** *Rates of target lesion failure among the three DES types evaluated. Kaplan-Meier estimates for target lesion failure at 12 months after randomisation (intention-to-treat population) by drug-eluting stent type in patients who underwent percutaneous coronary intervention. BP-DES: biodegradable polymer drug-eluting stent; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; Gen: generation*

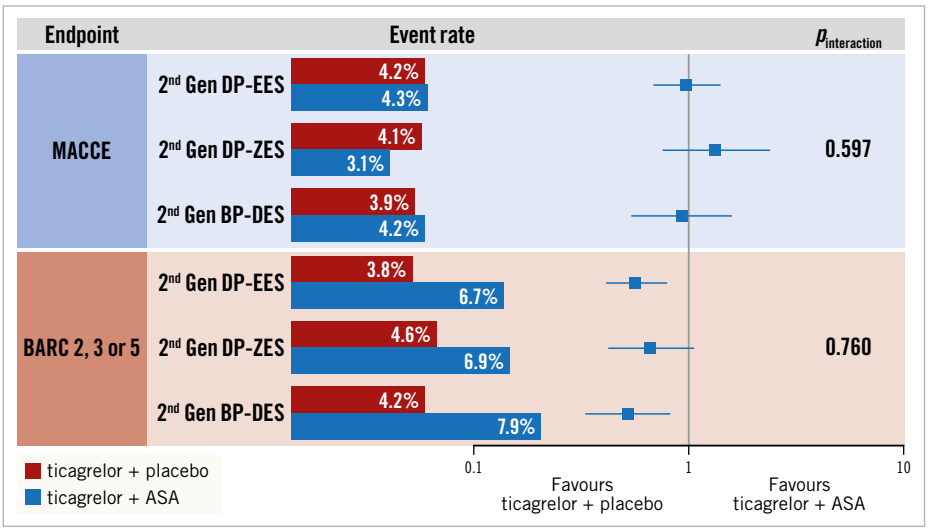



Number at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 2nd DP-EES | 3,014 | 2,987 | 2,970 | 2,959 | 2,938 | 2,920 | 2,904 |
| 2nd DP-ZES | 1,350 | 1,333 | 1,322 | 1,311 | 1,296 | 1,289 | 1,278 |
| 2nd BP-DES | 1,406 | 1,383 | 1,376 | 1,362 | 1,345 | 1,341 | 1,337 |

**Figure 3.** *Rates of BARC 3 or 5 bleeding among the three DES types evaluated. Kaplan-Meier estimates for BARC 3 or 5 bleeding at 12 months after randomisation by drug-eluting stent type in patients who underwent percutaneous coronary intervention. BARC: Bleeding Academic Research Consortium; BP-DES: biodegradable polymer drug-eluting stent; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; Gen: generation*

in MACCE between ticagrelor monotherapy and ticagrelor plus aspirin 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 ($p_{interaction}$=0.597). Additionally, there were no significant




**Central illustration.** *Bleeding and ischaemic effects of ticagrelor monotherapy versus ticagrelor plus aspirin after three months of DAPT in patients undergoing PCI with second-generation DES. Following three months of adherence to DAPT post-PCI and in the absence of major bleeding or ischaemic 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 one year consistently across the three studied DES types. There was no significant difference in the one-year rate of all-cause death, MI, or stroke between the two treatment arms; this was also consistent across the 3 DES types. ASA: aspirin; BARC: Bleeding Academic Research Consortium; BP-DES: biodegradable polymer drug-eluting stent; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; Gen: generation; MACCE: major adverse cardiac and cerebrovascular events, a composite of death, myocardial infarction or stroke.*

**Table 2. Bleeding and ischaemic events within each stent subgroup one year after randomisation.**

| no. of events (%) | DP-EES (N=3,014) | | | DP-ZES (N=1,350) | | | BP-DES (N=1,405) | | | Interaction *p*-value* |
|---|---|---|---|---|---|---|---|---|---|---|
| | Tica+ placebo (N=1,525) | Tica+ aspirin (N=1,489) | 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) | |
| **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 |
| **Ischaemic 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 |
| Ischaemic 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 revascularisation | 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 |
| 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 |

