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ORIGINAL RESEARCH

Polymer-free versus biodegradable-polymer drug-eluting stent in patients undergoing percutaneous coronary intervention: an assessor-blind, non-inferiority, randomised controlled trial

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ABSTRACT

BACKGROUND: Few data are available on polymer-free drug-eluting stents in patients undergoing percutaneous coronary intervention (PCI).

AIMS: We aimed to determine the efficacy and safety of a polymer-free amphilimus-eluting stent (AES), using a reservoir-based technology for drug delivery, compared with a biodegradable-polymer everolimus-eluting stent (EES).

METHODS: This was a randomised, investigator-initiated, assessor-blind, non-inferiority trial conducted at 14 hospitals in Italy (ClinicalTrials.gov: NCT04135989). All-comer patients undergoing PCI were randomly assigned to either polymer-free AES or biodegradable-polymer EES. The primary endpoint was a device-oriented composite endpoint, including cardiovascular death, target vessel myocardial infarction, or target lesion revascularisation at 1-year follow-up.

RESULTS: Between January 2020 and June 2022, a total of 2,107 patients with 3,042 coronary lesions were randomised to polymer-free AES (1,051 patients) or biodegradable-polymer EES (1,056 patients). At 1-year follow-up, the primary endpoint occurred in 86 (8.2%) patients randomised to polymer-free AES and 76 (7.2%) patients randomised to biodegradable-polymer EES (risk difference 1%, upper limit of the 1-sided 95% confidence interval [CI] of 2.9%; p for non-inferiority=0.041). There were no significant differences in the incidence of the components of the primary endpoint between groups. However, definite or probable stent thrombosis occurred more frequently in patients randomised to polymer-free stents (1.0% vs 0.3%; hazard ratio 3.72, 95% CI: 1.04-13.33; p=0.044) due to an increased risk of early stent thrombosis within 30 days.

CONCLUSIONS: In all-comer patients undergoing PCI, polymer-free AES were non-inferior to biodegradable-polymer EES at 1-year follow-up in terms of a device-oriented composite endpoint despite being associated with an increased risk of early stent thrombosis.

KEYWORDS: ACS/NSTE-ACS; adjunctive pharmacotherapy; drug-eluting stent; NSTEMI; polymer-free; stable angina; STEMI

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New-generation drug-eluting stents (DES) have consistently outperformed bare metal stents and early-generation DES in terms of safety and efficacy and represent the standard of care in patients undergoing percutaneous coronary intervention (PCI)[1]. Polymer-free DES are an additional iteration in stent technology that avoid the potential risks associated with chronic inflammatory responses to polymers and those related to polymer webbing, delamination, or cracking, which have been reported for both permanent and biodegradable polymers[2,3]. However, randomised data supporting the use of polymer-free DES for PCI remain limited, with trials yielding mixed results[4-7]. The Cre8 EVO amphilimus-eluting stent (AES; Alvimedica) is a thin-strut, polymer-free, cobalt-chromium stent with reservoirs located on the outer surface releasing sirolimus formulated with a non-polymeric mixture of long-chain fatty acids. This structure allows for a controlled sirolimus elution with a release kinetic analogous to other contemporary DES. To date, the polymer-free AES has been tested against durable-polymer DES in moderately sized randomised trials or in specific populations, such as diabetic patients[6-8]. Hence, whether the use of this polymer-free DES in a broader, unselected patient population provides similar outcomes to other new-generation DES remains to be conclusively established.

Against this background, we designed the Personalized Vs. Standard Duration of Dual Antiplatelet Therapy and New-generation Polymer-Free vs- Biodegradable-Polymer DES (PARTHENOPE) trial to evaluate the non-inferiority of polymer-free AES compared with biodegradable-polymer DES at 1-year follow-up in all-comers undergoing PCI.

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Impact on daily practice

The use of polymer-free stents in patients undergoing percutaneous coronary intervention has the potential to eliminate any risk associated with biodegradable or permanent polymers, which are currently used in coronary devices to control the release of the antiproliferative drug. In patients treated with polymer-free amphilimus-eluting stents, device-related outcomes were similar to those treated with biodegradable-polymer everolimus-eluting stents at 1-year follow-up. Although the antirestenotic properties of polymer-free stents have been questioned, the use of an amphilimus-eluting stent was associated with an excellent efficacy profile in comparison to biodegradable stents. The small excess of stent thrombosis within 30 days after amphilimus-eluting stent implantation requires additional studies.

Methods

STUDY DESIGN AND PATIENTS

PARTHENOPE was an investigator-initiated, assessor-blind, multicentre, randomised trial, with few exclusion criteria, conducted at 14 hospitals in Italy (ClinicalTrials.gov: NCT04135989). The trial had a 2-by-2 factorial design with two independent hypotheses: (1) the non-inferiority of the polymer-free AES to the biodegradable-polymer everolimus-eluting stent (EES; SYNERGY Stent [Boston Scientific]) at 1-year follow-up and (2) the superiority of a personalised duration of dual antiplatelet therapy (DAPT) compared with standard DAPT for 12 months at 2-year follow-up. The design of this study has been described previously[8]. A list of the investigators can be found in **Supplementary Appendix 1**. Herein, we report the results of the comparison between the two DES. The entire spectrum of coronary syndromes and lesions subsets were allowed, without limitations on the number of stents or lesions, or vessel to be treated. The inclusion and exclusion criteria are detailed in **Supplementary Appendix 2**. The trial protocol was approved by the medical ethics committee of the University of Naples Federico II and the ethics committee of each participating centre. The study adhered to the ethical principles outlined in the Declaration of Helsinki, the specifications of the International Conference of Harmonization, and the guidelines of Good Clinical Practice. All patients provided written informed consent. Patients could also provide initial oral consent, but written informed consent was required within 72 hours after randomisation.

RANDOMISATION AND MASKING

After successful crossing of the first target lesion with a coronary guidewire, patients were randomly allocated to receive either the polymer-free AES or the biodegradable-polymer EES, along with either a personalised or standard DAPT strategy, with each participant having an equal probability of being assigned to 1 of the 4 treatment combinations. Web-based randomisation was done using a computer-generated sequence stratified by centre, with variable block sizes of 4 or 8. The sequence of block sizes was randomly generated to further enforce concealment. Patients and treating physicians were aware of group allocations.

PROCEDURES

The Cre8 EVO stent is a thin-strut (70-80 µm), cobalt-chromium platform with a polymer-free design and a proprietary reservoir technology. The stent's outer surface has reservoirs that control the release of the amphilimus compound, which is based on sirolimus and formulated with a non-polymeric mixture of long-chain fatty acid as a carrier. The Cre8 EVO stent has an ultrathin (<3 µm) and high-density carbon film. Approximately 50% of the drug is released at 18 days, while the elution is completed at 90 days[9]. The SYNERGY biodegradable-polymer EES is a thin-strut (74-81 µm) platinum-chromium metal alloy stent with an abluminal polymer (poly lactic-co-glycolic

Abbreviations

AES	amphilimus-eluting stent	**DAPT**	dual antiplatelet therapy	**MI**	myocardial infarction
ARC-2	Academic Research Consortium-2	**DES**	drug-eluting stent	**PCI**	percutaneous coronary intervention
BARC	Bleeding Academic Research Consortium	**EES**	everolimus-eluting stent		

acid) that elutes everolimus (100 μg/cm^2) within 90 days with a drug release kinetic similar to the Cre8 EVO stent[10]. Additional details on the devices used in the trial are reported in **Supplementary Appendix 3**.

Lesion preparation (predilation, direct stenting, and post-dilation), the dose of unfractionated heparin, and the use of intravenous antiplatelet agents were left to the discretion of the operators. A low dose of aspirin (75 to 162 mg daily) was administered throughout the trial. The choice of the $P2Y_{12}$ inhibitor (clopidogrel, prasugrel, or ticagrelor) was left to the discretion of the treating physicians, although the trial protocol recommended clopidogrel (75 mg daily) in patients with chronic coronary syndrome and ticagrelor (90 mg twice daily) or prasugrel (10 mg daily, or 5 mg daily in patients weighing <60 kg or aged ≥75 years) in patients with acute coronary syndrome. DAPT duration in the trial was randomly assigned, and the DAPT score was used to stratify the ischaemic and bleeding risks **(Supplementary Appendix 4)**[11]. Patients randomised to personalised DAPT and at high bleeding risk (DAPT score <2) received DAPT for 3 or 6 months in case of chronic or acute coronary syndrome, respectively, whereas patients at high ischaemic risk (DAPT score ≥2) received DAPT for 24 months. Patients randomised to standard DAPT received DAPT for 12 months. Clinical follow-up was obtained at 3, 6, and 12 months by office visits or telephone interviews.

ENDPOINTS

The prespecified primary endpoint was a device-oriented composite endpoint of cardiovascular death, myocardial infarction (MI) not clearly attributed to a non-target vessel, or clinically driven target lesion revascularisation within 1 year of the index procedure, as recommended by the Academic Research Consortium-2 criteria (ARC-2)[12]. MI was defined based on the fourth universal definition of MI[13], and periprocedural MI was further adjudicated using the Society for Cardiovascular Angiography and Interventions (SCAI) and ARC-2 criteria[12,14]. Stent thrombosis was defined according to the ARC-2 criteria[12]. Additional secondary endpoints included any revascularisation, target vessel and target lesion revascularisation, and bleeding events. Endpoint definitions are reported in **Supplementary Appendix 5**. An independent clinical events committee blinded to treatment assignment adjudicated all study endpoints.

STATISTICAL ANALYSIS

The study was designed to show non-inferiority of the Cre8 EVO AES versus the SYNERGY EES regarding the primary composite endpoint. Based on prior trials with a similar design, we assumed an event rate of 8% for the primary endpoint in the control group[15,16]. Therefore, a total of 2,106 patients would provide 80% power to show non-inferiority with a margin of 3.0%, an upper 1-sided α of 0.05, and an attrition rate of 4%. The 1-sided p-value for non-inferiority was calculated from a Z-test comparing differences between groups with the margin of non-inferiority. A sensitivity *post hoc* analysis accounting for the competing risk of death (or non-cardiovascular death for endpoints including cardiovascular death) was also conducted. All analyses were done on an intention-to-treat basis, with all patients included in the analyses according to the allocated stent. In addition, per-protocol analyses were carried out by including patients that received the randomly allocated stents in all target lesions. Continuous variables are presented as means±standard deviations (SD), and categorical variables are presented as frequencies (percentage). The cumulative event rates for the primary and secondary endpoints were calculated by the Kaplan-Meier method. Hazard ratios (HR) with 95% confidence intervals (CI) from Cox regression analysis were used to compare differences in the primary and secondary endpoints. For the secondary endpoints, we prespecified the use of the Benjamini-Hochberg correction for multiple comparisons[8]. However, both unadjusted and adjusted p-values are reported. The treatment effect of the Cre8 EVO AES versus the biodegradable-polymer EES was compared in the following prespecified subgroups: age, sex, diabetes, acute coronary syndrome, ST-segment elevation myocardial infarction (STEMI), chronic kidney disease, complex PCI, small vessel disease, and DAPT strategy. All analyses were performed using R, version 3.6.0 (R Foundation for Statistical Computing).

Results

Between 22 January 2020 and 22 June 2022, we randomly assigned 2,107 patients with 3,042 target lesions to undergo PCI with the polymer-free AES (1,051 patients and 1,513 lesions) or the biodegradable-polymer EES (1,056 patients and 1,529 lesions) **(Figure 1)**. A total of 2,013 (95.5%) patients completed 1-year follow-up, and 88 (4.2%) died; thus, follow-up data were available for 2,101 (99.7%) patients. Six (0.3%) patients were lost to follow-up **(Figure 1)**. Participants were aged between 28 and 94 years (mean 63.9 [SD 10.6]), 465 (22.1%) were female, 658 (31.2%) had diabetes, and 1,607 (76.3%) presented with acute coronary syndrome **(Table 1)**. A high proportion of patients had acute STEMI (776 [36.8%] of 2,107). In nearly all patients (2,086 [99.0%] of 2,107), at least one randomly assigned stent was implanted **(Figure 1)**. Nineteen (0.9%) patients did not receive the allocated stent, and 2 (0.1%) patients did not undergo PCI **(Figure 1)**. One quarter of the patients underwent complex PCI (527 [25.0%] of 2,107) **(Table 2)**. The mean number of lesions treated per patient was 1.4 (SD 0.7), and 714 (33.9%) patients had more than one lesion treated; the mean total stent length per patient was 41 mm (SD 26.5). The mean total stent length per lesion was 29 mm (SD 15), and the mean stent diameter per lesion was 3 mm (SD 0.5). Almost all lesions were treated with stents (2,995 [98.4%] of 3,042). Direct stenting was performed in 1,145 (38.2%) of 2,995 stented lesions. Medications and antiplatelet therapy at baseline, discharge, and during follow-up did not differ between groups **(Supplementary Table 1)**.

