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ORIGINAL STUDIES

One-year clinical outcomes of patients treated with polymer-free amphilimus-eluting stents or zotarolimus-eluting stents: A propensity-score adjusted analysis

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Abstract

Background: Polymer-free amphilimus-eluting stents (PF-AES) represent a novel elution-technology in coronary stenting. We aimed to assess 1-year clinical outcomes of PF-AES as compared to latest-generation permanent polymer zotarolimus-eluting stents (PP-ZES) in a real-world all-comers setting.

Methods: A prospective registry of patients treated with either PF-AES or PP-ZES between 2014 and 2016 was conducted. The primary outcome was defined as major adverse cardiac and cerebrovascular events (MACCE), and the secondary outcome was defined as target-lesion failure (TLF) at 1 year. To account for measured confounders, a propensity-score adjusted Cox proportional-hazard model was built to evaluate clinical outcomes.

Results: A total of 734 consecutive patients with 1,269 DES implantations were enrolled. The population was characterized by 28% diabetes, 24% ST-segment elevation myocardial infarction, and a high number of complex lesions (69%). The rate of MACCE was 11.5% for PF-AES and 13.6% for PP-ZES, $p_{log-rank}$ = 0.11. TLF was numerically lower in PF-AES as compared to PP-ZES (5.4 vs. 6.1%, $p_{log-rank}$ = 0.68). After propensity-score adjustment, PF-AES showed a trend toward a lower rate of MACCE and a favorable rate of TLF as compared to PP-ZES (HR 0.70; 95%CI 0.45 to 1.10, *P* = 0.12; and HR 0.88; 95%CI 0.47 to 1.65, *P* = 0.68, respectively). Rates of definite ST were low (0.8 vs. 0.3%, $p_{log-rank}$ = 0.62).

Conclusions: Our study suggests that implantation of PF-AES was safe and effective in real-world patients, with low-rates of MACCE and TLF at 1 year. Our data needs to be confirmed by a large trial to evaluate the clinical outcomes of this novel polymer-free, eluting-technology used in PF-AES.

KEYWORDS

amphilimus-eluting stent, coronary artery disease, new-generation, percutaneous coronary intervention, polymer-free

Abbreviations: ARC, Academic Research Consortium; DAPT, dual anti-platelet therapy; DES, drug-eluting stent; DM, diabetes mellitus; MACCE, major adverse cardiac and cerebrovascular events; (N)STEMI, (non-)ST-segment-elevation myocardial infarct; PCI, percutaneous coronary intervention; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus-eluting stent; TLF, target-lesion failure; TLR, target-lesion revascularization; TVR, target-vessel revascularization.

1 | INTRODUCTION

Over the last decades major improvements have been made in drug-eluting stents (DES).[1] Most DES are composed a metallic stent platform, an antiproliferative agent, and a drug-carrier to control sustained drug-release. DES vastly reduced neointimal hyperplasia,

in-stent restenosis,[2] and lowered the rates of repeat revascularization as compared to bare-metal stents.[3] First-generation DES were, however, associated with delayed coronary vessel wall healing and an increased risk of late stent thrombosis.[4] Post-mortem human autopsies[5,6] revealed a chronic inflammatory response to permanent polymers and incomplete endothelialization that was associated with the occurrence of late stent thrombosis. It has been postulated that polymer-free DES may overcome the limitation of polymer-induced adverse events, and may further improve clinical outcomes.[7]

The polymer-free amphilimus-eluting stent (PF-AES) was designed to evaluate a novel elution strategy in coronary stenting. PF-AES is clearly distinctive from contemporary DES as it has thin cobalt-chromium struts that are coated with a de-ionized I-carbon layer to promote rapid endothelialization[8] and a novel elution-technology using laser-cut wells (i.e., abluminal reservoirs). A mixture of long-chain fatty acids is combined with sirolimus is found inside these abluminal reservoirs. After implantation of PF-AES, an initial peak concentration is obtained, followed by sustained drug-release in which 50% drug is eluted in the first 18 days, and complete drug-elution within 90 days.

Currently, only limited data on the clinical safety and efficacy of this novel elution-technology used in PF-AES are available. Hence, with this comprehensive analysis we aimed to assess the 1-year clinical outcomes of PF-AES as compared to latest-generation permanent polymer zotarolimus-eluting stents (PP-ZESs) in a real-world all-comers setting.