*P-value is for the test of interaction between randomised treatment assignment and stent type. The percentages mentioned above represent K-M rates at 1 year after randomisation. Hazard ratio comparing ticagrelor+placebo versus ticagrelor+aspirin. Target lesion failure: cardiac death/target vessel MI/clinically indicated revascularisation/definite or probable stent thrombosis. BARC: bleeding academic research consortium; BP-DES: biodegradable polymer drug-eluting stent; CI: confidence interval; DP-EES: durable polymer everolimus-eluting stent; DP-ZES: durable polymer zotarolimus-eluting stent; ISTH: International Society on Thrombosis and Haemostasis; MACCE: death/MI/stroke; MI: myocardial infarction; NACE: death/MI/stroke/BARC 3 or 5; TIMI: Thrombolysis in Myocardial Infarction; GUSTO: global utilization of streptokinase and TPA for occluded arteries

differences among groups regarding the individual ischaemic endpoints **(Central illustration, Table 2)**. The rates of DES thrombosis were <1% and not influenced by the randomised 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 three months of DAPT according to stent type, include: (i) ticagrelor monotherapy compared with ticagrelor plus aspirin resulted in significantly lower major bleeding complications, a finding that was consistent across new-generation DES types; (ii) ticagrelor monotherapy compared to ticagrelor plus aspirin was not associated with increased risk of ischaemic events irrespective of the type of new-generation DES; and (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 randomised treatment assignment.

Iteration in DES technologies including improved drug release kinetics, polymer biocompatibility, and endothelialisation patterns of new-generation DES significantly overcame the limitations observed with early-generation DES[4,10]. In the era of first-generation DES, an 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 ischaemic events, it may also result in higher risk of haemorrhagic complications which are strongly associated with increased risk of morbidity, mortality and healthcare costs[5,21,22]. 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[10,23]. In a previous large meta-analysis of randomised controlled trials investigating the efficacy and safety of longer versus 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; $p_{interaction}$=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 three and 15 months post-PCI). Among randomised 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 were randomised to one 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 ischaemic events compared with one-year DAPT[24]. In the GLOBAL LEADERS trial, a randomised, open-label superiority trial of all-comers undergoing PCI with a bioresorbable polymer biolimus A9-eluting DES (N=15,968), aspirin plus ticagrelor was tested for one month followed by 23 months of ticagrelor monotherapy and also resulted in similar rates of ischaemic 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[25]. Hence, the totality of evidence supports the efficacy and safety of a strategy of $P2Y_{12}$-receptor monotherapy following an initial short period of DAPT when using a latest-generation DES after PCI in patients with high-risk clinical or anatomic characteristics[26]. Furthermore, $P2Y_{12}$-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 randomised 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 six to 18 months following PCI[27]. 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 enthothelialisation after the implantation-induced arterial trauma is a key process in coronary devices adherence to the arterial wall[28]. 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 relatively safely after an initial three-month DAPT treatment after the index PCI, irrespective of DES type[29].

## Limitations

Our findings should be considered in the light of the following limitations. First, as a subgroup analysis from a randomised controlled trial, the current findings can only be considered hypothesis generating and should be further tested in adequately-powered studies for individual stent types. Second, the three 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 generalisable 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 three months of DAPT with ticagrelor plus aspirin without any major adverse events. Whether these findings across different new-generation DES types are generalisable 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

Among high-risk patients who underwent PCI, a regimen of ticagrelor monotherapy (after an initial three months of DAPT with ticagrelor plus aspirin) resulted in significantly lower clinically relevant bleeding without increasing the risk of ischaemic 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 three and 15 months. Rates of stent thrombosis were low (<1%) and not influenced by the randomised 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 three-month DAPT reduced bleeding without increasing ischaemic 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 are a safe bleeding avoidance strategy in patients receiving different types of newer-generation DES.

## Appendix. Authors' affilations

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G. Dangas reports receiving consulting fees and advisory board fees from AstraZeneca, consulting fees from Biosensors, and previously holding stock in Medtronic. U. Baber reports speaker honoraria from AstraZeneca and Boston Scientific. S. Sharma has received consulting fees or honoraria from Abbott, Boston Scientific, Abiomed, and Cardiovascular Systems, Inc. S. 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. D. Cohen reports receiving grant support, paid to his institution, and consulting fees from AstraZeneca, Medtronic, Abbott Vascular, and Boston Scientific. D. 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. He has also received institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead Sciences, Idorsia, Janssen, Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, RenalGuard Solutions, and the Scott R. MacKenzie Foundation. J. Escaned reports receiving consulting fees and lecture fees from Abbott, Philips, Boston Scientific, and Medtronic, and lecture fees from Abiomed, Terumo, and Biosensors. K. Huber reports receiving lecture fees from AstraZeneca and Bayer. V. Kunadian has received personal fees/honoraria from Bayer, Astra Zeneca, Abbott, Amgen, and Daichii Sankyo. D. Moliterno reports grants from AstraZeneca, during the conduct of the study. M. 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. G. 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 Solutions. M. Krucoff reports grants and/or personal fees from Abbott Vascular, Biosensors, Boston Scientific, Celonova, Medtronic, OrbusNeich, and Terumo. K. Oldroyd reports receiving grant support and lecture fees from AstraZeneca; and is employed by Biosensors. G. 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 from Abbott, Alvimedica, Shockwave, Medtronic, Biosensors. P.G. 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, and Servier; receiving fees for consulting or speaking from Amgen, BMS/Myokardia, Novo-Nordisk, and Regeneron;

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## 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;72:2915-31.