At 1-year follow-up, the primary endpoint had occurred in 86 (8.2%) patients randomised to the polymer-free AES group and in 76 (7.2%) patients randomised to the biodegradable-polymer EES group **(Figure 2A, Table 3, Central illustration)**. Non-inferiority of the polymer-free AES compared with the biodegradable-polymer EES was established with an absolute risk difference of 1% (95% CI: –0.9% to 2.9%; p for non-inferiority=0.041). Superiority testing for the primary endpoint did not show significant differences between the

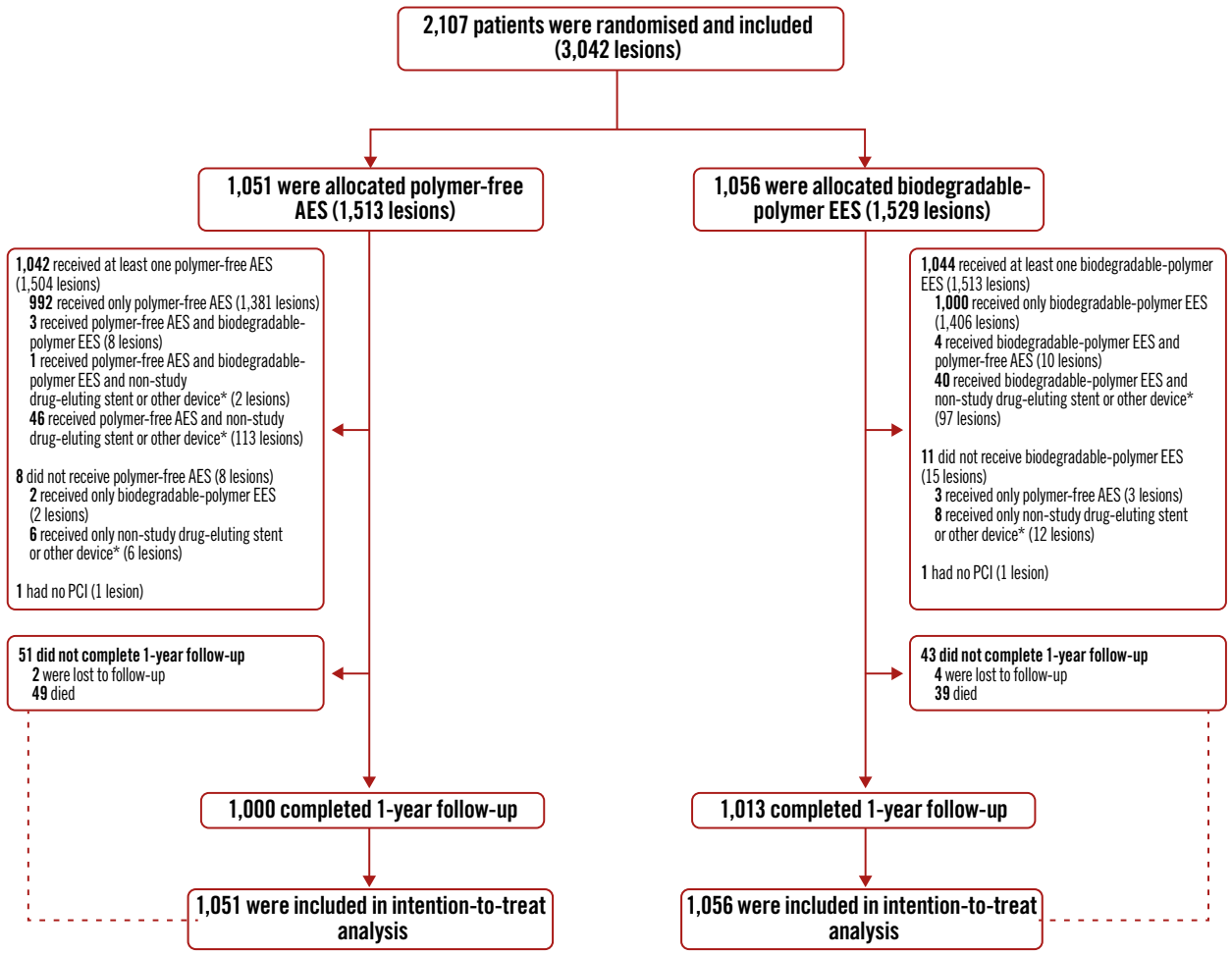


Figure 1. *Trial profile. *balloon angioplasty or drug-coated balloon. AES: amphilimus-eluting stent; EES: everolimus-eluting stent; PCI: percutaneous coronary intervention*

polymer-free AES and the biodegradable-polymer EES (HR 1.15, 95% CI: 0.84-1.56; p=0.388). A per-protocol analysis yielded consistent results (absolute risk difference 0.6%; p for non-inferiority 0.019) **(Supplementary Figure 1-Supplementary Figure 4, Supplementary Table 2)**. Cardiovascular death occurred in 36 (3.4%) patients randomised to the polymer-free AES and in 25 (2.4%) patients randomised to the biodegradable-polymer EES (HR 1.45, 95% CI: 0.87-2.42; p=0.150). This numerical increase was attributed to a higher number of undetermined deaths in the experimental arm. The complete adjudication of causes of death is provided in **Supplementary Table 3**. The risks of target vessel MI (4.3% vs 4.2%, HR 1.03, 95% CI: 0.68-1.56; p=0.885) and target lesion revascularisation (1.9% vs 1.5%, HR 1.27, 95% CI: 0.66-2.45; p=0.475) were similar between groups **(Figure 2, Table 3)**. Definite or probable stent thrombosis occurred in 11 (1.0%) patients in the polymer-free AES group and 3 (0.3%) patients in the biodegradable-polymer EES group (HR 3.72, 95% CI: 1.04-13.33; p=0.044). This difference was not significant when adjusted for multiple comparisons (adjusted p=0.292). Definite stent thrombosis occurred in 11 (1.0%) patients in the polymer-free AES group and 2 (0.2%) in the biodegradable-polymer EES group **(Table 3)**. Out of the 14 cases of definite or probable stent thrombosis, 4 occurred as acute events, 7 as subacute, and 3 as late (>30 days) occurrences. In 9 cases, stent thrombosis occurred in stents with a diameter less than 3 mm. A detailed description of stent thrombosis cases is provided in **Supplementary Table 4**. The frequencies of other secondary endpoints were similar in both study arms **(Table 3)**.

A *post hoc* analysis accounting for the competing risk of death showed consistent results for the primary and secondary endpoints **(Supplementary Table 5)**.

There was no heterogeneity in the treatment effect of polymer-free AES versus biodegradable-polymer EES across the stratified analyses for age, sex, diabetes, acute coronary syndrome, STEMI, chronic kidney disease, complex PCI, small vessel disease, or DAPT strategy. The results were consistent in the per-protocol population **(Figure 3, Supplementary Figure 5)**. Regarding the potential for heterogeneity introduced by different DAPT strategies, which could affect the study's external validity, we analysed the heterogeneity of the treatment effect of polymer-free AES versus biodegradable-polymer EES on the primary endpoint across DAPT strategies. Consistency in risk estimates for the primary endpoint was observed in

Table 1. Baseline characteristics.

	Polymer-free amphilimus-eluting stent (N=1,051)	Biodegradable-polymer everolimus-eluting stent (N=1,056)
Age, years		
N	1,051	1,056
Mean	63.8 (10.9)	64 (10.4)
Male	811/1,051 (77.2)	831/1,056 (78.7)
Body mass index, kg/m^2		
N	1,051	1,056
Mean	28 (4.7)	28.2 (4.7)
Family history of CAD	305/1,051 (29.0)	309/1,056 (29.3)
Diabetes mellitus	322/1,051 (30.6)	336/1,056 (31.8)
Diabetes treatment		
Diet	47/322 (14.6)	50/336 (14.9)
Oral treatment	176/322 (54.7)	190/336 (56.5)
Insulin therapy	99/322 (30.7)	96/336 (28.6)
Current smoker	524/1,051 (49.9)	526/1,056 (49.8)
Hypertension	777/1,051 (73.9)	799/1,056 (75.7)
Hypercholesterolaemia	656/1,051 (62.4)	660/1,056 (62.5)
Previous myocardial infarction	215/1,051 (20.5)	204/1,056 (19.3)
Congestive heart failure	76/1,051 (7.2)	61/1,056 (5.8)
Previous PCI	224/1,051 (21.3)	230/1,056 (21.8)
Previous CABG	36/1,051 (3.4)	44/1,056 (4.2)
Peripheral artery disease	83/1,051 (7.9)	72/1,056 (6.8)
Chronic kidney disease	169/1,051 (16.1)	162/1,056 (15.3)
Prior stroke or TIA	41/1,051 (3.9)	30/1,056 (2.8)
Chronic obstructive lung disease	140/1,051 (13.3)	136/1,056 (12.9)
Indication for revascularisation		
STEMI	378/1,051 (36.0)	398/1,056 (37.7)
NSTE-ACS	426/1,051 (40.5)	405/1,056 (38.4)
Chronic coronary syndrome	247/1,051 (23.5)	253/1,056 (23.7)
Anaemia	258/1,051 (24.5)	254/1,056 (24.1)
History of bleeding	18/1,051 (1.7)	12/1,056 (1.1)
Systolic blood pressure, mmHg		
N	1,051	1,056
Mean	137.1 (22.9)	137.6 (23.3)
Diastolic blood pressure, mmHg		
N	1,051	1,056
Mean	76 (12.9)	76.7 (13.6)
Heart rate, bpm		
N	1,051	1,056
Mean	74.2 (14)	74.6 (14.6)
Left ventricular ejection fraction, %		
N	1,028	1,035
Mean	49.1 (8.8)	49.2 (8.7)
DAPT score		
N	1,051	1,056
Mean	1.7 (1.4)	1.7 (1.4)

Table 1. Baseline characteristics (cont'd).

	Polymer-free amphilimus-eluting stent (N=1,051)	Biodegradable-polymer everolimus-eluting stent (N=1,056)
Baseline drugs		
Unfractionated heparin total dose		
N	1,051	1,056
Mean, IU	5,970 (1,998)	5,978 (2,037)
Current medication	825/1,051 (78.5)	821/1,056 (77.7)
Aspirin	462/825 (56.0)	463/821 (56.4)
$P2Y_{12}$ receptor inhibitor		
Clopidogrel	159/825 (19.3)	153/821 (18.6)
Prasugrel	2/825 (0.2)	1/821 (0.1)
Ticagrelor	32/825 (3.9)	38/821 (4.6)
None	632/825 (76.6)	629/821 (76.6)
Beta blocker	356/825 (43.2)	362/821 (44.1)
Statin	421/825 (51.0)	443/821 (54.0)
Other lipid-lowering drug	126/825 (15.3)	142/821 (17.3)
ACE inhibitors or ATII antagonist	499/825 (60.5)	539/821 (65.7)
PPI	409/825 (49.6)	418/821 (50.9)
SGLT-2 inhibitor	15/825 (1.8)	25/821 (3.0)
Oral antidiabetic	198/825 (24.0)	224/821 (27.3)
Insulin	100/825 (12.1)	98/821 (11.9)

Data are n/N (%) or mean (SD). Chronic kidney disease was defined as kidney damage or glomerular filtration rate <60 mL/min/1.73 m^2 for 3 months or more, irrespective of the cause. ACE: angiotensin converting enzyme; ATII: angiotensin II; CABG: coronary artery bypass grafting; CAD: coronary artery disease; DAPT: dual antiplatelet therapy; IU: international units; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; PPI: proton pump inhibitor; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2; STEMI: ST-segment elevation myocardial infarction; TIA: transient ischaemic attack

both the intention-to-treat (p-interaction=0.954) and per-protocol populations (p-interaction=0.901), across both personalised and standard DAPT strategies. Consequently, no significant interaction between the type of stent and the DAPT regimen was evident **(Figure 3, Supplementary Figure 5)**.

Discussion

In this randomised trial involving an all-comer cohort undergoing PCI, we found that polymer-free AES were non-inferior to biodegradable-polymer EES in terms of a device-oriented primary endpoint at 1-year follow-up. The trial included a broad patient population, with over 75% of the participants receiving treatment for acute coronary syndrome, including 37% with acute STEMI, which likely represents the highest proportion among similar all-comer stent trials. The broad age spectrum of participants, ranging from 28 to 94 years, reflects the inclusive nature of the enrolment and the diversity of contemporary clinical practice.

The Cre8 EVO AES has thus far only been evaluated in an all-comers setting in one trial[5], which, compared with our study, enrolled a smaller cohort of patients (1,491 vs 2,107 patients), included more patients with chronic coronary syndrome (58% vs 25%), and recruited fewer patients with diabetes (20% vs 31%). It is noteworthy that the observed 4.2% rate of all-cause death at 1 year was somewhat higher than that reported by other all-comer trials, such as the LEADERS, RESOLUTE, COMPARE-II, BIOSCIENCE, BIO-RESORT, BIONYX, and SORT OUT IX trials, in which the rates of all-cause death ranged from 1.6% to 3.3%[15-21]. This suggests the potential inclusion of higher-risk patients by the current study.

A potential drawback of polymer-free technologies is the rapid release of the antiproliferative agent, often accompanied by a decline in efficacy[22]. Initial studies on polymer-free DES indicated that their antirestenotic performance, measured using late loss, was inferior to that of durable- or biodegradable-polymer DES[23]. In line with this, the SORT OUT IX trial found a 3-fold higher risk of target lesion revascularisation with the polymer-free biolimus-eluting stent (BioFreedom [Biosensors]), which releases approximately 90% of biolimus within the first 48 hours after implantation[24]. Although the stainless steel platform of the BioFreedom stent was thought to be linked to neointimal hyperplasia, a randomised trial, comparing the same BioFreedom stent with a stainless steel (112-120 µm) or a cobalt-chromium platform (84-88 µm), revealed a similar late loss for both devices[25]. This suggests that the overly rapid release of the drug, rather than the type of metallic platform, is probably responsible for the insufficient suppression of neointimal hyperplasia in this polymer-free DES. Two other polymer-free DES are available, and these control drug release in the absence of the polymer by combining sirolimus with probucol in the VIVO ISAR (Translumina) and Coroflex ISAR stents (B. Braun). Similarly to amphilimus, probucol is lipophilic and enables longer and more controlled drug elution. The efficacy of the

Table 2. Angiographic and procedural characteristics.

	Polymer-free amphilimus-eluting stent (1,051 patients)	Biodegradable-polymer everolimus-eluting stent (1,056 patients)
Treated lesions, per patient		
N	1,051	1,056
Mean	1.4 (0.7)	1.4 (0.7)
1	700 (66.6)	693 (65.6)
2	252 (24.0)	269 (25.5)
≥3	99 (9.4)	94 (8.9)
Haemodynamic support, per patient		
IABP	3/1,051 (0.3)	2/1,056 (0.2)
LVAD	0/1,051 (0)	0/1,056 (0)
Vasopressor	2/1,051 (0.2)	8/1,056 (0.8)
Impella[a]	5/1,051 (0.5)	0/1,056 (0)
Others	0/1,051 (0)	1/1,056 (0.1)
None	1041/1,051 (99.0)	1,045/1,056 (99.0)
Small vessel disease, per patient	236/1,051 (22.5)	251/1,056 (23.8)
Complex PCI, per patient (≥1 criteria)	265/1,051 (25.2)	262/1,056 (24.8)
≥3 coronary vessels treated	99/1,051 (9.4)	94/1,056 (8.9)
≥3 stents implanted	192/1,051 (18.3)	218/1,056 (20.6)
≥3 lesions treated	99/1,051 (9.4)	94/1,056 (8.9)
Bifurcation with 2 stents implanted	29/1,051 (2.8)	31/1,056 (2.9)
Total stent length ≥60 mm	202/1,051 (19.2)	222/1,056 (21.0)
Treatment of chronic total occlusion	11/1,051 (1.0)	12/1,056 (1.1)
Number of lesions	**1,513**	**1,529**
Target vessel location, per lesion		
Left main artery	20/1,513 (1.3)	37/1,529 (2.4)
Left anterior descending artery	700/1,513 (46.3)	682/1,529 (44.6)
Left circumflex artery	347/1,513 (22.9)	357/1,529 (23.3)
Right coronary artery	446/1,513 (29.5)	453/1,529 (29.6)
Bypass graft	3/1,513 (0.2)	5/1,529 (0.3)
Saphenous vein graft	2/3 (66.7)	4/5 (80.0)
Arterial graft	1/3 (33.3)	1/5 (20.0)
Restenotic lesion	66/1,513 (4.4)	80/1,529 (5.2)
Total occlusion	254/1,513 (16.8)	228/1,529 (14.9)
Evidence of thrombus	424/1,513 (28.0)	422/1,529 (27.6)
Thrombus aspiration	38/1,513 (2.5)	40/1,529 (2.6)
Treatment of bifurcation lesion	151/1,513 (10.0)	133/1,529 (8.7)
TIMI flow pre-PCI, per lesion		
0 or 1	337/1,513 (22.3)	315/1,529 (20.6)
2	189/1,513 (12.5)	173/1,529 (11.3)
3	987/1,513 (65.2)	1,041/1,529 (68.1)
TIMI flow post-PCI, per lesion		
0 or 1	3/1,513 (0.2)	7/1,529 (0.5)
2	22/1,513 (1.5)	19/1,529 (1.2)
3	1,488/1,513 (98.3)	1,503/1,529 (98.3)
Type of intervention, per lesion		
Stent implantation	1,485/1,512 (98.2)	1,510/1,528 (98.8)
Balloon dilation only	27/1,512 (1.8)	18/1,528 (1.2)
Direct stenting	555/1,485 (37.4)	590/1,510 (39.1)
Post-dilation	920/1,485 (62.0)	865/1,510 (57.3)

Table 2. Angiographic and procedural characteristics (cont'd).