2 | METHODS

2.1 | Study design

This prospective registry was conducted at our tertiary center. The polymer-free PF-AES (Cre8, coronary stent system, Alvimedica, Istanbul, Turkey) was compared to a widely used latest-generation PP-ZES (Resolute Integrity, Medtronic Vascular, Santa Rosa, USA). All-comers patients with stable coronary artery disease or acute coronary syndromes, and at least one coronary artery lesion with more than 50% diameter stenosis eligible for treatment with either PF-AES or PP-ZES implantation between January 2014 and February 2016 were consecutively enrolled. Exclusion criteria were (1) implantation of bare-metal stents, (2) a combination of DES, or (3) revascularization prior to transcatheter aortic valve implantation. This registry was reported according to the STROBE statement,[9] and conducted according to the principles of the Declaration of Helsinki. Our study was approved by local Ethics Committee and each patient provided informed consent for data collection and subsequent analysis.
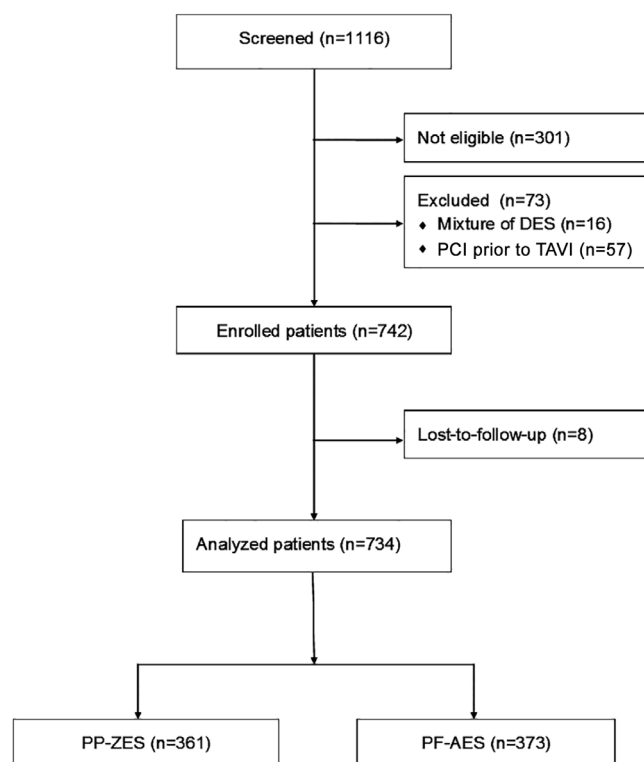
2.2 | Percutaneous coronary intervention

Coronary lesions were treated according to standard interventional techniques, and radial route of access as the default strategy. Revascularization strategies (e.g., intravascular imaging guidance, atherectomy,

direct stenting, and post-dilatation), or the use of Glycoprotein IIb/IIIa inhibitors was left to the operators' discretion. Post-procedural dual antiplatelet therapy (DAPT) was prescribed for 3-6 months in stable coronary artery disease and 12 months in acute coronary syndrome as according to current ESC guidelines. Thereafter, acetylsalicylic acid was continued indefinitely.

2.3 | Clinical outcomes and definitions

The primary outcome of the study was major adverse cardiac and cerebrovascular events (MACCE) at 1-year follow-up, defined as a composite of: cardiac death, myocardial infarction, stroke, target-lesion revascularization (TLR), clinically driven target-vessel revascularization (CD-TVR), or major bleeding defined by the Bleeding Academic Research Consortium (BARC)[10] as BARC 3 or 5. The secondary outcome of 1-year target-lesion failure (TLF) was defined as: cardiac death, myocardial infarction not clearly attributable to a non-target vessel or TLR in accordance with the Academic Research Consortium criteria.[11] Deaths were considered cardiac unless an unequivocal cause of death could be identified. Myocardial infarction was identified by evaluation of the electrocardiogram, and a typical rise and fall in cardiac markers of at least three times the upper reference limit as defined by the joint task force for the universal definition of myocardial infarction.[12] A revascularization was considered clinically driven if a visually estimated stenosis of 50% or more was found on coronary angiogram, and at least one of the following: (1) a positive history of recurrent angina pectoris, or (2) objective signs of ischemia at rest (i.e., ECG changes) or during

FIGURE 1 Flowchart. PCI, percutaneous coronary intervention; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus eluting stent; TAVI, transcatheter aortic valve implantation