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; SORT OUT II Investigators. 10-Year Clinical Outcome After Randomization to Treatment by Sirolimus-or Paclitaxel-Eluting Coronary Stents. *J Am Coll Cardiol.* 2017;69:616-24.

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;2:855-62.

4. Madhavan MV, Kirtane AJ, Redfors B, Généreux 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;75:590-604.

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;66:1036-45.

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;9:1349-57.

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; DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. *JAMA.* 2016;315:1735-49.

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; PRECISE-DAPT Study Investigators. 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;389:1025-34.

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;38:804-10.

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;65:1298-310.

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;381:2032-42.

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. *Catheter Cardiovasc Interv.* 2021;97:63-71.

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;182:125-34.

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;382:1714-22.

15. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, Kaul S, Wiviott SD, Menon V, Nikolsky E, Serebruany V, Valgimigli M, Vranckx P, Taggart D, Sabik JF, Cutlip DE, Krucoff MW, Ohman EM, Steg PG, White H. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation.* 2011;123:2736-47.

16. Bovill EG, Terrin ML, Stump DC, Berke AD, Frederick M, Collen D, Feit F, Gore JM, Hillis LD, Lambrew CT, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction: Results of the Thrombolysis in Myocardial Infarction (TIMI), phase II trial. *Ann Intern Med.* 1991;115:256-65.

17. GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-82.

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

19. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for Universal Definition of Myocardial Infarction; Authors/Task Force Members Chairpersons, Thygesen K, Alpert JS, White HD; Biomarker Subcommittee, Jaffe AS, Katus HA, Apple FS, Lindahl B, Morrow DA; ECG Subcommittee, Chaitman BR, Clemmensen PM, Johanson P, Hod H; Imaging Subcommittee, Underwood R, Bax JJ, Bonow JJ, Pinto F, Gibbons RJ; Classification Subcommittee, Fox KA, Atar D, Newby LK, Galvani M, Hamm CW; Intervention Subcommittee, Uretsky BF, Steg PG, Wijns W, Bassand JP, Menasche P, Ravkilde J; Trials & Registries Subcommittee, Ohman EM, Antman EM, Wallentin LC, Armstrong PW, Simoons ML; Trials & Registries Subcommittee, Januzzi JL, Nieminen MS, Gheorghiade M, Filippatos G; Trials & Registries Subcommittee,

Luepker RV, Fortmann SP, Rosamond WD, Levy D, Wood D; Trials & Registries Subcommittee, Smith SC, Hu D, Lopez-Sendon JL, Robertson RM, Weaver D, Tendera M, Bove AA, Parkhomenko AN, Vasilieva EJ, Mendis S; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Morais J, Aguiar C, Almahmeed W, Arnar DO, Barili F, Bloch KD, Bolger AF, Botker HE, Bozkurt B, Bugiardini R, Cannon C, de Lemos J, Eberli FR, Escobar E, Hlatky M, James S, Kern KB, Moliterno DJ, Mueller C, Neskovic AN, Pieske BM, Schulman SP, Storey RF, Taubert KA, Vranckx P, Wagner DR. Third universal definition of myocardial infarction. *J Am Coll Cardiol.* 2012;60:1581-98.

20. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation.* 2007;115:2344-51.

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: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;118:1997-2005.

23. 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;65:1092-102.

24. 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; STOPDAPT-2 Investigators. 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;321:2414-27.

25. 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; GLOBAL LEADERS Investigators. 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;392:940-9.

26. 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;75:2414-24.

27. 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; HOST-EXAM investigators. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet.* 2021;397:2487-96.

28. 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;17:37-51.

29. 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;75:578-86.