	Polymer-free amphilimus-eluting stent (1,051 patients)	Biodegradable-polymer everolimus-eluting stent (1,056 patients)
Number of stents, per lesion		
N	1,485	1,510
Mean	1.2 (0.5)	1.3 (0.6)
1	1,204/1,485 (81.1)	1,157/1,510 (76.6)
2	236/1,485 (15.9)	298/1,510 (19.7)
3	40/1,485 (2.7)	45/1,510 (3.0)
4	5/1,485 (0.3)	9/1,510 (0.6)
5	0/1,485 (0)	1/1,510 (0.1)
6	0/1,485 (0)	0/1,510 (0)
Overlapping stents, per lesion	250/281 (89.0)	320/353 (90.7)
Number of stents	**1,816**	**1,929**
Type of stent, per lesion		
Study stent polymer-free AES	1,760/1,816 (96.9)	11/1,929 (0.6)
Study stent biodegradable-polymer EES	9/1,816 (0.5)	1,867/1,929 (96.8)
Other drug-eluting stents	47/1,816 (2.6)	51/1,929 (2.6)
Total stent length per lesion, mm		
N	1,485	1,510
Mean	29.1 (14.9)	29.1 (14.7)
Mean stent diameter per lesion, mm		
N	1,485	1,510
Mean	3 (0.4)	3 (0.5)
Maximum stent diameter per lesion, mm		
N	1,485	1,510
Mean	3 (0.5)	3.1 (0.5)

Data are mean (SD), n (%) or n/N (%). [a]By Abiomed. AES: amphilimus-eluting stent; CTO: chronic total occlusion; EES: everolimus-eluting stent; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; PCI: percutaneous coronary intervention; SD: standard deviation; TIMI: Thrombolysis in Myocardial Infarction

probucol-based, polymer-free DES has been reported up to 10-year follow-up in the ISAR-TEST-5 trial[4]. Our trial, which is the largest to date to have investigated the Cre8 EVO AES, found very low rates of target lesion revascularisation at 1-year follow-up. These efficacy findings are well aligned with the ReCre8 and SUGAR trials, which showed a similar risk of target lesion revascularisation with the polymer-free AES compared with the durable-polymer zotarolimus-eluting stents in 1,491 all-comers and 1,175 diabetic patients, respectively[5,6]. In the SUGAR trial, the Cre8 EVO AES was shown to be non-inferior and superior to the Resolute Onyx zotarolimus-eluting device (Medtronic) regarding target lesion failure at 1 year, with the difference largely driven by reductions in target vessel MI and target lesion revascularisation[6]. However, in our trial, the rates of target vessel MI (4.3% vs 4.2%, HR 1.03) and clinically driven target lesion revascularisation (1.9% vs 1.5%, HR 1.27) did not differ between the AES and EES groups. Moreover, there was no heterogeneity in the treatment effect between the two randomly assigned devices with respect to the primary endpoint according to the presence or absence of diabetes. In terms of safety, we found a higher incidence of definite or probable stent thrombosis in patients undergoing polymer-free AES implantation compared with biodegradable-polymer EES implantation (1.0% vs 0.3%). This risk difference was notable in the first 30 days after PCI. Definite stent thrombosis accounted for 13 cases, whereas the only case of probable stent thrombosis occurred in a patient who died suddenly at home 19 days after revascularisation for a non-STEMI. In 2 cases occurring at days 4 and 13 after treatment with the Cre8 EVO, patients disrupted the two antiplatelet agents and the $P2Y_{12}$ receptor inhibitor, respectively. Only 1 patient with stent thrombosis died; this occurred at 358 days due to a non-cardiac cause. It is worth noting that a potential signal of increased risk of early stent thrombosis was already observed in the ReCre8 trial, with 7 cases reported in patients randomised to polymer-free AES versus 2 cases in those receiving zotarolimus-eluting stents. However, when considering all cases of definite or probable stent thrombosis, this difference narrowed to 9 vs 6 cases, respectively[5]. Data from the largest meta-analysis comparing new-generation DES with bare-metal stents, among more than 25,000 patients, indicated a rate of definite stent thrombosis of 0.6% at 1-year follow-up. In more recent head-to-head trials comparing new-generation DES, the observed rates of definite stent thrombosis at 1 year ranged from 0.1% to ≤1%[18-21,26,27], although in the ONYX One trial, definite or probable stent thrombosis exceeded 1% at 1-year follow-up[28]. Taken together, these data suggest that although stent thrombosis remains infrequent in absolute terms, the overall rate might be higher with the Cre8 EVO AES than

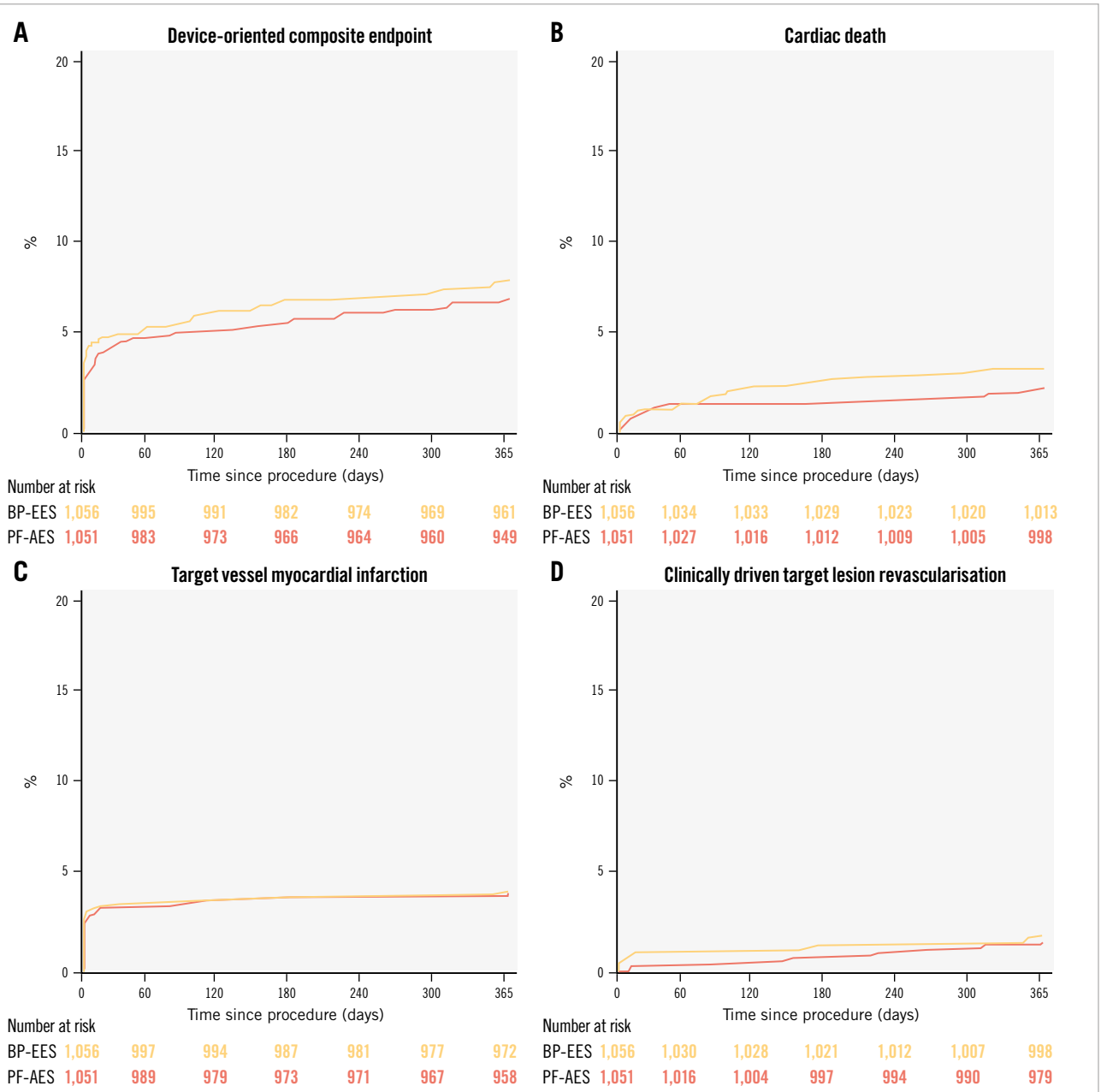


Figure 2. *Kaplan-Meier curves at 1-year follow-up. Device-oriented composite endpoint (A), cardiac death (B), target vessel myocardial infarction (C), and clinically driven target lesion revascularisation (D). BP-EES: biodegradable-polymer everolimus-eluting stent (orange); PF-AES: polymer-free amphilimus-eluting stent (red).*

with other contemporary DES. Notably, thrombosed polymer-free AES stents were more frequently smaller in diameter and longer in length, characteristics that have been consistently associated with stent thrombosis[29-31].

Limitations

The results of this study should be interpreted in view of several limitations. Although the trial established the non-inferiority between the two devices, non-inferiority should be interpreted within the confines of the pre-established margin and the proximity of the upper limit of the 1-sided 95% CI of 2.9% to the non-inferiority threshold of 3.0%. Our trial protocol did not mandate the use of a screening log; as a result, we are unable to provide information on the number of patients assessed for eligibility but not included. Moreover, measurement of baseline and postprocedural cardiac biomarkers were highly recommended but not mandatory, and this could have influenced the rates of periprocedural MIs. The observed higher incidence of early stent thrombosis among patients randomised to the Cre8 EVO AES warrants further investigation. When p-values were adjusted for multiple comparisons using the Benjamini-Hochberg procedure, the p-value for stent thrombosis did not reach statistical significance. Therefore, while this finding

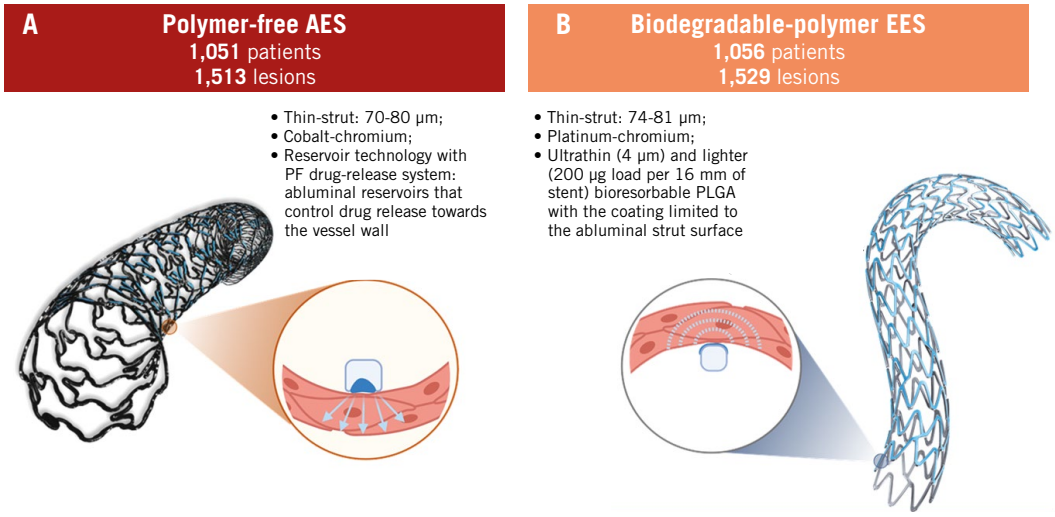
Table 3. Outcomes at 1-year follow-up.

	Polymer-free amphilimus-eluting stent (N=1,051)	Biodegradable-polymer everolimus-eluting stent (N=1,056)	HR (95% CI)	*p*-value
Primary endpoint (device-oriented composite endpoint)	**86 (8.2)**	**76 (7.2)**	**1.15 (0.84-1.56)**	**0.388**
Cardiovascular death	36 (3.4)	25 (2.4)	1.45 (0.87-2.42)	0.150
Target vessel myocardial infarction	45 (4.3)	44 (4.2)	1.03 (0.68-1.56)	0.885
Clinically driven target lesion revascularisation	20 (1.9)	16 (1.5)	1.27 (0.66-2.45)	0.475
Secondary outcomes				
All-cause death	49 (4.7)	39 (3.7)	1.27 (0.83-1.93)	0.266
Any myocardial infarction	50 (4.8)	48 (4.5)	1.05 (0.71-1.56)	0.807
Periprocedural myocardial infarction				
Fourth universal definition of myocardial infarction	36 (3.4)	35 (3.3)	1.04 (0.65-1.65)	0.883
ARC-2	22 (2.1)	14 (1.3)	1.59 (0.81-3.1)	0.177
SCAI hierarchical[a]	20 (1.9)	12 (1.1)	1.68 (0.82-3.45)	0.153
SCAI non-hierarchical[b]	34 (3.2)	25 (2.4)	1.37 (0.82-2.3)	0.227
Cardiovascular death or myocardial infarction	81 (7.7)	70 (6.6)	1.17 (0.85-1.61)	0.339
Any revascularisation	34 (3.2)	34 (3.2)	1.02 (0.63-1.63)	0.949
Any clinically driven revascularisation	32 (3.0)	32 (3.0)	1.02 (0.62-1.66)	0.949
Any target vessel revascularisation	21 (2.0)	21 (2.0)	1.02 (0.55-1.86)	0.961
Clinically driven target vessel revascularisation	20 (1.9)	20 (1.9)	1.02 (0.55-1.89)	0.962
Any target lesion revascularisation	20 (1.9)	17 (1.6)	1.2 (0.63-2.28)	0.588
Definite or probable stent thrombosis	11 (1.0)	3 (0.3)	3.72 (1.04-13.33)	0.044[c]
Early definite or probable stent thrombosis	9 (0.9)	2 (0.2)	4.55 (0.98-21.07)	0.053[c]
Late definite or probable stent thrombosis	2 (0.2)	1 (0.1)	2.03 (0.18-22.39)	0.563
Definite stent thrombosis	11 (1.0)	2 (0.2)	5.58 (1.24-25.16)	0.025[c]
Early definite stent thrombosis	9 (0.9)	1 (0.1)	9.1 (1.15-71.83)	0.036[c]
Late definite stent thrombosis	2 (0.2)	1 (0.1)	2.03 (0.18-22.39)	0.563
Cerebrovascular event	6 (0.6)	5 (0.5)	1.21 (0.37-3.96)	0.756
Target vessel failure	86 (8.2)	79 (7.5)	1.1 (0.81-1.49)	0.538
Any BARC bleeding	157 (14.9)	155 (14.7)	1.03 (0.82-1.28)	0.808
BARC type 2 to 5	83 (7.9)	86 (8.1)	0.98 (0.72-1.32)	0.872

