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Dual antiplatelet therapy strategies and clinical outcomes in patients treated with polymer-free biolimus A9-coated stents

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KEYWORDS

- ACS/NSTE-ACS
- bleeding
- drug-eluting stent
- stable angina
- STEMI
- stent thrombosis

Abstract

Aims: A large trial established the favourable clinical profile of a new polymer-free biolimus A9-eluting stent (PF-BES) with a one-month dual antiplatelet therapy (DAPT) regimen in patients at high bleeding risk (HBR). We aimed to evaluate the real-world patterns of indications, DAPT strategies and outcomes for the PF-BES following this evidence.

Methods and results: CHANCE is a multicentre registry including all patients who underwent percutaneous coronary intervention (PCI) with at least one PF-BES. The reasons for the PF-BES PCI and planned antithrombotic regimens were collected. Primary outcomes were the 390-day Kaplan-Meier estimates of patient-oriented and device-oriented composite endpoints (POCE: death, myocardial infarction [MI] or target vessel revascularisation [TVR]; DOCE: cardiac death, target vessel MI or ischaemia-driven target lesion revascularisation [ID-TLR]). Between January 2016 and July 2018, 858 patients (age 74±10 years, 64.6% male, 58.7% acute coronary syndrome presentation) underwent PF-BES PCI. The main reasons for the physicians' choice of PF-BES reflected a perceived HBR in 77.7% of patients. One-month DAPT was planned in 40.3% of patients. At 390-day follow-up (median 340 days, interquartile range: 187-390 days), the estimated incidence of POCE was 13.1% (any MI 3.7%, any TVR 3.4%) and of DOCE was 7.1% (TV-MI 3.6%, ID-TLR 1.4%), while the 390-day estimate of any bleeding event was 11.1% (BARC 3-5 bleeding 3.0%).

Conclusions: In a large all-comers registry, PF-BES was used mostly in HBR patients, frequently followed by a very short DAPT regimen. The reported outcomes suggest a favourable safety and efficacy profile for the PF-BES in a real-world clinical setting. ClinicalTrials.gov identifier: NCT03622203

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Abbreviations

ACS	acute coronary syndrome
BMS	bare metal stent
DAPT	dual antiplatelet therapy
DES	drug-eluting stent
DOCE	device-oriented composite endpoint
HBR	high bleeding risk
ID-TLR	ischaemia-driven target lesion revascularisation
MI	myocardial infarction
OAC	oral anticoagulation
PCI	percutaneous coronary intervention
POCE	patient-oriented composite endpoint
PF-BES	polymer-free biolimus-eluting stent
SCAD	stable coronary artery disease
ST	stent thrombosis
TVR	target vessel revascularisation

Introduction

Successfully developed to overcome the high rates of bare metal stent (BMS) restenosis, the drug-eluting stent (DES) initially had the downside of increased late stent thrombosis (ST) and in-stent neoatherosclerosis, even in high-risk settings[1,2]. These phenomena, related to negative clinical outcomes, may be caused partly by the persistence of the polymer coating, which may trigger chronic inflammation, compromising arterial healing in the treated coronary segment[3,4].

The BioFreedom™ stent (Biosensors Interventional Technologies, Singapore) is a stainless steel polymer-free biolimus-eluting stent (PF-BES) with a strut thickness of 112 µm. The bare metal platform of this stent presents a selectively micro-structured, abluminal surface harbouring biolimus, a highly lipophilic sirolimus analogue absorbed by the vessel wall within a period of one month[5]. The absence of a polymer coating along with the fast drug elution seems to prevent the delayed or incomplete healing and the resulting risk of late ST observed with polymer-coated DES[1,6,7].

While the safety of early dual antiplatelet therapy (DAPT) cessation with polymer-coated DESs is still a matter of debate[8], the large-scale LEADERS FREE trial established the favourable clinical profile of the PF-BES when used with a one-month DAPT strategy in high bleeding risk (HBR) patients[9]. This evidence, along with current guidance recommending BMS avoidance across any clinical scenario[10], might have favoured the operator choice for PF-BES in HBR patients, a constantly growing subset of patients requiring percutaneous coronary intervention (PCI)[9]. However, most of the HBR features such as diabetes or renal failure increase in parallel with the incidence of restenosis and of ST, stressing the need for data from a real-world scenario - currently limited to a single all-comers registry, enrolling most patients before the publication of the LEADERS FREE trial[11]. Thus, no data exist on the contemporary indications and outcomes for the PF-BES following demonstration of the safety of a one-month DAPT strategy with this stent. The aim of this study was to evaluate contemporary real-world patterns of use, DAPT strategies and associated outcomes for the PF-BES in patients undergoing PCI.

Methods

STUDY DESIGN

The CHANCE registry (Outcome of CHAllenging lesioNs and Patients Treated With Polymer Free Drug-CoatEd Stent; ClinicalTrials.gov identifier: NCT03622203) is an Italian multicentre observational prospective all-comers registry including all patients who underwent PCI with at least one PF-BES implantation across 10 Italian sites, following publication of the LEADERS FREE trial results (from January 2016 to July 2018). All consecutive patients undergoing PCI with attempted placement of at least one PF-BES as part of routine clinical care were enrolled in the registry.