## Supplementary data

**Supplementary Table 1.** Types of drug-eluting stents.

**Supplementary Table 2.** Definitions of study endpoints.

**Supplementary Table 3.** Baseline clinical and procedural characteristics within each stent group.

**Supplementary Table 4.** Outcomes associated with DES types one year after randomisation.

**Supplementary Figure 1.** Study flow diagram.

*The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00721*

# Supplementary data

## Supplementary Table 1. Types of drug-eluting stents.

| DES Type | Specifications |
|---|---|
| Included DES types in the present analysis (n=5,769 patients) | |
| DP-EES | PROMUS Premier, PROMUS Element, XIENCE Alpine, XIENCE Xpedition, XIENCE prime II, XIENCE pro |
| DP-ZES | Onyx, Endeavor |
| BP DES | Osiro, Ultimaster, ALEX, Abluminus, Tetriflex, Supraflex, 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 |

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

**Supplementary Table 2. 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, hospitalisation or treatment by a healthcare professional |
| **2** | Any clinically overt sign of haemorrhage 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 healthcare professional, includes (but are not limited to) temporary/permanent cessation of a medication, coiling, compression, local injection<br>• leading to hospitalisation 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 haemoglobin (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/haemorrhoid)<br>• Bleeding requiring intravenous vasoactive drugs |
| **3c** | Intracranial haemorrhage (does not include microbleeds or haemorrhagic 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. Categorised 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:<br>• Any intracranial bleeding (excluding microhaemorrhages <10 mm evident only on gradient-echo MRI)<br>• Clinically overt signs of haemorrhage associated with a drop in haemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit<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 haemorrhage<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 haemoglobin drop of 3 to <5 g/dL or ≥10% decrease in haematocrit<br>• No observed blood loss: ≥4 g/dL decrease in the haemoglobin concentration or ≥12% decrease in haematocrit<br>• Any overt sign of haemorrhage 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 hospitalisation<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 haemorrhage (including imaging) associated with a <3 g/dL decrease in haemoglobin concentration or <9% decrease in haematocrit<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-hr period; cell saver transfusion will not be counted in calculations of blood products.<br>• Chest tube output >2 L within a 24-hr period |

**GUSTO bleeding definitions**

| Type | Definition |
|---|---|
| **Severe or life-threatening** | Intracerebral bleeding or bleeding resulting in substantial haemodynamic 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 haemodynamic 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 haemoglobin 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 (e.g., 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 non-coronary vascular causes, such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm or other causes. |
| Non-cardiovascular 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 ischaemic 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 99$^{th}$ percentile URL and with at least one of the following:
    - Symptoms of ischaemia
    - (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 ischaemic 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 99$^{th}$ 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 ischaemia
- New ischaemic 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 ischaemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99$^{th}$ percentile URL
- CABG related MI is arbitrarily defined by elevation of cardiac biomarkers >10 x 99$^{th}$ 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:

- Ischaemic stroke: infarction due to prolonged ischaemia. Causes include (but are not limited to) arterial and venous thrombosis, embolism, and systemic hypoperfusion.
- Haemorrhagic stroke: caused by a non-traumatic intraparenchymal, intraventricular or subarachnoid haemorrhage
- Undetermined: stroke with insufficient information to determine ischaemic or haemorrhagic cause

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

*Stent thrombosis*

Stent thrombosis is classified according to the level of certainty and timing following PCI[4].

- 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 ischaemic symptoms at rest
    - New ischaemic 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 ischaemia 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 revascularisation**

Clinically driven revascularisation includes repeat PCI or CABG for recurrent or persistent symptomatic ischaemia and can be defined according to the relationship to the index PCI (target lesion)[4]:

- Target lesion revascularisation, at the previously stented segment
- Non-target lesion, target vessel revascularisation, of the previously treated vessel or its side branches AND
- Non-target vessel lesion revascularisation, 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 haemodynamic 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.

Abbreviations.

BARC: bleeding academic research consortium; CABG: coronary artery bypass graft; ECG: electrocardiogram; GUSTO: Global Use of Strategies to Open Occluded Coronary Arteries; ISTH; International Society on Thrombosis and Haemostasis; LBBB: left bundle branch block; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention; PRBC: packed red blood cells; TIMI: Thrombolysis In Myocardial Infarction; URL: upper reference limit

**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=1,525)** | **Tica+ aspirin (N=1,489)** | ***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 |
| Anaemia | 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 |
| Hypercholesterolaemia | 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 |
| 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=1,525)** | **Tica+ aspirin (N=1,489)** | ***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[†] | | | | | | | | | |
| 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 |

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

[†]Lesion morphology assessed by operators
[‡]Stent length calculated as the addition of individual stent lengths per lesion.