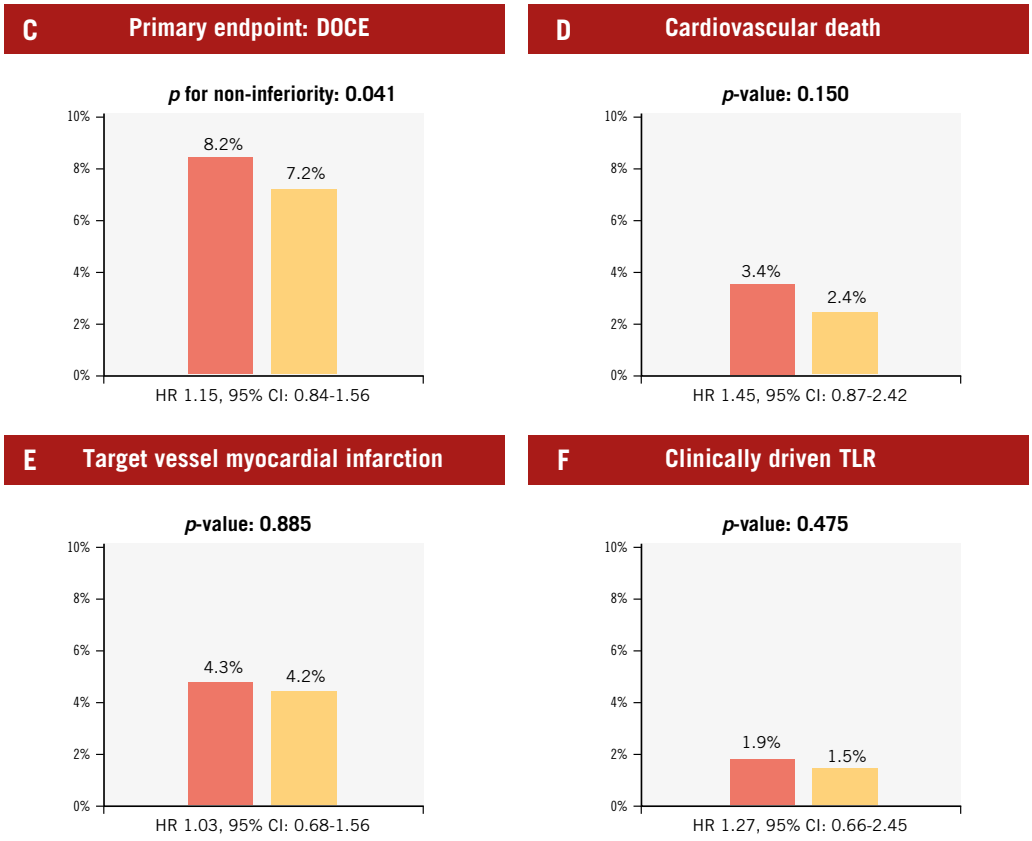
Data are n (%) unless otherwise indicated. Percentages are cumulative incidence estimates. [a]In the hierarchical approach, CK-MB is used as the leading biomarker for adjudication, whereas cardiac troponin is used only if CK-MB is missing. [b]In the non-hierarchical approach, adjudication of either CK-MB or cardiac troponin need to fulfil the definition's criteria **(Supplementary Appendix 5)**. [c]P-values not significant (all p-values=0.292) after adjustment for multiple testing (Benjamini-Hochberg procedure). ARC-2: Academic Research Consortium-2; BARC: Bleeding Academic Research Consortium; CI: confidence interval; CK-MB: creatine kinase-myocardial band; HR: hazard ratio; MI: myocardial infarction; SCAI: Society for Cardiovascular Angiography and Interventions

could potentially be a false positive result, the increased risk still represents a potential safety concern that requires attention. Our findings cannot be extrapolated to other polymer-free DES. There may be several interrelated elements, including the drug release kinetic, the metallic platform, and the drug penetration into the coronary vessel, that collectively influence the overall efficacy and safety of the device. Finally, as with other all-comers stent trials, a further limitation is the

One-year results of the PARTHENOPE trial.



1-year primary endpoint and its single components



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Trial design with the main characteristics of the two study devices (A, B). The polymer-free AES (red) was non-inferior when compared to the biodegradable-polymer EES (orange). Non-inferiority testing for the primary endpoint (C) and superiority testing for the individual components of the primary endpoint (D, E, F) did not show significant differences between the polymer-free AES and the biodegradable-polymer EES. AES: amphilimus-eluting stent; CI: confidence interval; DOCE: device-oriented composite endpoint; EES: everolimus-eluting stent; HR: hazard ratio; PF: polymer-free; PLGA: poly lactic-co-glycolic acid; TLR: target lesion revascularisation

Subgroup	Polymer-free amphilimus-eluting stent (N=1,051)	Biodegradable-polymer everolimus-eluting stent (N=1,056)	Hazard ratio (95%CI)	P-value	P-value for interaction
	no. of patients/total no. (%)				
Age					**0.932**
≥75 years	32/183 (17.5)	27/171 (15.8)	1.10 (0.66-1.84)	0.715	
<75 years	54/868 (6.2)	49/885 (5.5)	1.13 (0.77-1.67)	0.526	
Sex					**0.265**
Female	32/240 (13.3)	21/225 (9.3)	1.47 (0.85-2.55)	0.168	
Male	54/811 (6.7)	55/831 (6.6)	1.01 (0.69-1.47)	0.970	
Diabetes					**0.493**
Yes	35/322 (10.9)	36/336 (10.7)	1.02 (0.64-1.63)	0.928	
No	51/729 (7.0)	40/720 (5.6)	1.27 (0.84-1.92)	0.259	
Acute coronary syndrome					**0.793**
Yes	25/426 (5.9)	22/405 (5.4)	1.09 (0.61-1.93)	0.778	
No	61/625 (9.8)	54/651 (8.3)	1.19 (0.82-1.71)	0.355	
STEMI					**0.217**
Yes	24/378 (6.3)	16/398 (4.0)	1.60 (0.85-3.02)	0.144	
No	62/673 (9.2)	60/658 (9.1)	1.01 (0.71-1.45)	0.941	
Complex PCI					**0.905**
Yes	27/265 (10.2)	23/262 (8.8)	1.18 (0.67-2.05)	0.566	
No	59/786 (7.5)	53/794 (6.7)	1.13 (0.78-1.64)	0.518	
Small vessel disease					**0.151**
Yes	31/236 (13.1)	21/251 (8.4)	1.62 (0.93-2.82)	0.088	
No	55/815 (6.7)	55/805 (6.8)	0.99 (0.68-1.44)	0.957	
Chronic kidney disease					**0.550**
Yes	31/169 (18.3)	30/162 (18.5)	1.00 (0.61-1.66)	0.992	
No	55/882 (6.2)	46/894 (5.1)	1.22 (0.82-1.80)	0.322	
DAPT strategy					**0.954**
Personalised DAPT	45/528 (8.6)	40/527 (7.6)	1.13 (0.74-1.74)	0.564	
Standard DAPT	41/523 (7.8)	36/529 (6.8)	1.15 (0.74-1.80)	0.533	

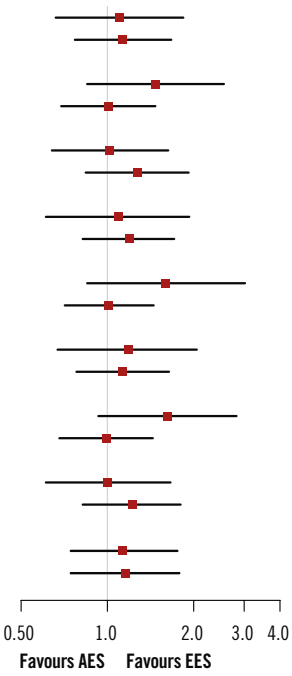

Figure 3. *Subgroup analysis for the primary outcome in the intention-to-treat population. Chronic kidney disease was defined as kidney damage or glomerular filtration rate <60 mL/min/1.73 m² for 3 months or more, irrespective of the cause. Complex PCI was defined as one of the following characteristics: ≥3 coronary vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length ≥60 mm, or treatment of chronic total occlusion. Small vessel disease was defined as the implantation of stent(s) <3 mm in diameter in the target lesion(s). AES: amphilimus-eluting stent; CI: confidence interval; DAPT: dual antiplatelet therapy; EES: everolimus-eluting stent; PCI: percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction*

open-label design whereby patients and treating physicians were not masked to treatment allocation. However, the members of the clinical events committee were unaware of the randomised arm.

Conclusions

Among all-comer patients undergoing PCI, the use of polymer-free AES in patients was non-inferior to biodegradable-polymer EES in terms of a device-oriented composite endpoint at 1-year follow-up. While the efficacy between the two devices was comparable, there was an increased risk of stent thrombosis within 30 days among patients who received the polymer-free DES, and this warrants further investigation.

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Guest Editor

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The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-24-00657

Supplementary data

Supplementary Appendix 1. Trial organisation and participating centres.

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Participating centers and enrolled patients:
The following centers participated in the PARTHENOPE trial (centers are listed per number of patients enrolled, given in brackets):

- AOU Federico II, Naples, Italy (691)
- AORN S. Anna e S. Sebastiano, Caserta, Italy (312)
- Ospedale Santa Maria della Pietà, Nola, Italy (174)
- AOU S. Giovanni di Dio e R. D' Aragona, Salerno, Italy (166)
- Ospedale San Giuliano, Giugliano in Campania, Italy (136)
- Villa dei Fiori, Acerra, Italy (130)
- AORN Antonio Cardarelli, Naples, Italy (125)
- Ospedale San Giuseppe Moscati, Aversa, Italy (108)
- Casa di Cura Montevergine, Mercogliano, Italy (101)
- Ospedale Santa Maria delle Grazie, Pozzuoli, Italy (54)
- Ospedale del Mare, Naples, Italy (49)
- Ospedale SS. Addolorata, Eboli, Italy (32)
- Ospedale San Giovanni Bosco, Naples, Italy (25)
- AORN San Giuseppe Moscati, Avellino, Italy (4)

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Supplementary Appendix 2. Inclusion and exclusion criteria.

Inclusion criteria

1. Age ≥18 years;
2. Clinical evidence of coronary artery disease requiring PCI with DES implantation;
3. Any coronary lesion sized 2.25-4.5 mm by visual estimation.

Exclusion criteria

1. Inability to provide informed consent;
2. Active bleeding requiring medical attention (BARC ≥2);
3. Need for chronic oral anticoagulant therapy;
4. Planned surgery within 3 months;
5. Known hypersensitivity or allergy to aspirin or any $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, ticagrelor), heparin, contrast agent, or any DES-components;
6. Previous treatment with bioresorbable vascular scaffolds;
7. Participation in another study that has not reached the primary endpoint;
8. A life expectancy of less than 24 months;
9. Female of childbearing potential;
10. Under judicial protection, tutorship or curatorship.

Supplementary Appendix 3. Study devices.

Cre8 EVO amphilimus-eluting stent

The Cre8 EVO amphilimus-eluting stent (Cre8 EVO AES, Alvimedica, Instanbul, Turkey) is a polymer-free drug-eluting stent with an alternative design. The device is a thin-strut (70-80 μm), cobalt-chromium stent, based on a reservoir technology, which is a proprietary polymer-free drug-release system consisting of reservoirs on the stent's outer surface (abluminal) that control and direct drug release exclusively towards the vessel wall. The presence of reservoirs influences drug dose and release kinetics, allowing peak drug tissue concentration during the first days post-implantation, 50% drug elution in approximately 18 days, 65–70% elution within 30 days, and a complete drug elution within 90 days.
The reservoirs release the Amphilimus™ formulation, which is based on sirolimus (0.9 μm/mm^2) formulated with a non-polymeric mixture of long-chain fatty acid to serve as carrier. In addition, the Cre8 EVO AES has a permanent ultra-thin (<3 μm) and high-density turbostratic carbon film (i-Carbofilm™) that allows for enhanced hemocompability owing to a selective albumin absorption that causes minimal platelets activation and endothelialization. Moreover, in the EVO version the frame has been reduced in crown width and number of links to improve flexibility and conformability.
The Cre8 AES were available in diameters of 2.00-4.5 mm and in lengths of 9, 13, 16, 20, 26, 33, 40, and 46 mm.

SYNERGY everolimus-eluting stent

The SYNERGY everolimus-eluting stent (EES, Boston Scientific Corporation, Marlborough, MA, USA) is a thin-strut (74–81 μm), platinum chromium metal alloy platform with an abluminal PLGA (Poly-lactic co-glycolic acid) polymer, which elutes everolimus (100 μg/cm^2). The SYNERGY platform is built upon the PROMUS Premier platform with several differences, which included replacing the durable polyvinylidene difluoride (PVDF) polymer with an ultrathin (4 μm) and lighter (200 μg load per 16 mm of stent) bioresorbable PLGA with the coating limited to the abluminal strut surface and thinner stent struts. In addition, the end rings of SYNERGY EES were reinforced four connectors versus two throughout the body of the stent to prevent longitudinal compression. The SYNERGY EES were available in diameters of 2.00-4.5 mm and in lengths of 8, 12, 16, 20, 24, 28, 32, 38 and 48 mm.

Supplementary Appendix 4. DAPT risk score.

The DAPT score was prospectively collected in all patients, including those randomized to standard DAPT, and was calculated during the hospital stay and before discharge.

The score is calculated by assigning points to patient-related (0 for age <65 years, -1 for age ≥65 and <75 years, -2 for age ≥75 years, 1 for diabetes mellitus, 1 for current smokers, 1 for previous PCI or prior myocardial infarction, 2 for history of congestive heart failure or left ventricular ejection fraction <30%), and procedure-related characteristics (1 for acute myocardial infarction at presentation, 2 for PCI of saphenous vein graft, 1 for implantation of paclitaxel-eluting stent, 1 for stent diameter less than 3 mm).[11] Since paclitaxel-eluting stents are no longer used, no patient received the point assigned for paclitaxel-eluting stent implantation. The score was developed by considering two separate models that predict the reduction in ischemic events and the increase in bleeding events with extended DAPT duration. Variables associated with both bleeding and ischemia, such as peripheral artery disease, hypertension, and chronic kidney disease, were excluded from the two models. A low DAPT score (<2) indicates that the risk of bleeding outweighs the benefits of DAPT in terms of preventing ischemic events, whereas a high DAPT score (≥2) indicates that the benefits of DAPT outweigh the bleeding risks. In the arm of personalized DAPT duration, patients with a high DAPT score (≥2) received DAPT for 24 months, whereas those with a low DAPT score (<2) received DAPT for 3 or 6 months, followed by aspirin monotherapy until 24 months in the case of chronic or acute coronary syndrome, respectively. Patients randomized to standard DAPT received a duration of DAPT for 12 months regardless of their clinical presentation and score.