TABLE 1 Baseline demographics of patients scheduled for PCI

	Overall (n=734)	PP-ZES (n=361)	PF-AES (n=373)	p-value
Clinical Characteristics				
Age years, (years), mean ± sd	66.6 ± 12.3	66.8 ± 12.7	66.5 ± 11.8	0.79
Male sex, n (%)	505 (68.8)	233 (64.5)	272 (72.9)	0.014
Body-Mass Index (kg/m^2), mean ± sd	27.0 ± 4.5	26.7 ± 4.2	27.4 ± 4.8	0.14
Hypertension, n (%)	426 (58.4)	205 (57.1)	221 (59.6)	0.50
Dyslipidaemia, n (%)	301 (41.2)	145 (40.3)	156 (42.0)	0.63
Diabetes Mellitus, n (%)	205 (27.9)	93 (25.8)	112 (30.0)	0.20
Insulin-dependent Diabetes Mellitus, n (%)	84 (11.4)	42 (11.6)	42 (11.4)	0.91
Current smoker, n (%)	271 (36.9)	143 (39.6)	128 (34.3)	0.14
Family history of CAD, n (%)	308 (42.9)	153 (43.6)	156 (42.0)	0.71
Chronic Kidney Failure*, n (%)	46 (6.3)	21 (5.9)	25 (6.8)	0.64
Multivessel Disease, n (%)	440 (60.4)	210 (59.0)	230 (61.8)	0.43
Relevant Medical History				
Myocardial infarction, n (%)	186 (25.3)	91 (27.3)	95 (25.5)	0.94
Percutaneous coronary intervention, n (%)	215 (29.4)	98 (27.3)	117 (31.5)	0.22
Coronary Artery Bypass graft, n (%)	91 (12.4)	48 (13.4)	43 (11.6)	0.46
Valvular Heart Disease, n (%)	62 (8.6)	30 (8.6)	32 (8.7)	0.95
Stroke, n (%)	52 (7.2)	25 (7.0)	27 (7.3)	0.88
Peripheral Artery Disease, n (%)	72 (10.0)	33 (9.3)	39 (10.6)	0.60
Chronic obstructive pulmonary disease, n (%)	75 (10.3)	33 (9.2)	42 (11.3)	0.36
Clinical Presentation				
Stable Angina, n (%)	304 (41.4)	149 (41.3)	155 (41.6)	0.94
Silent Ischemia, n (%)	40 (5.4)	14 (3.9)	26 (7.0)	0.065
Acute Coronary Syndrome	390 (53.1)	198 (54.8)	192 (51.4)	0.40
Unstable Angina, n (%)	84 (11.5)	36 (10.0)	48 (12.9)	0.22
NSTEMI, n (%)	126 (17.2)	68 (18.8)	58 (15.5)	0.24
STEMI, n (%)	180 (24.5)	94 (26.0)	86 (23.1)	0.35
Medication at hospital admission				
Aspirin, n (%)	548 (75.7)	267 (75.0)	281 (76.4)	0.67
Beta Blockers, n (%)	437 (60.4)	208 (58.4)	229 (62.4)	0.28
Calcium Channel Blocker, n (%)	162 (22.4)	79 (22.2)	83 (22.6)	0.89
ACE inhibitor, n (%)	281 (38.9)	127 (35.7)	154 (42.0)	0.083
Angiotensin Receptor Blockers, n (%)	115 (15.9)	60 (16.9)	55 (15.0)	0.49
Statins, n (%)	464 (64.2)	219 (61.5)	245 (66.8)	0.14
Medication at discharge				
3-month DAPT	210 (28.6)	96 (26.6)	114 (30.6)	0.27
6-month DAPT	88 (12.0)	42 (11.6)	46 (12.3)	0.86
12-month DAPT	390 (53.1)	198 (54.8)	192 (51.5)	0.40
P_2Y_{12} inhibitor				
Clopidorel	391 (53.3)	191 (51.5)	215 (55.0)	0.22
Prasugrel	4 (0.5)	2 (0.6)	2 (0.5)	0.97
Ticagrelor	293 (39.9)	148 (41.0)	145 (38.9)	0.61
Triple therapy†	46 (6.3)	25 (6.9)	21 (5.6)	0.57

*Chronic Kidney Failure was defined as an estimated glomerular filtration rate of less than 30 mL per min per 1·73 m^2
†Triple therapy was defined as aspirin, clopidogrel and acenocoumarol.
ACE = angiotensin-converting-enzyme, CAD = Coronary Artery Disease, DAPT = Dual Antiplatelet Therapy, NSTEMI = non- ST-segment elevation-myocardial infarction, PCI = Percutaneous Coronary Intervention, PF-AES = Polymer-free amphilimus-eluting stent, PP-ZES = Zotarolimus-eluting Stent, STEMI = ST-segment elevation-myocardial infarction.

exercise testing, or (3) abnormal results of any invasive functional diagnostic test, or (4) a diameter stenosis 70% even in the absence of the above-mentioned ischemic signs or symptoms. Separate components of the primary and secondary outcomes were also evaluated. Adverse clinical events were revised, evaluated, and adjudicated by an independent clinical event committee consisting of two independent cardiologists. In case of disagreement, a third interventional cardiologist was consulted and consensus was reached.

TABLE 2 Lesion and procedural characteristics

	Overall (n = 1,113)	PP-ZES (n = 564)	PF-AES (n = 549)	P-value
Coronary anatomy				
Left main, n (%)	63 (5.7)	28 (5.0)	35 (6.4)	0.31
Left anterior descending, n (%)	448 (40.3)	232 (41.1)	216 (39.3)	0.54
Ramus circumflex, n (%)	261 (23.5)	146 (25.9)	115 (20.9)	0.052
Right coronary artery, n (%)	310 (27.9)	141 (25.0)	169 (30.8)	0.031
Vein graft, n (%)	31 (2.8)	17 (3.0)	14 (2.6)	0.40
Lesion characteristics				
Lesion complexity B2/C,[a] n (%)	767 (68.9)	386 (68.4)	381 (69.4)	0.73
Lesion complexity A	36 (3.2)	23 (4.1)	13 (2.4)	0.11
Lesion complexity B1	310 (27.9)	155 (27.5)	155 (28.2)	0.78
Lesion complexity B2	469 (42.1)	239 (42.4)	230 (41.9)	0.87
Lesion complexity C	298 (26.8)	147 (26.1)	151 (27.5)	0.59
De-novo lesion	1,072 (96.3)	542 (96.1)	530 (95.6)	0.68
In-stent restenosis, n (%)	21 (1.9)	10 (1.8)	11 (2.0)	0.78
Chronic total occlusion, n (%)	54 (4.9)	19 (3.4)	35 (6.4)	0.28
Bifurcation lesion, n (%)	187 (16.8)	96 (17.0)	91 (16.6)	0.84
Ostial lesion, n (%)	132 (11.9)	69 (12.2)	63 (11.5)	0.69
Moderate or severe calcified lesion, n (%)	357 (32.0)	177 (31.3)	180 (32.7)	0.61
Procedural characteristics				
Number of stents per lesion	1.25 ± 0.26	1.23 ± 0.13	1.28 ± 0.18	0.31
Stent diameter, (mm)	3.0 ± 0.94	2.9 ± 1.2	3.0 ± 0.45	0.56
Stent length, (mm)	20.6 ± 8.0	19.8 ± 7.3	21.4 ± 8.5	0.002
Pre-procedural TIMI flow grade < 3, n (%)	298 (26.8)	156 (27.7)	142 (25.9)	0.49
Pre-dilatation, n (%)	878 (78.9)	433 (76.8)	445 (81.1)	0.17
Post-dilatation, n (%)	859 (77.2)	466 (82.6)	393 (71.6)	<0.001
Max inflation pressure (atm)	18.5 ± 4.3	18.6 ± 3.6	18.4 ± 5.2	0.45
Post-procedural TIMI flow grade < 3, n (%)	23 (2.1)	13 (2.3)	10 (1.8)	0.57
Rotational atherectomy, n (%)	14 (1.3)	5 (0.7)	9 (1.8)	0.26
Image-guided PCI, n (%)	42 (3.8)	22 (3.9)	20 (3.6)	0.67
Contrast use, (cc)	202 ± 98	205 ± 91	199 ± 105	0.32
Glycoprotein IIb/IIIa inhibitors, n (%)	189 (17.0)	91 (16.1)	98 (17.9)	0.49
Procedural success,[b] n (%)	1,086 (97.6)	549 (97.3)	537 (97.8)	0.60