## Supplementary Table 4. Outcomes associated with DES types one year after randomisation.

| | 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=3,014) | 229 (7.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 157 (5.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 127 (4.2%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 30 (1.0%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 91 (3.0%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 37 (2.7%) | 0.88 (0.60-1.28) | 0.498 | 0.93 (0.63-1.37) | 0.728 | |
| **Ischaemic stroke** | | | | | | |
| 2nd Gen DP-EES (n=3,014) | 8 (0.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 6 (0.4%) | 1.62 (0.56-4.67) | 0.371 | 1.56 (0.53-4.53) | 0.417 | |
| **Target vessel revascularisation** | | | | | | |
| 2nd Gen DP-EES (n=3,014) | 111 (3.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 14 (0.5%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 9 (0.7%) | 1.39 (0.60-3.21) | 0.442 | 1.51 (0.65-3.52) | 0.336 | |
| **BARC 3 or 5 bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3,014) | 35 (1.2%) | Ref. | | Ref. | | |

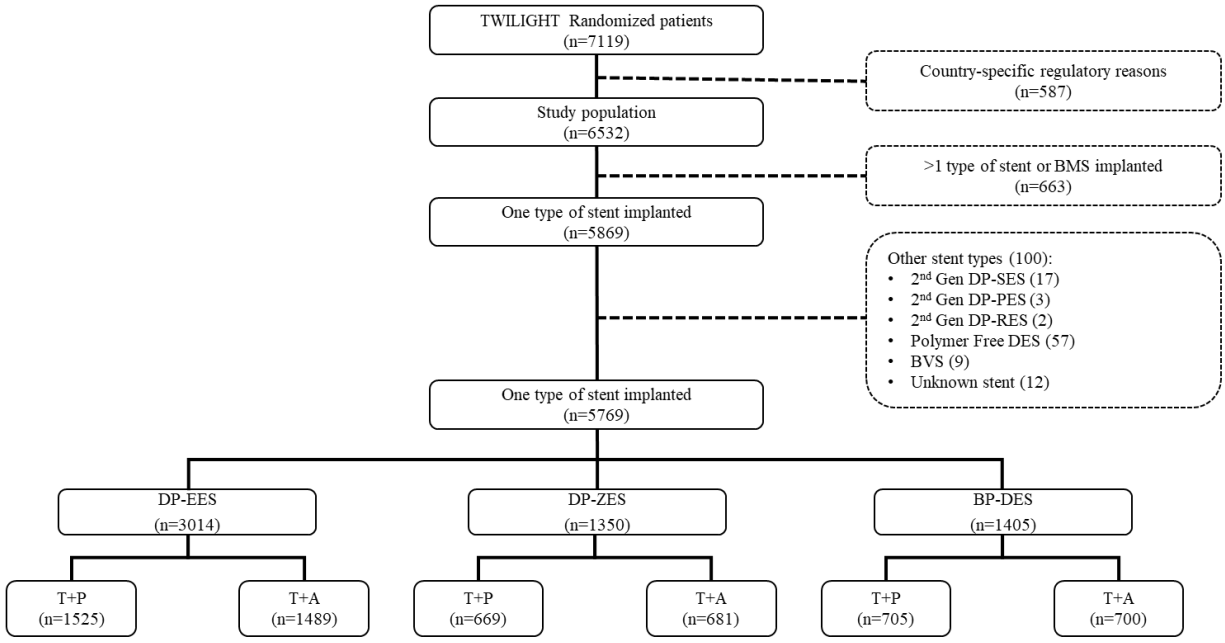
| | Event (%) | Hazard ratio (95% CI) | *p*-value | Adjusted hazard ratio (95% CI)[†] | *p*-value | Interaction *p*-value[‡] |
|---|---|---|---|---|---|---|
| 2nd Gen DP-ZES (n=1,350) | 20 (1.5%) | 1.29 (0.74-2.23) | 0.369 | 1.20 (0.69-2.08) | 0.517 | 0.705 |
| 2nd Gen BP-DES (n=1,405) | 25 (1.8%) | 1.55 (0.93-2.58) | 0.096 | 1.56 (0.93-2.62) | 0.093 | |
| **TIMI major bleeding** | | | | | | |
| 2nd Gen DP-EES (n=3,014) | 15 (0.5%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 22 (0.7%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 38 (1.3%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 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=3,014) | 153 (5.1%) | Ref. | | Ref. | | |
| 2nd Gen DP-ZES (n=1,350) | 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=1,405) | 79 (5.7%) | 1.12 (0.85-1.47) | 0.417 | 1.16 (0.88-1.53) | 0.280 | |

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

[†]Model adjusted for body mass index (kg/m$^2$), hypercholesterolaemia, 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 randomised treatment assignment and stent type with model adjustment

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




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.

**Supplementary Figure 1. Study flow diagram.**