Supplementary Appendix 5. Definitions of endpoints.

Death

All deaths are classified and reported according to the Academic Research Consortium (ARC)-2 consensus document. Therefore, deaths are categorized as cardiovascular, non- cardiovascular or undetermined based on the definitions below.

- **Cardiovascular death**
  Cardiovascular death is defined as death resulting from cardiovascular causes.
  The following categories are collected:
  1. Death caused by acute myocardial infarction
  2. Death caused by sudden cardiac death, including unwitnessed, death
  3. Death resulting from heart failure
  4. Death caused by stroke
  5. Death caused by cardiovascular procedures
  6. Death resulting from cardiovascular hemorrhage
  7. Death resulting from other cardiovascular cause

1. Death caused by acute myocardial infarction:
   - Death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or refractory arrhythmia.
   - If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)).
   - The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus.
   - Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
   - Death resulting from a procedure to treat a myocardial infarction percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.
   - Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e. chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. Death caused by sudden cardiac death, including unwitnessed, death:

   Death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:
   - Death witnessed and occurring without new or worsening symptoms.
   - Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless documented (i.e. by ECG or other objective) to be due to acute myocardial infarction.
   - Death witnessed and attributed to an identified arrhythmia (e.g., captured on an

electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review). Death after unsuccessful resuscitation from cardiac arrest.

- Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology.
- Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available).

General Considerations: A subject seen alive and clinically stable 24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Typical scenarios include:

- Subject well the previous day but found dead in bed the next day.
- Subject found dead at home on the couch with the television on.
- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes".

3. Death resulting from heart failure:

   Death due to Congestive Heart Failure refers to a death in association with clinically worsening symptoms and/or signs of heart failure not following an acute MI. Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

   a. Cool, clammy skin or
   b. Oliguria (urine output < 30 mL/hour) or
   c. Altered sensorium or Cardiac index < 2.2 L/min/m²
   d. Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

4. Death caused by stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.

5. Death caused by cardiovascular procedures refers to death caused by the immediate complications of a cardiac procedure and excludes death resulting from procedures to treat an acute MI or the complications resulting from an acute MI.

6. Death resulting from cardiovascular hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage, non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. Death resulting from other cardiovascular cause refers to a cardiovascular death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

- **Non-cardiovascular death**

Non-cardiovascular death is defined as any death that is not thought to be the result of a cardiovascular cause.

The following categories are collected:

1. Death resulting from malignancy
2. Death resulting from pulmonary causes
3. Death caused by infection (includes sepsis)
4. Death resulting from gastrointestinal causes
5. Death resulting from accident/trauma
6. Death caused by other noncardiovascular organ failure
7. Death resulting from other noncardiovascular cause

Examples: Death due to GI bleeding is not considered a CV death. Death due to retroperitoneal hematoma following PCI is considered CV death. Death due to intracerebral hemorrhage is considered CV death.

Malignant Causes:

- Death results directly from the cancer; OR
- Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy); OR
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer.

- **Undetermined cause of death**

Undetermined cause of death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause, due to absence of any information (e.g., the only available information is "patient died"). The use of this category of death is discouraged and should apply to a minimal number of cases when no information at all on the circumstances of death are available (i.e. found on obituary of local newspaper).

Myocardial infarction

Myocardial infarction (MI) is defined based on the fourth Universal Definition of MI. This definition is also used for periprocedural MI. However, periprocedural MI is additionally adjudicated according to the SCAI and ARC-2 definitions.

- **Type 1 MI (Spontaneous MI, >48 hours after intervention)**: MI caused by atherothrombotic coronary artery disease and usually precipitated by atherosclerotic plaque disruption (rupture or erosion).

  Type 1 MI requires the detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and with at least one of the following:
  - Symptoms of acute myocardial ischemia;

- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology;
- Identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy (Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values).

- **Type 2 MI**: Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, requiring at least one of the following:
  - Symptoms of acute myocardial ischemia;
  - New ischemic ECG changes;
  - Development of pathological Q waves;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

- **Type 3 MI**: Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

- **Type 4a MI**: Coronary intervention-related MI is arbitrarily defined by an elevation of cTn values more than five times the 99th percentile URL in patients with normal baseline values. In patients with elevated pre-procedure cTn in whom the cTn level are stable ($\leq$ 20% variation) or falling, the post-procedure cTn must rise by > 20%. However, the absolute post-procedural value must still be at least five times the 99th percentile URL. In addition, one of the following elements is required:
  - New ischemic ECG changes;
  - Development of new pathological Q waves (isolated development of new pathological Q waves meets the type 4a MI criteria if cTn values are elevated and rising but less than five times the 99th percentile URL);
  - Imaging evidence of new loss of viable myocardium or new regional wall motion

abnormality in a pattern consistent with an ischemic etiology;
    - Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or a side branch occlusion/thrombus, disruption of collateral flow, or distal embolization (Post-mortem demonstration of a procedure-related thrombus in the culprit artery, or a macroscopically large circumscribed area of necrosis with or without intra-myocardial haemorrhage meets the type 4a MI criteria).

Increasing levels after the procedure can only be attributed with certainty to procedural myocardial injury when the pre-procedural cTn values are normal (≤ 99th percentile URL), or if they are stable or falling. For patients that present with an acute coronary syndrome and undergo a prompt coronary revascularization procedure resulting in only a single pre-procedural baseline value that is normal or mildly elevated, followed by subsequent post-procedural values that continue to increase, the post- procedural increase should be attributed to the index event.

- **Type 4b MI**: Stent or scaffold thrombosis associated with MI when documented by angiography or autopsy using the same criteria utilized for type 1 MI.

- **Type 4c MI**: Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI.

- **Type 5 MI**: CABG-related MI is arbitrarily defined as elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre- procedure cTn in whom cTn levels are stable (≤20% variation) or falling, the post-procedure cTn must rise by >20%. However, the absolute post-procedural value still must be >10 times the 99th percentile URL. In addition, one of the following elements is required:
    - Development of new pathological Q waves (Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but <10 times the 99th percentile URL);
    - Angiographic documented new graft occlusion or new native coronary artery occlusion;
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

Based on ST-segment changes, MI is also classified as:
- STEMI
- NSTEMI
- Unknown (LBBB, paced rhythm, unreadable)
- No ECG available

Based on the development of new pathologic Q-waves, MI is defined as:
- Q-wave myocardial infarction
- Non-Q-wave myocardial infarction

For the assessment of the primary endpoint of DOCE, MI will be adjudicated as to whether it is not clearly attributable to a nontarget vessel or, rather, it is clearly attributable to a nontarget

vessel.

Periprocedural MI according to SCAI criteria:

Defined as the occurrence within 72 hours after PCI (or CABG) of either:

- CK-MB ≥10x ULN or cTn* (I or T) ≥70x ULN,
- OR: CK-MB ≥5x ULN or cTn* (I or T) ≥35x ULN in combination with any of the following:
    - new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB, or
    - angiographically documented native coronary artery occlusion or new severe stenosis with thrombosis and/or diminished epicardial flow, or
    - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

*while EXCEL definition did not comprise cTn, we consider equivalence between CK-MB ≥10x and cTn ≥70x and between CK-MB ≥5x and cTn ≥35x

Adjudication of periprocedural MI according to the study protocol is done based on non-hierarchical availability of biomarkers, meaning that either CK-MB or Tn need to fulfil the definition's criteria. In addition to the protocol definition, given that recent data suggest that cardiac troponins may overestimate the rate of periprocedural MI, in the PARTHENOPE trial all procedural MIs will also be adjudicated based on a hierarchical approach, where CK-MB will be used as leading biomarker for adjudication, and Tn only if CK-MB is missing.

Periprocedural MI according to ARC-2 criteria:

A myocardial infarction is defined by:

- Absolute rise in cardiac troponin (from baseline) ≥35 times upper reference limit (or ULN) OR CK-MB ≥5 times URL/ULN;
- Plus 1 (or more) of the following criteria:
    - New significant* Q waves or equivalent
    - Flow-limiting angiographic complications
    - New "substantial" loss of myocardium on imaging

Significant peri-procedural myocardial injury is defined by:
An absolute rise in cardiac troponin (from baseline) ≥ 70 times upper reference limit (or ULN) OR CK-MB≥10 times URL/ULN.

These definitions are applicable to patients with normal (or elevated and stable or falling) baseline biomarkers. Diagnosis of peri-procedural MI in patients with rising biomarkers due to the presentation is not possible according to ARC-2.

*Q-wave criteria requires the development of new Q waves ≥40 ms in duration and ≥1 mm deep in voltage in ≥2 contiguous leads.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by central nervous system (CNS) vascular injury as a result of haemorrhage or infarction. CNS includes brain, spinal cord and retina.

Classification:

Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by CNS infarction. Evidence of infarction is defined as "Pathological, imaging, or other objective evidence of acute cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or in absence of the above (i.e. imaging or autopsy unavailable), clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury is based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Note, haemorrhagic infarction, defined as a parenchymal haemorrhage after CNS infarction, is considered an ischemic stroke.

Cerebral Haemorrhage

Haemorrhages in the CNS are classified as stroke if they are non-traumatic, caused by a vascular event, and result in injury to the CNS. In contrast, traumatic haemorrhages will not be characterized as stroke. Subdural hematoma will not be classified as a stroke. The diagnoses included in this section are intracerebral haemorrhage (intra-parenchymal and intraventricular) and subarachnoid haemorrhage (both aneurysmal and non-aneurysmal).

Stroke caused by intracerebral haemorrhage

Rapidly developing clinical signs of neurological dysfunction (focal or global) attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.

Stroke caused by subarachnoid haemorrhage

Rapidly developing signs of neurological dysfunction (focal or global) and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.
Haemorrhage's may be further classified according to location (example, supratentorial, subtentorial, etc.)

Stroke not otherwise specified

An episode of acute neurological dysfunction presumed to be caused by ischemia or haemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Transient ischemic attack

Transient focal neurological signs or symptoms (lasting <24 h) presumed to be due to focal brain,

spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology (or in the absence of imaging)

Stent thrombosis

Stent thrombosis is defined by the ARC-2 consensus document. The time frame for stent thrombosis starts when the patient has been undraped and taken off the catheterization laboratory table.

Definite stent thrombosis is considered to have occurred by either angiographic or pathological confirmation.

- Angiographic confirmation of stent thrombosis: the presence of a thrombus* that originates in the stent or in the segment 5 mm proximal or distal to the stent or in a side branch originating from the stented segment and the presence of at least 1 of the following criteria:
    - Acute onset of ischemic symptoms at rest
    - New ECG changes suggestive of acute ischemia
    - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous myocardial infarction)
- Pathological confirmation of stent thrombosis:
    - Evidence of recent thrombus within the stent determined at autopsy
    - Examination of tissue retrieved following thrombectomy (visual/histology)

Probable stent thrombosis: Regardless of the time after the index procedure, any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent and in the absence of any other obvious cause.†

The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered stent thrombosis.

*Occlusive thrombus: Thrombolysis in Myocardial Infarction grade 0 or 1 flow within or proximal to a stent segment. Nonocclusive thrombus: intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, persistence of contrast material within the lumen, or visible embolization of intraluminal material downstream.
†When the stented segment is in the left circumflex coronary artery or in the presence of preexisting electrocardiographic abnormalities (e.g., left bundle branch block, paced rhythms), definitive evidence of localization may be absent and Clinical Events Committee adjudication is based on review of all available evidence).

According to the timing of the event, stent thrombosis is classified as:

- Acute: from 0 to 24 hours. Time 0 is defined as the moment the patient is undraped and taken off the catheterization table.
- Subacute: >24-30 days.
- Late: >30 days-1 year.
- Very late: >1 year.

Repeat revascularization

Urgent coronary revascularization: One or more episodes of rest pain, presumed to be ischemic in origin, which results in either urgent repeat PCI or urgent CABG. In the absence of pain, new ST segment changes (a new ST segment shift >0.05 mV (0.5 mm) on a 12-lead ECG), indicative of ischemia, acute pulmonary edema, ventricular arrhythmias, or hemodynamic instability presumed to be ischemic in origin, constitute sufficient evidence of ischemia. To be considered urgent, the repeat PCI or CABG is initiated within 24 hours of the last episode of ischemia and not identified as planned/staged. The episode of ischemia leading to urgent repeat PCI must occur following completion of the index PCI and guide wire removal. CABG initiated within 24 hours of PCI (index or repeat) due to an unsatisfactory result, even in the absence of documented ischemia, is also considered an urgent coronary revascularization endpoint.

Target-lesion revascularization: The target lesion is defined as the treated segment including the 5-mm margin proximal and distal to the stent. Target lesion revascularization is defined as a repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel performed for restenosis or other complication of the target lesion.[61]

Target-vessel revascularization: The target vessel is defined as the entire major intervened coronary vessel, including side branches. Target vessel revascularization is defined as any repeat percutaneous intervention or surgical bypass of any segment of the target vessel including the target lesion.

Target-vessel non-target lesion revascularization: Target vessel nontarget lesion revascularization is defined as any repeat percutaneous intervention or surgical bypass of the target vessel for pre-existing disease, disease progression or other reasons unrelated to the target lesion as defined above.

For the definition of the target lesion, the following additional scenarios should be considered as proposed by a consensus document on staged procedures:

- The inclusion of the proximal and distal 5 mm coronary portions from the edge of a device in the target lesion extends to the side branches.
- When a side branch originates outside the stented area but within the target lesion, the proximal portion of the side branch included in the target lesion should sum up to 5 mm from the edge of the stent.
- When a side branch emerges from the stented area, the proximal 5 mm of the side branch are part of the target lesion.
- When the left main is treated at baseline, the entire left coronary system becomes the target vessel (both circumflex and left anterior descending [LAD] coronary arteries).
- If the intermediate branch is treated at index, the target vessel is formed by the intermediate branch and the left main. Moreover, if the treated lesion is within 5 mm of the left main, then the left main also becomes a target lesion.
- When assessing arterial or venous grafts, the target vessel is defined by the insertion of the distal anastomosis. For example, if an aortocoronary bypass with a distal anastomosis in the

right posterior descending coronary artery is treated during a first procedure, the native right coronary artery, as well as the bypass, are components of the target vessel.

- When the proximal portions of the LAD, intermediate branch, or left circumflex are treated, if the implanted device is within 5 mm of the ostium of the treated artery, the proximal portion of the other vessel(s) up to 5 mm will be considered component(s) of the target lesion. More specifically, if a proximal LAD has an implanted device 2 mm from its ostium, the proximal 3 mm of the left circumflex are considered part of the target lesion. However, exceptionally, the rest of the left circumflex is not analyzed as a target vessel. Thus, in this scenario, treatment of a distal circumflex in a subsequent procedure would qualify as a non-target vessel revascularization.