Abbreviations: NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus eluting stent; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.
Values are mean ± SD, or n (%).
[a] Lesion classification according to the American College of Cardiology/American Heart Association.
[b] Procedural success was defined as a post-procedural TIMI-flow grade 3, residual angiographic stenosis of ≤20%, and no peri-procedural adverse clinical events.

2.4 | Data acquisition and patient follow-up

Detailed clinical data, procedural data, and angiographic parameters were collected. All patients enrolled were prospectively followed during visits to the out-patient clinics, by a medical questionnaire, and by telephone assessment at 1-year follow-up by a trained research coordinator. Data regarding patient survival status were collected from the Dutch Civil Registry. Angiographic follow-up was performed when clinically indicated.

2.5 | Statistical analysis

Categorical variables were reported as frequencies (n) and percentages (%) and compared using the Chi-square or Fisher's exact test as appropriate. Continuous variables were expressed as mean ± standard deviation

and compared using Student's t-test when normally distributed, and compared using the Mann–Whitney test when non-parametrical distributed. Time-to-event was evaluated using the Kaplan–Meier method, analyzed using the log-rank test, and reported according to good clinical practice statement.[13] Clinical follow-up was censored at the date of last contact or at 1 year, whichever came first. Missing data, if not exceeding 10%, were imputed using multiple imputation chained equation with 10 imputed datasets with 10 iterations[14] after visual checking the randomness of missing data. A propensity-score (i.e., the probability of a patient being assigned to PF-AES or PP-ZES implantation) was calculated with a non-parsimonious approach using binary logistic regression based on: age, sex, body-mass index, clinical indication, diabetes mellitus, hypertension, dyslipidemia, obstructive pulmonary disease, peripheral artery disease, a history of: acute coronary syndrome, PCI,

TABLE 3 One-year clinical outcomes of PF-AES as compared to PP-ZES

	Overall (n = 734)	PP-ZES (n = 361)	PF-AES (n = 373)	*P*-value
MACCE,[a] n (%)	92 (12.5)	49 (13.6)	43 (11.5)	0.11
TLF,[b] n (%)	42 (5.7)	22 (6.1)	20 (5.4)	0.68
Death	36 (4.9)	16 (4.4)	20 (5.3)	0.56
Cardiac death, n (%)	18 (2.5)	9 (2.5)	9 (2.4)	0.97
Non-cardiac death, n (%)	18 (2.5)	7 (1.9)	11 (2.9)	0.21
MI, n (%)	13 (1.8)	7 (1.9)	6 (1.6)	0.74
Target-vessel MI, n (%)	6 (0.8)	3 (0.8)	3 (0.8)	1.00
Non-target vessel MI, n (%)	7 (1.0)	4 (1.1)	3 (0.8)	0.72
Q-wave MI, n (%)	2 (0.3)	2 (0.6)	0 (0.0)	0.24
Non-Q-wave MI, n (%)	11 (1.5)	5 (1.4)	6 (1.6)	1.00
ST (definite, or probable), n (%)	10 (1.4)	4 (1.1)	6 (1.6)	0.75
Definite ST, n (%)	4 (0.5)	1 (0.3)	3 (0.8)	0.62
Probable ST, n (%)	6 (0.8)	3 (0.8)	3 (0.8)	1.00
Stroke, n (%)	3 (0.4)	3 (0.8)	0 (0.0)	0.12
TLR, n (%)	22 (3.0)	12 (3.3)	10 (2.7)	0.54
CD-TVR, n (%)	32 (4.4)	19 (5.3)	13 (3.5)	0.25
Major bleeding (BARC 3,5), n (%)	12 (1.6)	8 (2.2)	4 (1.1)	0.26

Abbreviations: BARC, Bleeding Academic Research Consortium; CD-TVR, clinically driven target-vessel revascularization; MACCE, major adverse cardiac and cerebrovascular events; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus eluting stent; TLF, target-lesion failure; TLR, target-lesions revascularization; ST, stent thrombosis.