Repeat revascularization procedures are defined as clinically-driven in case one of the following conditions:

Repeat revascularization in the context of an acute coronary syndrome: the target-lesion is the culprit-lesion. Alternatively, other criteria for clinically-driven revascularization in the context of chronic coronary syndrome must apply.

- Repeat revascularization in the context of chronic coronary syndrome:
    - Presence of symptoms or signs of ischemia and evidence of diameter stenosis >50% by visual estimation.
    - Presence of symptoms or signs of ischemia and evidence of invasive ischemia by using a functional assessment method irrespective of stenosis severity.

Bleeding

All potential bleeding events are primarily adjudicated according to the Bleeding Academic Research Consortium (BARC) classification.

<u>BARC Criteria</u>

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional; may include episodes leading to self-discontinuation of medical therapy by the patient, without consulting a health care professional.
Type 2	Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance; including bleeding found by imaging alone) that does not fit the criteria for Types 3, 4, or 5 but does meet at least one of the following criteria: • Requiring non-surgical, medical intervention by a health care professional • Leading to hospitalization of increased level of care • Prompting evaluation

Type 3a **Type 3b** **Type 3c**	• Overt bleeding plus hemoglobin drop of 3 to <5** g/dL (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding • Overt bleeding plus hemoglobin drop ≥5** g/dL (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental / nasal / skin / hemorrhoid) • Bleeding requiring intravenous vasoactive agents • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation; does include intraspinal) • Subcategories: confirmed by autopsy or imaging or LP • Intra-ocular bleed compromising vision
Type 4	CABG-related bleeding • Perioperative intracranial bleeding within 48 hours • Reoperation following closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 units of whole blood or packed red blood cells within 48-hour period* • Chest tube output ≥2 L within a 24-hour period Notes: If a CABG-related bleed is not adjudicated as at least a type-3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e., within a 48-hour time frame) but does not meet type-4 severity criteria, it will be classified as not a bleeding event.
Type 5a **Type 5b**	• Probable fatal bleeding; no autopsy or imaging confirmation, but clinically suspicious • Definite fatal bleeding: overt bleeding or autopsy or imaging confirmation

Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood_1g/dL hemoglobin).
†Cell saver products will not be counted.

TIMI Bleeding Criteria

Non-CABG Related Bleeding:

1. **Major**
   - Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI).
   - Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in hematocrit.
   - Fatal bleeding (bleeding that directly results in death within 7 days).
2. **Minor**

- Clinically overt (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL or
  ≥10% decrease in hematocrit.

3. **Bleeding requiring medical attention**
   - Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above:
     - 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).
     - Leading to or prolonging hospitalization.
     - Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging).

4. **Minimal**
   - Any overt bleeding event that does not meet the criteria above.
   - Any clinically overt sign of hemorrhage (including imaging) associated with a <3 g/dL decrease in hemoglobin concentration or <9% decrease in hematocrit.

Bleeding in the Setting of CABG:

- Fatal bleeding (bleeding that directly results in death).
- Perioperative intracranial bleeding.
- Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
- 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.
- Chest tube output >2 L within a 24-h period.

GUSTO Bleeding Criteria

- **Severe or life-threatening**
  - Intracerebral haemorrhage
  - Resulting in substantial hemodynamic compromise requiring treatment
- **Moderate**
  - Requiring blood transfusion but not resulting in hemodynamic compromise
- **Mild**
  - Overt Bleeding that does not meet above criteria.

All BARC and TIMI definitions take into account blood transfusions, so that hemoglobin and hematocrit values are adjusted by 1 g/dL or 3%, respectively, for each unit of blood transfused. Therefore, the true change in hemoglobin or hematocrit if there has been an intervening transfusion between 2 blood measurements is calculated as follows: Δ Hemoglobin (Hgb) = [baseline Hgb - post-transfusion Hgb] + [number of transfused units]; ΔHematocrit (Hct) = [baseline Hct - post-transfusion Hct] + [number of transfused units x 3].

Supplementary Table 1. Medication at baseline and during follow-up.

	Polymer-free amphilimus-eluting stent (N=1,051)	Biodegradable-polymer everolimus-eluting stent (N=1,056)
Medication at home		
Currently in medication	825/1,051 (78.5%)	821/1,056 (77.7%)
Aspirin	462/825 (56%)	463/821 (56.4%)
P2Y12 receptor inhibitor		
Clopidogrel	159/825 (19.3%)	153/821 (18.6%)
Prasugrel	2/825 (0.2%)	1/821 (0.1%)
Ticagrelor	32/825 (3.9%)	38/821 (4.6%)
None	632/825 (76.6%)	629/821 (76.6%)
DAPT	150/825 (18.2%)	149/821 (18.1%)
Statin	421/825 (51%)	443/821 (54%)
Other lipid-lowering drug	126/825 (15.3%)	142/821 (17.3%)
Beta-blocker	356/825 (43.2%)	362/821 (44.1%)
ACE-inhibitors or ATII antagonist	499/825 (60.5%)	539/821 (65.7%)
PPI	409/825 (49.6%)	418/821 (50.9%)
SGLT-2 inhibitor	15/825 (1.8%)	25/821 (3%)
Oral antidiabetic	198/825 (24%)	224/821 (27.3%)
Insulin	100/825 (12.1%)	98/821 (11.9%)
In-hospital at discharge		
Aspirin	1,034/1,040 (99.4%)	1,034/1,042 (99.2%)
P2Y12 receptor inhibitor		
Clopidogrel	268/1,040 (25.8%)	287/1,042 (27.5%)
Prasugrel 10 mg	20/1,040 (1.9%)	23/1,042 (2.2%)
Prasugrel 5 mg	3/1,040 (0.3%)	0/1,042 (0%)
Ticagrelor 90 mg BID	743/1,040 (71.4%)	720/1,042 (69.1%)
Ticagrelor 60 mg BID	5/1,040 (0.5%)	9/1,042 (0.9%)
None	1/1,040 (0.1%)	3/1,042 (0.3%)
DAPT	1,033/1,040 (99.3%)	1,031/1,042 (98.9%)
Oral anticoagulant therapy	25/1,040 (2.4%)	30/1,041 (2.9%)
Statin	999/1,040 (96.1%)	1,013/1,042 (97.2%)
Other lipid-lowering drug	460/1,040 (44.2%)	462/1,042 (44.3%)
Beta-blocker	768/1,040 (73.8%)	770/1,042 (73.9%)
ACE-inhibitors or ATII antagonist	807/1,040 (77.6%)	839/1,042 (80.5%)
PPI	1,003/1,040 (96.4%)	1,014/1,042 (97.3%)
SGLT-2 inhibitor	25/1,039 (2.4%)	31/1,041 (3%)
Oral antidiabetic	183/1,040 (17.6%)	192/1,041 (18.4%)
Insulin	124/1,039 (11.9%)	138/1,041 (13.3%)
3-months follow-up	1,031	1,038
Aspirin	1,022/1,031 (99.1%)	1,021/1,038 (98.4%)
P2Y12 receptor inhibitor		
Clopidogrel	263/1,030 (25.5%)	281/1,038 (27.1%)
Prasugrel 10 mg	21/1,030 (2%)	24/1,038 (2.3%)
Prasugrel 5 mg	2/1,030 (0.2%)	0/1,038 (0%)

Ticagrelor 90 mg BID	739/1,030 (71.7%)	716/1,038 (69%)
Ticagrelor 60 mg BID	2/1,030 (0.2%)	5/1,038 (0.5%)
None	3/1,030 (0.3%)	12/1,038 (1.2%)
DAPT	1,019/1,030 (98.9%)	1,010/1,038 (97.3%)
6-months follow-up	1015	1033
Aspirin	999/1,015 (98.4%)	998/1,033 (96.6%)
P2Y12 receptor inhibitor		
Clopidogrel	220/1,015 (21.7%)	242/1,033 (23.4%)
Prasugrel 10 mg	24/1,015 (2.4%)	27/1,033 (2.6%)
Prasugrel 5 mg	1/1,015 (0.1%)	1/1,033 (0.1%)
Ticagrelor 90 mg BID	696/1,015 (68.6%)	703/1,033 (68.1%)
Ticagrelor 60 mg BID	2/1,015 (0.2%)	1/1,033 (0.1%)
None	72/1,015 (7.1%)	59/1,033 (5.7%)
DAPT	930/1,015 (91.6%)	944/1,033 (91.4%)
12-months follow-up	1,007	1,023
Aspirin	978/1,007 (97.1%)	985/1,023 (96.3%)
P2Y12 receptor inhibitor		
Clopidogrel	223/1,005 (22.2%)	239/1,023 (23.4%)
Prasugrel 10 mg	21/1,005 (2.1%)	28/1,023 (2.7%)
Prasugrel 5 mg	1/1,005 (0.1%)	0/1,023 (0%)
Ticagrelor 90 mg BID	604/1,005 (60.1%)	611/1,023 (59.7%)
Ticagrelor 60 mg BID	6/1,005 (0.6%)	2/1,023 (0.2%)
None	150/1,005 (14.9%)	143/1,023 (14%)
DAPT	830/1,005 (82.6%)	849/1,023 (83%)

ACE: Angiotensin Converting Enzyme; ATII: Angiotensin II; DAPT: dual antiplatelet therapy; PPI: Proton Pump Inhibitor; SGLT-2: Sodium-glucose Cotransporter-2.

Supplementary Table 2. Primary and secondary outcomes in the per-protocol population.

	Polymer-free amphilimus-eluting stent (N=992)	Biodegradable-polymer everolimus-eluting stent (N=1,000)	HR (95% CI)	P-value
Primary endpoint (Device-oriented clinical endpoint)	77/992 (7.8%)	72/1,000 (7.2%)	1.08 (0.79-1.49)	0.628
Cardiovascular death	35/992 (3.5%)	25/1,000 (2.5%)	1.42 (0.85-2.37)	0.182
Target-vessel MI	38/992 (3.8%)	42/1,000 (4.2%)	0.91 (0.59-1.42)	0.686
Clinically-driven Target lesion revascularization	16/992 (1.6%)	14/1,000 (1.4%)	1.16 (0.57-2.38)	0.680
Secondary outcomes				
All-cause death	48/992 (4.8%)	39/1,000 (3.9%)	1.25 (0.82-1.9)	0.305
Any myocardial infarction	42/992 (4.2%)	46/1,000 (4.6%)	0.92 (0.61-1.4)	0.701
Periprocedural myocardial infarction				
4th UDMI	30/992 (3%)	33/1,000 (3.3%)	0.92 (0.56-1.5)	0.731
ARC-2	17/992 (1.7%)	14/1,000 (1.4%)	1.23 (0.61-2.49)	0.570
SCAI hierarchical[a]	17/992 (1.7%)	10/1,000 (1%)	1.72 (0.79-3.76)	0.172
SCAI non-hierarchical[b]	29/992 (2.9%)	25/1,000 (2.5%)	1.17 (0.69-2)	0.556
Cardiovascular death or myocardial infarction	72/992 (7.3%)	68/1,000 (6.8%)	1.07 (0.77-1.49)	0.694
Any revascularization	30/992 (3%)	30/1,000 (3%)	1.02 (0.61-1.69)	0.945
Any Clinically-driven Revascularization	28/992 (2.8%)	28/1,000 (2.8%)	1.02 (0.6-1.72)	0.946
Any target vessel revascularization	17/992 (1.7%)	18/1,000 (1.8%)	0.96 (0.49-1.86)	0.905
Clinically-driven target vessel revascularization	16/992 (1.6%)	17/1,000 (1.7%)	0.96 (0.48-1.89)	0.899
Any target lesion revascularization	16/992 (1.6%)	15/1,000 (1.5%)	1.09 (0.54-2.19)	0.820
Definite or probable stent thrombosis	8/992 (0.8%)	3/1,000 (0.3%)	2.71 (0.72-10.21)	0.141
Early definite or probable stent thrombosis	7/992 (0.7%)	2/1,000 (0.2%)	3.55 (0.74-17.07)	0.114

Late definite or probable stent thrombosis	1/992 (0.1%)	1/1,000 (0.1%)	1.02 (0.06-16.27)	0.990
Definite stent thrombosis	8/992 (0.8%)	2/1,000 (0.2%)	4.06 (0.86-19.12)	0.076
Early definite stent thrombosis	7/992 (0.7%)	1/1,000 (0.1%)	7.09 (0.87-57.64)	0.067
Late definite stent thrombosis	1/992 (0.1%)	1/1,000 (0.1%)	1.02 (0.06-16.27)	0.990
Cerebrovascular event	6/992 (0.6%)	3/1,000 (0.3%)	2.02 (0.51-8.08)	0.320
Target-vessel failure	77/992 (7.8%)	74/1,000 (7.4%)	1.05 (0.76-1.45)	0.754
Any BARC bleeding	146/992 (14.7%)	144/1,000 (14.4%)	1.03 (0.82-1.3)	0.796
BARC type 2 to 5	75/992 (7.6%)	79/1,000 (7.9%)	0.96 (0.7-1.32)	0.807

[a]In the hierarchical approach, CK-MB is used as leading biomarker for adjudication, whereas cardiac troponin only if CK-MB is missing. [b]In the non-hierarchical approach, adjudication either CK-MB or cardiac troponin need to fulfil the definition's criteria. Data are n (%) unless otherwise indicated. ARC-2: Academic Research Consortium-2; BARC: Bleeding Academic Research Consortium; MI: Myocardial Infarction; SCAI: Society for Cardiovascular Angiography and Interventions.

Supplementary Table 3. Adjudicated causes of death.

Cause of death	All (N=88)	Polymer-free amphilimus-eluting stent (N = 49)	Biodegradable-polymer everolimus-eluting stent (N = 39)
Cardiovascular, n (%)	29 (33.0%)	12 (24.5%)	17 (43.6%)
Acute myocardial infarction, n (%)	16 (55.2%)	9 (75.0%)	7 (41.2%)
Sudden cardiac death, n (%)	3 (10.3%)	0 (0.0%)	3 (17.6%)
Heart failure, n (%)	5 (17.2%)	1 (8.3%)	4 (23.5%)
Stroke, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cardiovascular procedures, n (%)	3 (10.3%)	1 (8.3%)	2 (11.8%)
Cardiovascular haemorrhage, n (%)	1 (3.4%)	1 (8.3%)	0 (0.0%)
Other, n (%)	1 (3.4%)	0 (0.0%)	1 (5.9%)
Undetermined, n (%)	32 (36.4%)	24 (49.0%)	8 (20.5%)
Non cardiovascular, n (%)	27 (30.7%)	13 (26.5%)	14 (35.9%)
Malignancy, n (%)	9 (33.3%)	6 (46.2%)	3 (21.4%)
Pulmonary, n (%)	3 (11.1%)	2 (15.4%)	1 (7.1%)
Infection (including sepsis), n (%)	9 (33.3%)	4 (30.8%)	5 (35.7%)
Gastrointestinal, n (%)	3 (11.1%)	1 (7.7%)	2 (14.3%)
Accident/trauma, n (%)	1 (3.7%)	0 (0.0%)	1 (7.1%)
Non cardiovascular organ failure, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other non cardiovascular cause, n (%)	2 (7.4%)	0 (0.0%)	2 (14.3%)

Supplementary Table 4. Stent thrombosis cases.