[a] MACCE was defined as cardiac death, myocardial infarction, stroke, target-lesion revascularization, clinically driven target-lesion revascularization, or major bleeding according to Bleeding Academic Research Consortium (BARC) at 1-year follow-up.

[b] TLF was defined according to Academic Research Consortium Criteria, and a composite of cardiac death, target-vessel myocardial infarction, and target-lesion revascularization.

coronary artery bypass grafting, or valvular heart disease, multivessel disease, target-vessel territory, saphenous vein graft, bifurcation lesions, chronic total occlusions, pre-dilatation, post-dilatation, stent type, and total stent length, if the standardized differences were <0.10 (10%). A propensity-score covariate adjusted Cox proportional-hazards regression was used to correct for all measured confounders since this method performs well and leads to reliable results in cardiovascular observational studies.[15] Hazard ratio's ($HR_{PF-AES/PP-ZES}$) with 95% confidence intervals (CI) were reported as a summary statistic. Post hoc subgroup analyses[16] were performed to investigate the consistency of the primary outcome including a possible interaction with the allocated stent type across various subgroups. All statistical analyses were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Figures were generated using GraphPad Prism software version 7 (GraphPad, Inc., San Diego, CA, USA).

3 | RESULTS

3.1 | Baseline patient characteristics

We prospectively enrolled 734 consecutive patients (Figure 1), with 1,269 stents implantations (PF-AES n = 636 and PP-ZES n = 633). Patient were not eligible if they received a bare-metal stent, or a mixture of DES (n = 16), or underwent revascularization prior to transcatheter aortic valve implantation (n = 57). Baseline demographics of our cohort are summarized in Table 1. The population was characterized by 24% ST-segment elevation myocardial infarction, 28% diabetes mellitus, 25% prior myocardial infarction, and 6.3% chronic kidney disease. Patients receiving PF-AES versus PP-ZES were comparable, with slightly more diabetic patients receiving PF-AES versus PP-ZES (30.0% vs. 25.8%, *P* = 0.20). Duration and type of DAPT prescribed to patients at discharge did not differ significantly between PF-AES and PP-ZES.

3.2 | Procedural characteristics

Lesion and procedural characteristics are summarized in Table 2. The left main coronary artery was treated in roughly 6%. The majority of the lesions (70%) was considered complex type B2 or C according to the American College of Cardiology/American Heart Association classification, with high numbers of bifurcation lesions (16.8%), chronic total occlusions (4.9%), and saphenous grafts (2.8%). Pre-dilatation, the use of GpIIb/IIIa inhibitors, image-guided PCI, and the use of rotational atherectomy together with all other procedural characteristics were comparable for both groups. Stent length per patient was slightly higher in PF-AES as compared to PP-ZES (19.8 vs. 21.4, *P* = 0.002). Finally, the rate of post-dilatation was lower in PF-AES as compared to PP-ZES (71.6 vs. 82.6, *P* < 0.001).