Case ID	**26-26**	**26-83**	**26-442**	**28-10**	**28-151**	**28-161**	**36-52**	**37-38**	**40-76**	**40-123**	**43-80**	**28-168**	**38-57**	**41-14**
Study device	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Polymer-free AES**	**Biodegradable polymer EES**	**Biodegradable polymer EES**	**Biodegradable polymer EES**
Category	Subacute	Acute	Late	Acute	Acute	Acute	Subacute	Late	Subacute	Subacute	Subacute	Subacute	Subacute	Late
Time (day)	4	0	363	0	0	0	7	94	13	3	7	9	19	141
Definite or Probable	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Definite	Probable	Definite
Device type (study device or not)	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device	Study device
Timing of implantation	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure	Index procedure
Age	46	66	80	60	58	42	68	62	71	47	76	64	79	71
Gender	female	male	male	male	male	female	male	male	male	male	male	male	male	female
Smoking	former	former	current	no	yes	yes	former	yes	former	yes	no	yes	former	former
Hypertension	yes	yes	yes	no	no	no	yes	yes	yes	yes	yes	yes	yes	yes
Dyslipidemia	no	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	no	yes
DM	yes	no	no	no	no	no	no	no	yes	no	no	no	yes	yes
Family history of CAD	yes	no	no	no	yes	yes	yes	no	no	no	no	no	yes	no

Previous PCI/CABG	no	CABG	PCI	no	no	no	yes	PCI	no	no	no	PCI	yes	CABG
Previous MI	no	no	yes	no	no	no	yes	yes	no	yes	no	yes	yes	yes
Indication for PCI	Chronic coronary syndrome	Chronic coronary syndrome	STEMI	NSTE-ACS	STEMI	STEMI	NSTE-ACS	NSTE-ACS	STEMI	STEMI	STEMI	STEMI	NSTE-ACS	NSTE-ACS
Target	LAD	RCA	LAD	LAD	LAD	LAD	LAD	LCx	RCA	RCA	LAD	LAD	LAD	LCx
CASS Number	13	1	11	13	12	11	13	22	5	2	11	11	11	23
Pre- procedure														
Stenosis %	80	99	80	99	100	100	100	80	100	100	100	100	80	100
Aspirin	no	yes	yes	no	yes	no	yes	yes	no	yes	no	yes	yes	no
Clopidogrel vs. Ticagrelor vs. Prasugrel	clopidogrel	no	clopidogrel	no	no	no	no	no	no	clopidogrel	no	no	clopidogrel	no
Procedure														
Nominal size of stent	2.5	2.5	3.5	3	2.5	3	2.5	2.5	2.25	2.75	2.5	3	3	2.75
Length of stent	33	40	40	46	33	33	33	26	35	26	20	28	24	38
Deployment pressure (atm)	16	20	18	9	14	16	16	12	9	12	14	16	18	14

Pre-dilation	no	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	yes
Maximum balloon size		2.5	3.5	2.75	2.25	3	2	3			2	2	3.0	2.5
Non-compliant		yes	yes		no	no	yes	yes				no	yes	no
Maximum pressure (atm)		14	18			12	12	18			14		20	14
Post-dilation	yes	yes	no	yes	no	yes	yes	yes	no	no	no	yes	yes	yes
Maximum balloon size	2.5	2.75		3		3.5	3	3				3.5	3.5	2.75
Non-compliant	yes	yes		yes		no	yes	yes				yes	yes	yes
Maximum pressure (atm)	18	20		22			22	18					20	18
Aspirin load	no	no	no	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes
Ticagrelor vs. Prasugrel vs. Clopidogrel load	clopidogrel	ticagrelor	ticagrelor	ticagrelor	clopidogrel	ticagrelor	clopidogrel	clopidogrel	ticagrelor	ticagrelor	ticagrelor	ticagrelor	ticagrelor	ticagrelor
Cangrelor	no	no	no	no	no	yes	no	no	yes	no	no	yes	no	no
Tirofiban	no	no	yes	yes	yes	no	no	yes	no	yes	no	no	no	no

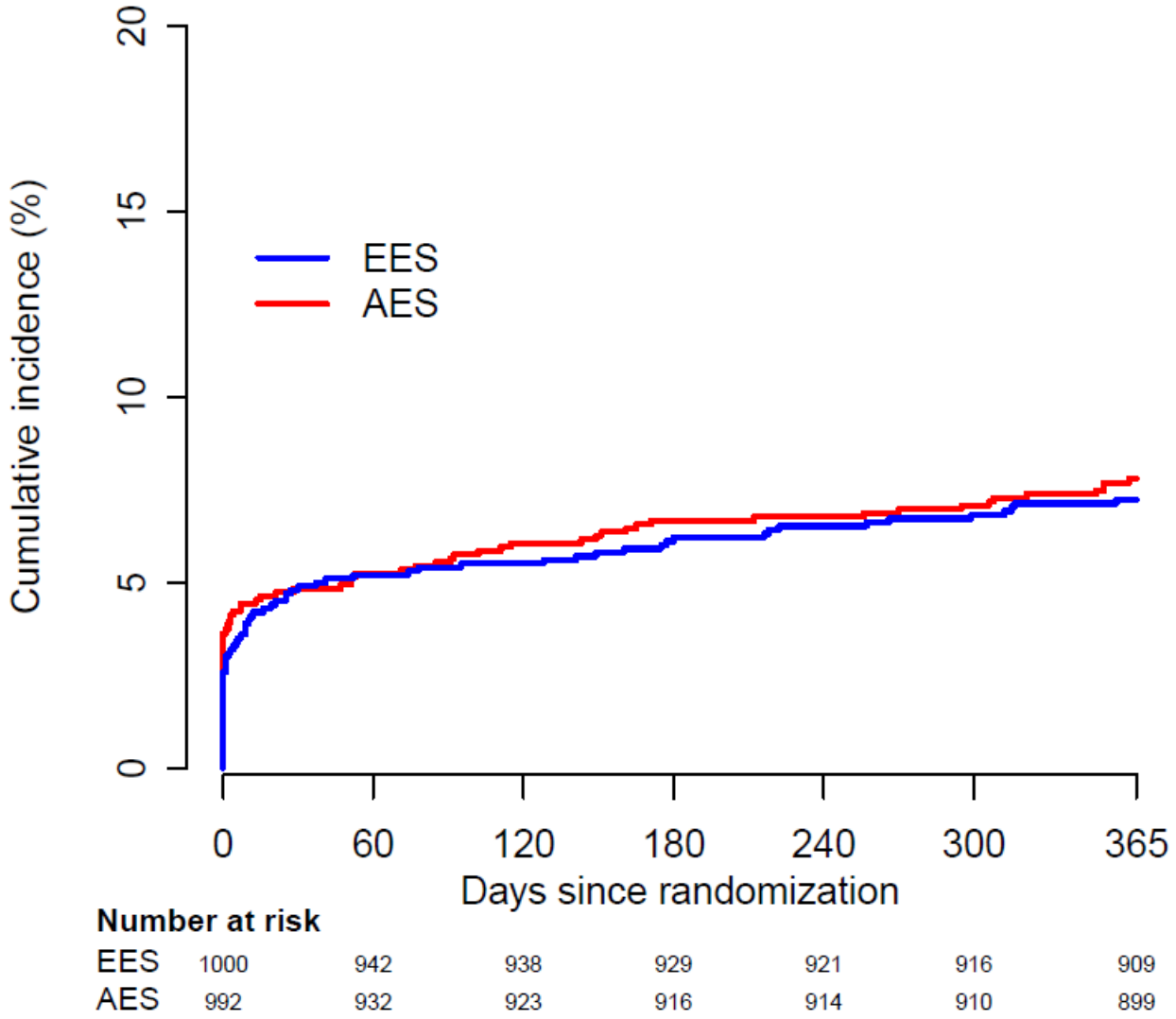
UFH dose (I.U./kg)	88	109	100	76	104	62	77	68	70	56	67	62	119	67
UFH total dose (I.U.)	10000	7000	5000	6000	10000	5000	5000	5000	5000	5000	5000	5000	9500	5000
Post-procedure														
In-stent: diameter stenosis (%)	0	10	0	0	0	0	0	0	0	0	0	0	0	0
TIMI flow after PCI	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Medication at the time of event														
Antiplatelet therapy	no	DAPT	SAPT	DAPT	DAPT	DAPT	DAPT	DAPT	SAPT	DAPT	DAPT	DAPT	DAPT	DAPT
Clopidgrel vs. Ticagrelor vs. Prasugrel	no	ticagrelor	clopidogrel	ticagrelor	clopidogrel	ticagrelor	clopidogrel	ticagrelor	no	ticagrelor	ticagrelor	ticagrelor	ticagrelor	ticagrelor
Statin	yes	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	no	yes	yes
ACEi/ATIIa	yes	yes	yes	no	no	no	yes	no	no	no	yes	yes	yes	no
Beta Blocker	yes	yes	yes	yes	no	no	yes	yes	yes	yes	yes	yes	yes	yes
Event														
Clinical presentation	STEMI	STEMI	STEMI	NSTE-ACS	NSTE-ACS	STEMI	NSTE-ACS	NSTE-ACS	STEMI	STEMI	STEMI	STEMI	Unknown	STEMI
Treatment	PCI	PCI	PCI	PCI	PCI	PCI	PCI	PCI	PCI	Medical	PCI	PCI		PCI

IVUS at event	no	no	no	no	no	yes	no	no	no	no	no	no		no
OCT at event	yes	no	no	no	no	no	no	no	no	no	no	no		no
Thrombectomy	no	no	no	no	no	yes	no	no	no	no	no	no		no
Stenting	no	yes	yes	no	no	no	yes	no	no	no	no	no		yes
DAPT	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes		yes
Clopidgrel vs. Ticagrelor vs. Prasugrel	prasugrel	ticagrelor	ticagrelor	ticagrelor	ticagrelor	ticagrelor	ticagrelor	clopidogrel	ticagrelor	ticagrelor	clopidogrel	ticagrelor		ticagrelor
Re-thrombosis	no	no	no	no	no	no	no	no	no	no	no	no		no
Death at 365 days	no	no	no	no	no	no	yes	no	no	no	no	no	yes	no
Comments	disruption of both antiplatelet agents (clopidogrel and aspirin)	STEMI immediately after the procedure		NSTEMI at the end of the procedure	NSTE 90 minutes after the procedure	STEMI immediately after the procedure	Non cardiac death 358 days after the procedure	Unsuccessful PCI for ST	Unsuccessful PCI for ST. Patient noncompliance to DAPT medication (Disruption)	Treated with titofiban i.v. and nitrates i.c.	ST treated with DCB		Patient died at home. no further information provided	

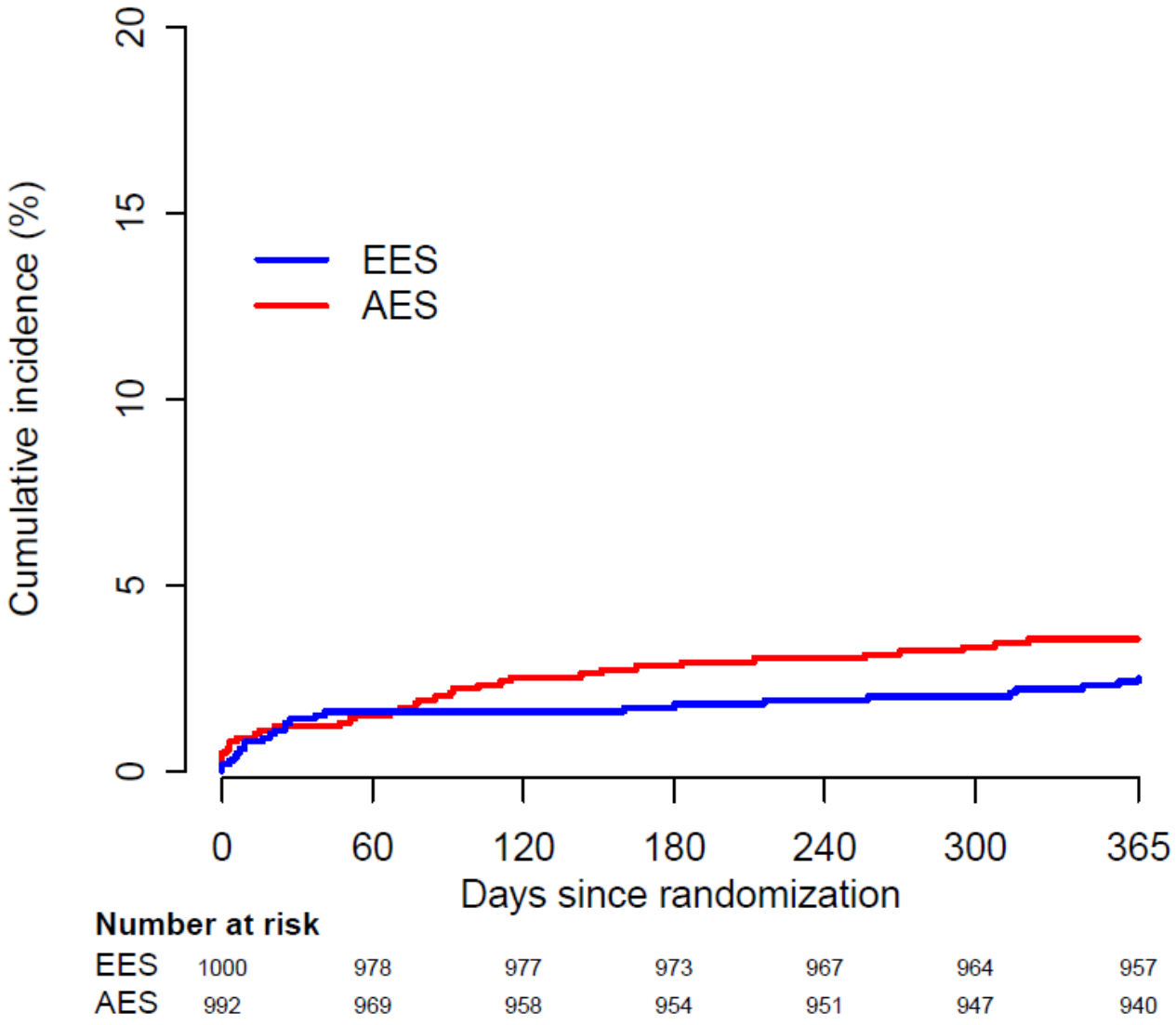
Supplementary Table 5. *Post hoc* intention-to-treat analysis with competing risk of all-cause death and non-cardiovascular death.