3.3 | Clinical outcomes

One-year adverse clinical events stratified by stent type are summarized in Table 3. Clinical follow-up at 1 year was available for 726 patients 98.9% (PF-AES 98.7% vs. PP-ZES 99.2%, *P* = 0.73). The primary outcome of MACCE (Figure 2) occurred in 92 patients and was similar in the crude unadjusted analysis for PF-AES as compared to PP-ZES (11.5% vs. 13.6% respectively). The secondary outcome of TLF occurred in
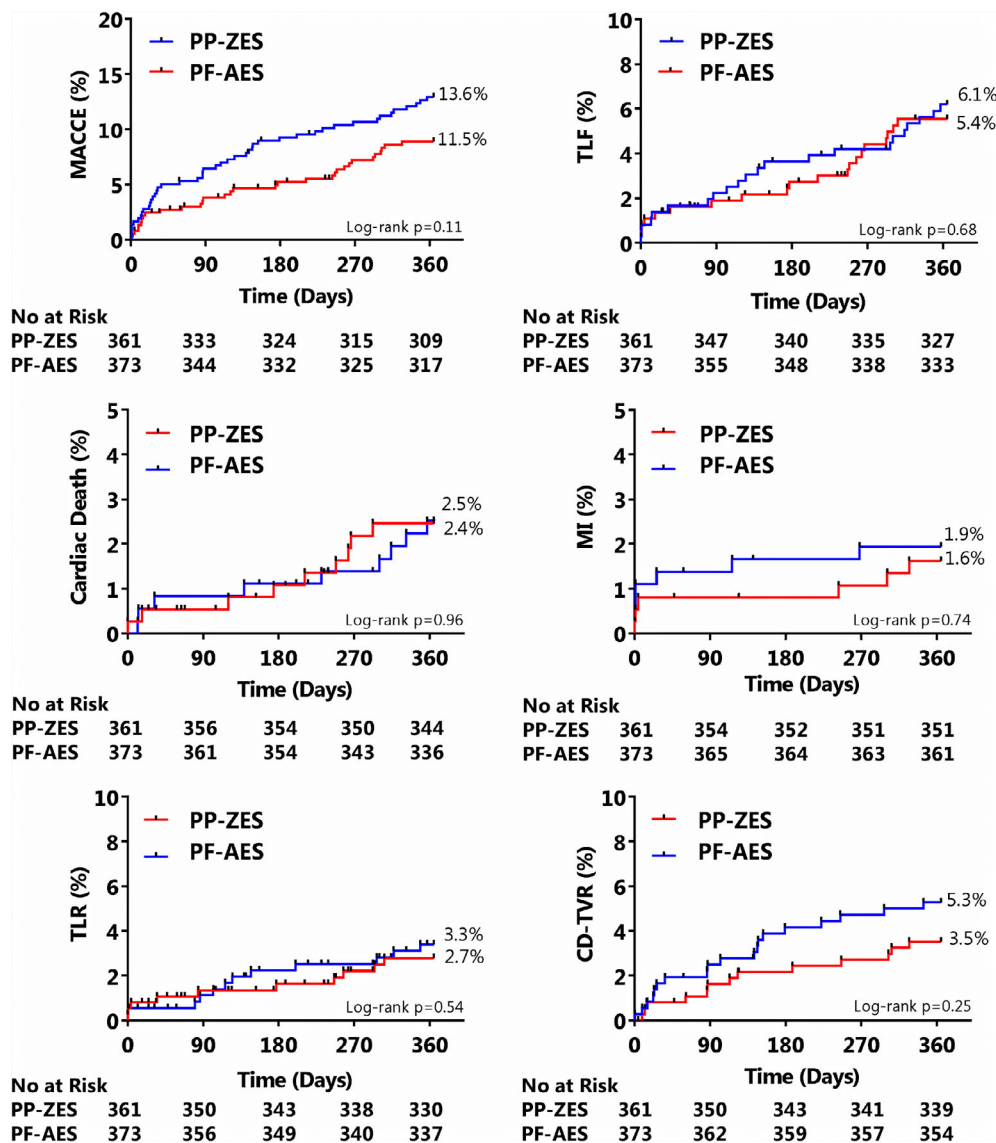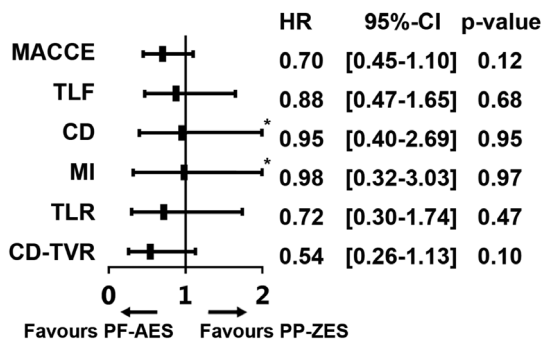
FIGURE 2 The Kaplan–Kaplan estimates of one-year clinical outcomes. CD-TVR, clinically driven target-vessel revascularization; MACCE major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus eluting stent; TLF, target-lesion failure; TLR, target-lesions revascularization [Color figure can be viewed at wileyonlinelibrary.com]

42 patients (5.7%), and was numerically lower in PF-AES as compared to PP-ZES (5.4% vs. 6.1%, $p_{\text{log-rank}}$ = 0.68). No differences were found in terms of cardiac death for PF-AES vs. PP-ZES (2.4% vs. 2.5%, $p_{\text{log-rank}}$ = 0.97), or myocardial infarction (PF-AES 1.6% vs. PP-ZES 1.9%, $p_{\text{log-rank}}$ = 0.74). Target-lesion revascularization was similar in both groups (2.7 vs. 3.3%, $p_{\text{log-rank}}$ = 0.54). Clinically driven TVR was required in 4.4% of patients (PF-AES 3.5% vs. PP-ZES 5.3%, $p_{\text{log-rank}}$ = 0.25). The cumulative incidence of definite stent thrombosis was very low among the two groups (PF-AES 0.8% vs. PP-ZES 0.3% $p_{\text{log-rank}}$ = 0.62). Definite stent thrombosis occurred in four patients: (1) a 78-year old diabetic patient suffered subacute stent thrombosis 4 days after PCI with PF-AES for STEMI, (2) a 77-year old diabetic patient suffered an acute stent thrombosis 1 day after PCI with PF-AES for NSTEMI, (3) a 43-year old patient suffered an acute stent thrombosis after he underwent PCI with PF-AES for STEMI, and (4) a 91-year old patient suffered acute stent thrombosis 1 day after PCI with PP-ZES for STEMI.

The propensity-score adjusted Cox models of the 1-year clinical outcomes are shown in Figure 3. After correction for measured confounding, a trend toward a lower rate of the primary outcome was shown in PF-AES as compared to PP-ZES (hazard ratio [HR] 0.70; 95%CI: 0.45–1.10, P = 0.12). One-year TLF was numerically lower in PF-AES as compared to PP-ZES (HR 0.88; 95%CI 0.47–1.65, P = 0.68). Cardiac death was not statistically different for both groups (adjusted HR 0.95; 95%CI: 0.40–2.69, P = 0.95). The rate of myocardial infarction was also similar (HR 0.98; 95%CI: 0.32–3.03, P = 0.97). A numerical difference of PF-AES was found for TLR (HR 0.72; 95%CI: 0.30–1.74, P = 0.47), and a trend of a lower CD-TVR was observed for PF-AES as compared to PP-ZES (HR 0.54; 95%CI: 0.26–1.13, P = 0.10).

Subgroup analyses (Figure 4) indicated consistency of the treatment effect across various subgroups (e.g., diabetes mellitus, chronic kidney failure, current smoker, prior myocardial infarction, age > 65 or <65, and sex) with no significant between-group differences for the primary outcome.

FIGURE 3 Propensity-score adjusted cox proportional-hazard regression of one-year clinical outcomes. BARC, Bleeding Academic Research Consortium; CD, cardiac death; CD-TVR, clinically driven target-vessel revascularization; CI, confidence interval; HR, hazard ratio; MACCE major adverse cardiac and cerebrovascular events; MI, myocardial infarction; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus eluting stent; TLF, target-lesion failure; TLR, target-lesions revascularization

4 | DISCUSSION

To the best of our knowledge this is the first prospective registry comparing PF-AES with latest-generation PP-ZES in an all-comers setting. The principle findings are (1) favorable 1-year clinical outcomes for PF-AES as compared to the widely used PP-ZES in real-world patients after adjustment for confounders, (2) low rates of definite stent thrombosis, reflecting similar and excellent safety profiles of both stents, and (3) a trend of reduced CD-TVR in favor of PF-AES as compared to PP-ZES. Despite the fact that this registry was not powered to evaluate separate outcomes, our data suggest that PF-AES is safe and effective in routine clinical practice. Given the comorbidities of our patients with complex coronary anatomy and challenging lesion subsets, we consider the rates 1-year MACCE and TLF encouraging, and consistent with previous real-world registries[17,18] using latest-generation DES.

Indeed, latest-generation zotarolimus-, and everolimus-eluting stents (EES) are associated with the lowest rates of 1-year TLR, TVR, and stent thrombosis[19] and have been used repeatedly in randomized clinical trials evaluating the safety and efficacy of novel stent platforms. A recent propensity-score matched registry[20] reports that PF-AES was non-inferior to latest-generation EES in terms of 1-year major adverse cardiac events (MACEs), TLR, and stent thrombosis. Consistent with our findings, the hazard ratio ($HR_{[PF-AES/EES]}$ 0.75, 95%CI 0.37–1.53, $P = 0.43$) was similar in magnitude to our results. Also consistent with our data, another propensity-score matched analysis[21] reported a similar 1-year TLF rate of PF-AES (4.9%) as we found, and compared them to biodegradable polymer biolimus-eluting stents (8.2%, $P < 0.001$) in patients with and without diabetes mellitus. Importantly, the rate of definite stent thrombosis at 1-year follow-up was low for PF-AES and biolimus-eluting stents. Finally, ASTUTE[22] (1-year clinical outcome of amphilimus polymer-free DES in diabetes mellitus patients: Insight from AmphilimuS iTalian mUlticenTre rEgistry) describes 1-year MACE (7.8%), TLF (5.3%), TLR (2.5%), and definite stent thrombosis (0.5%) that approximate the rates of 1-year adverse events in this registry.

Currently, three randomized clinical trials have been conducted to assess the role of the polymer-free eluting-technology of PF-AES. First, NEXT[23] (International Randomized Comparison Between DES Limus Carbostent and Taxus Drug Eluting Stents in the Treatment of De-novo Coronary Lesions) demonstrated that PF-AES was non-inferior to first-generation paclitaxel-eluting stents with significantly lower in-stent late lumen loss at 6 months, and a trend of better clinical safety and efficacy at 12 months. Second, DEMONSTRATE[24] (The randomized coMparisOn betweeN novel Cre8 DES and BMS to assess neoinTimal coveRAge by OCT Evaluation) revealed a homogenous tissue coverage 3 months after implantation of PF-AES, that was comparable to that of bare-metal stents at 1 month post-implant. Third, RESERVOIR[25] (Randomized Trial Comparing Reservoir-Based Polymer Polymer-Free Amphilimus-Eluting Stents Versus Everolimus-Eluting Stents With Durable Polymer in Patients With Diabetes Mellitus) demonstrated PF-AES was non-inferior to latest-generation EES, and suggest a high efficacy of PF-AES in diabetes. Notably, the ongoing physician-initiated, prospective, multicentre ReCre8 trial[26] (Randomized All-comers Evaluation of a Permanent Polymer Zotarolimus-eluting Stent Versus a Polymer-Free Amphilimus-eluting Stent) will evaluate clinical non-inferiority of PF-AES as compared to latest-generation PP-ZES.