	HR (95% CI)	P-value
Primary endpoint (Device-oriented clinical endpoint)	1.14 (0.84-1.55)	0.39
Cardiovascular death	1.45 (0.87-2.42)	0.15
Target-vessel MI	1.03 (0.68-1.55)	0.9
Clinically-driven Target lesion revascularization	1.26 (0.65-2.43)	0.49
Secondary outcomes		
All-cause death		
Any myocardial infarction	1.05 (0.71-1.55)	0.82
Periprocedural myocardial infarction		
4th UDMI	1.03 (0.65-1.64)	0.89
ARC-2	1.58 (0.81-3.08)	0.18
SCAI hierarchical	1.68 (0.82-3.42)	0.15
SCAI non-hierarchical	1.37 (0.82-2.28)	0.23
Cardiovascular death or myocardial infarction	1.17 (0.85-1.6)	0.34
Any revascularization	1.01 (0.63-1.62)	0.98
Any Clinically-driven Revascularization	1.01 (0.62-1.64)	0.98
Any target vessel revascularization	1.01 (0.55-1.84)	0.98
Clinically-driven target vessel revascularization	1.01 (0.54-1.87)	0.98
Any target lesion revascularization	1.19 (0.62-2.26)	0.61
Definite or probable stent thrombosis	3.7 (1.03-13.24)	0.044
Early definite or probable stent thrombosis	4.54 (0.98-20.95)	0.053
Late definite or probable stent thrombosis	2.01 (0.18-22.14)	0.57
Definite stent thrombosis	5.55 (1.23-24.99)	0.026
Early definite stent thrombosis	9.07 (1.15-71.46)	0.036
Late definite stent thrombosis	2.01 (0.18-22.14)	0.57
Cerebrovascular event	1.2 (0.37-3.94)	0.76
Target-vessel failure	1.1 (0.81-1.49)	0.55
Any BARC bleeding	1.02 (0.82-1.27)	0.85
BARC type 2 to 5	0.97 (0.72-1.31)	0.84

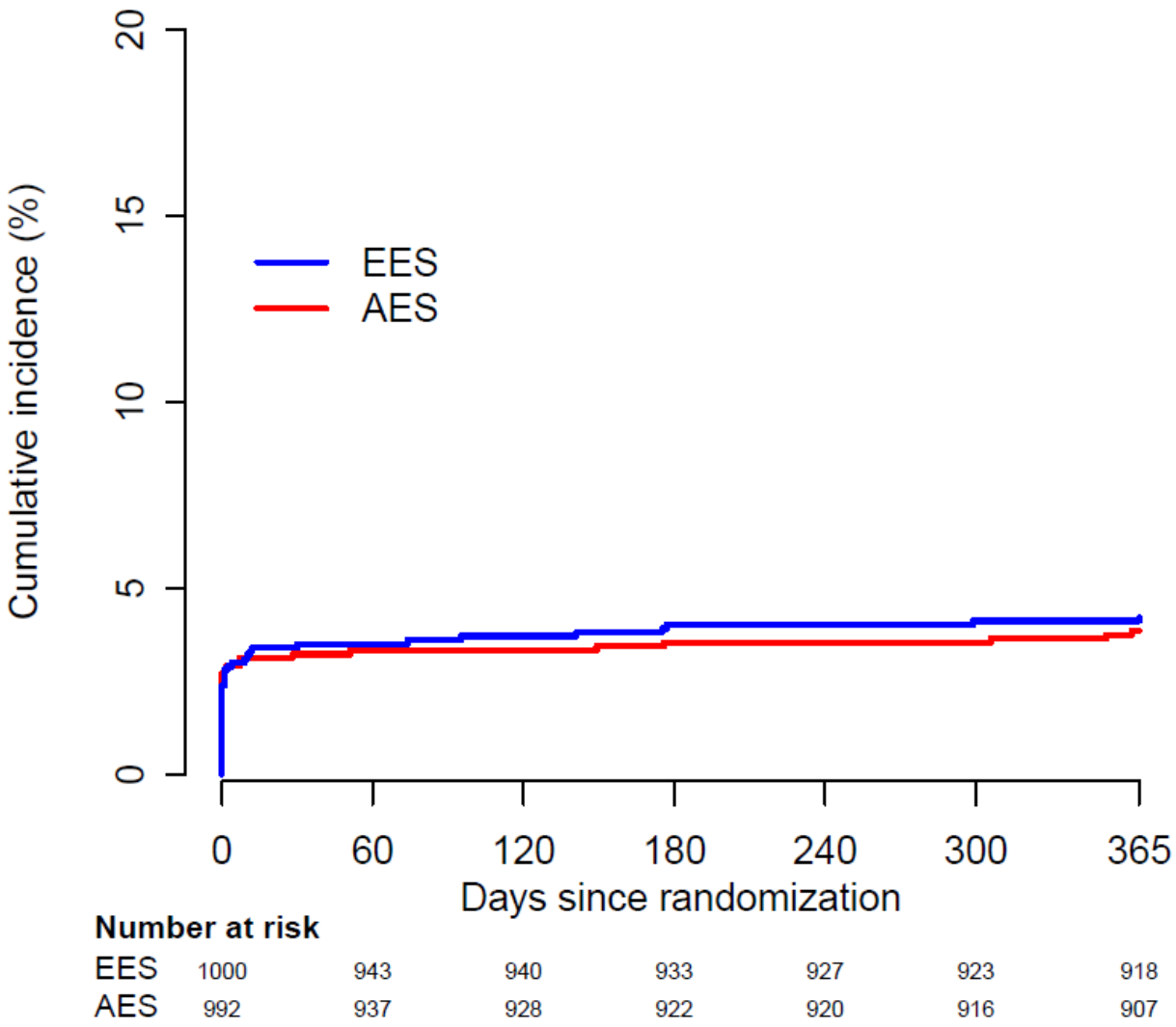
Risk estimates for the endpoints that included cardiovascular death were adjusted for the competing risk of non-cardiovascular death. Other endpoints were adjusted for the competing risk of death. HR: hazard ratio. ARC-2: Academic Research Consortium-2; BARC: Bleeding Academic Research Consortium; MI: Myocardial Infarction; SCAI: Society for Cardiovascular Angiography and Interventions.



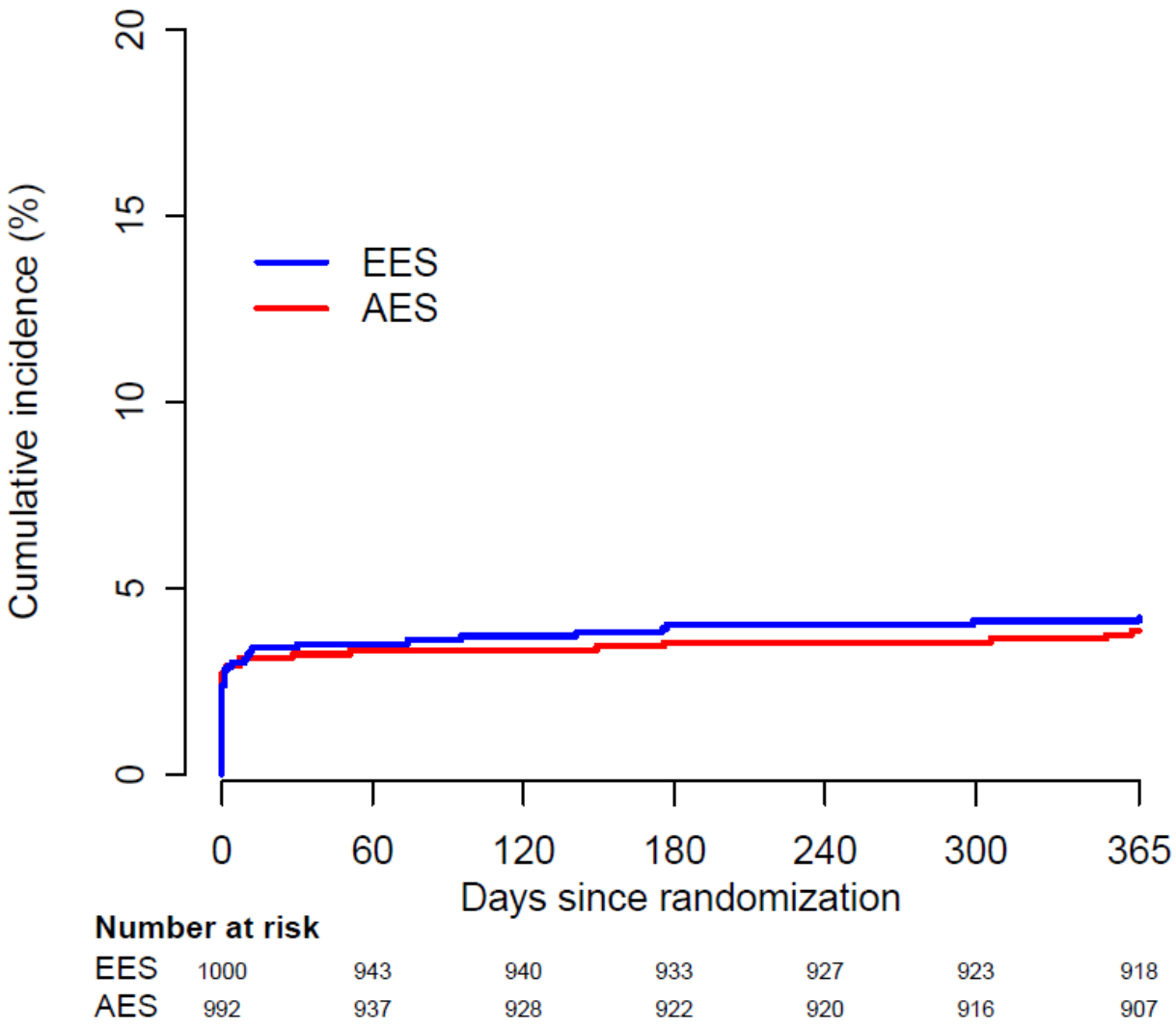
Supplementary Figure 1. Kaplan-Meier curves at 1-year follow-up for device-oriented composite endpoint in the per-protocol population.



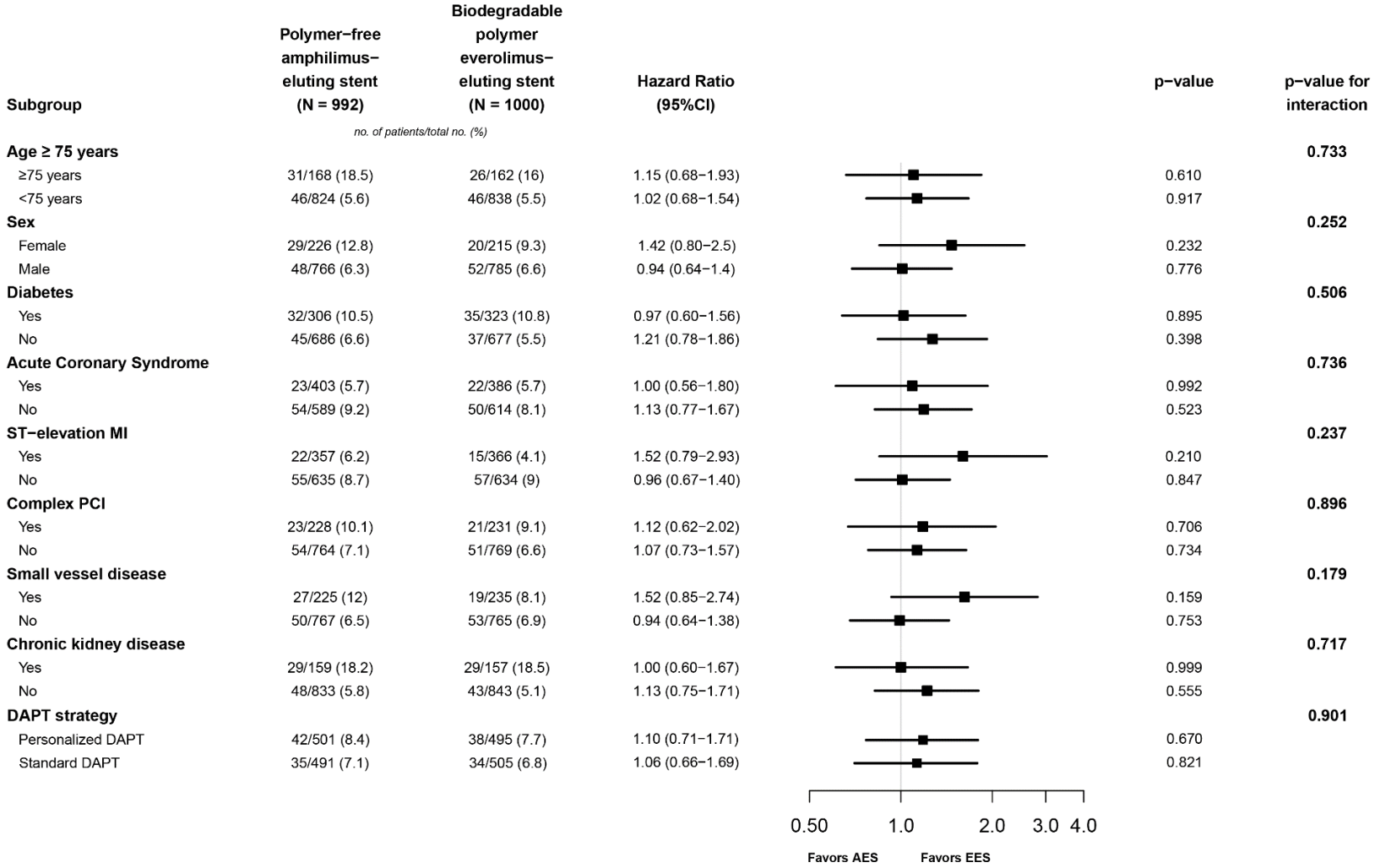
Supplementary Figure 2. Kaplan-Meier curves at 1-year follow-up for cardiac death in the per protocol population.



Supplementary Figure 3. Kaplan-Meier curves at 1-year follow-up for target vessel myocardial infarction in the per-protocol population.



Supplementary Figure 4. Kaplan-Meier curves at 1-year follow-up for clinically driven target lesion revascularisation in the per-protocol population.



Supplementary Figure 5. Subgroup analysis for the primary outcome in the per-protocol population.

MI: myocardial infarction. PCI: percutaneous coronary intervention. Chronic kidney disease was defined as kidney damage or glomerular filtration rate <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause. Complex PCI was defined as one of the following characteristics: ≥3 coronary vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with 2 stents implanted, total stent length ≥60 mm, or treatment of chronic total occlusion. Small vessel disease was defined as implantation of stent(s) <3 mm in diameter in all the target-lesion(s).