Polymers that are used in contemporary DES for stabilizing anti-inflammatory drugs and sustained drug-release, lose function at the time the drug is fully eluted. Even more important, polymers are associated with hypersensitivity reactions leading to chronic inflammation, delayed and incomplete stent strut endothelialization that may eventually predispose for late or very late stent thrombosis.[27] In fact, the cumulative incidence of definite stent thrombosis in our study was low, despite a relatively short period of DAPT in stable coronary artery disease, supporting that PF-AES are safe. Even though these findings are positive, the lack of polymer in PF-AES cannot rule out late or very late stent thrombosis as this phenomenon can be the result of other triggers (e.g., complex or calcified lesions, stent under expansion, uncovered stent edge dissection, or stent malposition). A
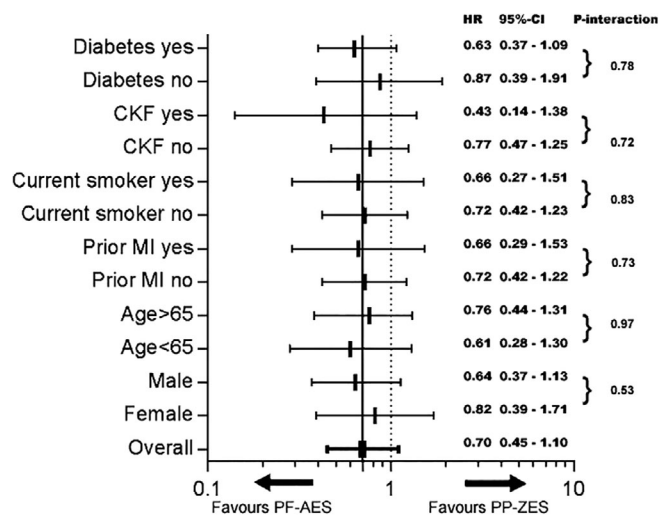
FIGURE 4 Subgroup analyses for the primary outcome at 1-year follow-up. CKF, chronic kidney failure; MI, myocardial infarction; PF-AES, polymer-free amphilimus-eluting stent; PP-ZES, permanent polymer zotarolimus-eluting stent
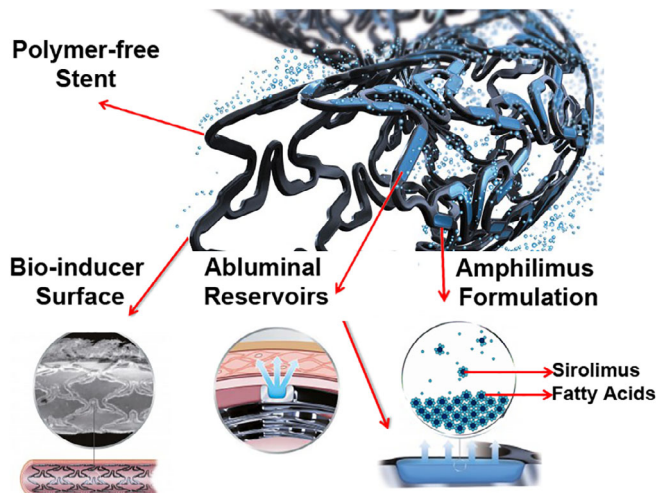
FIGURE 5 Principal characteristics of the polymer-free amphilimus-eluting stent. The coronary stent platform is made from a thin-strut (80 μm) cobalt-chromium alloy, coated with a passive ultra-thin (<0.3 mm) layer that optimizes hemocompatibility (bio-inducer surface)[32,33] to accelerate endothelialization.[8,31] Sustained and homogeneous release of sirolimus (90 pg/cm^2) is facilitated according to Fick's law and completed over 90 days by laser-dug wells on the stent surface (abluminal reservoirs) that are filled with a mixture of the drug and long-chained fatty acids (amphilimus formulation). This distinct feature acts as an active drug-carrier to enhance drug-penetration and modulates bioavailability directly into the vessel wall[34] [Color figure can be viewed at wileyonlinelibrary.com]

previous report[28] investigating patients needing short DAPT (i.e. ≤3 months) showed that PF-AES was safe regarding recurrent ischemic events and was associated with a reduction of major bleeding events related to DAPT. Our data showed low stent-related adverse clinical events in PF-AES as compared to PP-ZES. We speculate that a short duration of DAPT (3 months) following latest-generation DES in stable coronary artery disease may be safe, as we observed relatively low rates of ischemic events.

A growing body of evidence[20,21,25,29,30] demonstrates that PF-AES performs well in diabetic and non-diabetic patients. These findings may be explained by the distinct features of PF-AES (Figure 5): thinner struts (80 μm vs. 91 μm), coating with a pure i-carbofilm supposed to induce faster stent strut endothelialisation,[31,32] and a formulation for controlled and sustained drug-release directly into the vessel wall. The amphilimus formulation in PF-AES uses long-chained fatty acids that function as drug-carriers which are easily transported by fatty acid cell membrane transporters (CD36), and other fatty acid binding proteins. It has been postulated that the use of fatty acids as drug-carriers may increase the uptake of mTOR inhibitors[31] as this pathway is used for approximately 70% of the adenosine triphosphate generation in non-diabetic cells, and even more in diabetic cells. The numerical difference in favor of PF-AES versus PP-ZES in this particular subgroup may support these hypotheses. We emphasize that the potential antirestenotic potency of this novel device in diabetes mellitus needs further investigation. Despite the fact that adverse events in this registry were numerically lower in PF-AES, we advocate that our data should be confirmed in a large randomized trial to evaluate the safety and efficacy of this polymer-free amphilimus-eluting technology.

4.1 | Study limitations

Some limitations of our analysis should be acknowledged. First, the absence of randomization was controlled by a propensity-score adjusted Cox proportional-hazards regression. With this methodology it is not able to correct for unmeasured confounders, and therefore some degree of bias cannot be excluded. We believe, however, that the lack of randomization will not change the overall conclusion of our findings. Second, our comprehensive analysis should be viewed in the scope of the sample size as the number of events were relatively low, and it was not primarily powered to evaluate individual clinical outcomes. Third, long-term clinical outcomes should be evaluated to confirm the safety and efficacy of the novel-elution technology used in PF-AES.

5 | CONCLUSION

In this prospective registry, PF-AES was associated with promising 1-year clinical outcomes and a safety profile similar to latest-generation PP-ZES. A randomized trial should aim to evaluate clinical non-inferiority of PF-AES and confirm our data on the clinical safety and efficacy of this novel-eluting technology.

CONFLICT OF INTEREST

None declared.

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