The PCI procedure was performed as per standard of care at each site. DAPT selection and duration were at the discretion of the treating physician and according to local policy.

ENDPOINTS AND DEFINITIONS

Primary outcomes were the cumulative incidence at 390 days of the patient-oriented composite endpoint (POCE: a composite of death, any myocardial infarction or any target vessel revascularisation [TVR]) and of the device-oriented composite endpoint (DOCE: a composite of cardiac death, target vessel myocardial infarction [TV-MI], and ischaemia-driven target lesion revascularisation [ID-TLR]). Other outcomes included the 390-day cumulative incidence of ST, any bleeding (defined according to the Bleeding Academic Research Consortium [BARC] definition), BARC 3-5 bleedings, and the individual composite endpoint components. Endpoint definitions, patient consent and statistical methods are detailed in **Supplementary Appendix 1**.

Results

STUDY POPULATION

Between January 2016 and April 2018, 858 patients were enrolled across 10 Italian sites. **Table 1** and **Supplementary Table 1** present the baseline characteristics of the included patients. Mean age was 74±10 years, 64.6% of patients were male. At admission, 26.5% of patients were on oral anticoagulant (OAC) therapy, 10.4% had a cancer (81.4% active) and 14.7% had a planned surgery (24.1% cardiac); 58.7% of patients presented with an acute coronary syndrome (ACS) and 41.3% with stable coronary artery disease (SCAD).

Reasons for PF-BES implantation as reported by the treating physician are presented in **Figure 1**. The main reasons (not mutually exclusive) were advanced age (>75 years, 26.0%), OAC planned to continue after PCI (25.3%), operator preference for PF-BES (9.9%), planned major surgery (8.6%), cancer (8.6%), anaemia (7.9%), recent bleeding (7.0%), expected low DAPT compliance (1.7%), thrombocytopaenia (1.0%), severe liver disease (1.0%), severely impaired renal function (1.0%), recent stroke (0.8%) and glucocorticoid or non-steroidal anti-inflammatory drug chronic treatment (0.3%). Overall, the operator choice to implant a PF-BES reflected a perceived HBR or need for a short DAPT regimen in 77.7% of the population, as defined by the presence of at least one inclusion criterion of the LEADERS FREE trial[9].

Table 1. Baseline patient characteristics (N=858 patients).

Age, years		74±10 (n=858)
Male		554/858 (64.6)
Smoker	Prior smoker	217/856 (25.4)
	Current smoker	67/856 (7.8)
Arterial hypertension		693/856 (81.0)
Dyslipidaemia		485/856 (56.7)
Diabetes mellitus		331/857 (38.5)
ID		99/857 (11.5)
Non-ID		232/857 (27.0)
eGFR <60 mL/min/1.73 m^2		198/856 (23.1)
Prior MI		161/853 (18.9)
Prior PCI		253/855 (29.6)
Prior CABG		73/855 (8.5)
Cancer		79/763 (10.4)
Active		64/79 (81.0)
Planned surgery		112/763 (14.7)
Cardiac surgery		27/112 (24.1)
OAC		225/849 (26.5)
Presentation	ACS	491/837 (58.7)
	SCAD	346/837 (41.3)

Values are expressed as n/N of patients (%) or mean±standard deviation. ACS: acute coronary syndrome; CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; ID: insulin-dependent; MI: myocardial infarction; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease

PROCEDURAL CHARACTERISTICS AND OUTCOMES

Lesion and procedural characteristics are shown in **Table 2**. Overall, 55.0% of patients had multivessel disease, with 29.2% having diffuse disease. A total of 1,127 lesions (mean 1.32±0.47 lesions per patient) were treated with PF-BES (mean 1.03±0.19 stents per lesion). Lesions were homogeneously distributed among the epicardial vessels, with the majority being located in the left anterior descending artery (42.4%). Total stent length per lesion was 20.92±8.43 mm, with maximum stent diameter per lesion being 3.14±0.70 mm. Among the lesions, 38.8% displayed American College of Cardiology/American Heart Association (ACC/AHA) type C features, 13.0% were severely calcified, and 19.7% were bifurcation lesions. Predilation and post-dilation were performed in 81.5% and 71.6% of all lesions, respectively.

Angiographic success was achieved in 98.3% and procedural success in 97.0% of patients.

Antithrombotic therapy at discharge is shown in **Table 3** and **Supplementary Table 2**. Aspirin and P2Y$_{12}$ inhibitors were prescribed at discharge in 99.8% and 99.4% of patients, respectively. Overall, 99.2% of patients were discharged on DAPT, 19.5% on triple therapy, and 0.8% on single antiplatelet therapy plus OAC. Planned DAPT duration at discharge was one month in 40.3% of patients, with 33.8% of these being on triple therapy. Among patients on triple therapy, 66.5% had a planned duration of one month.

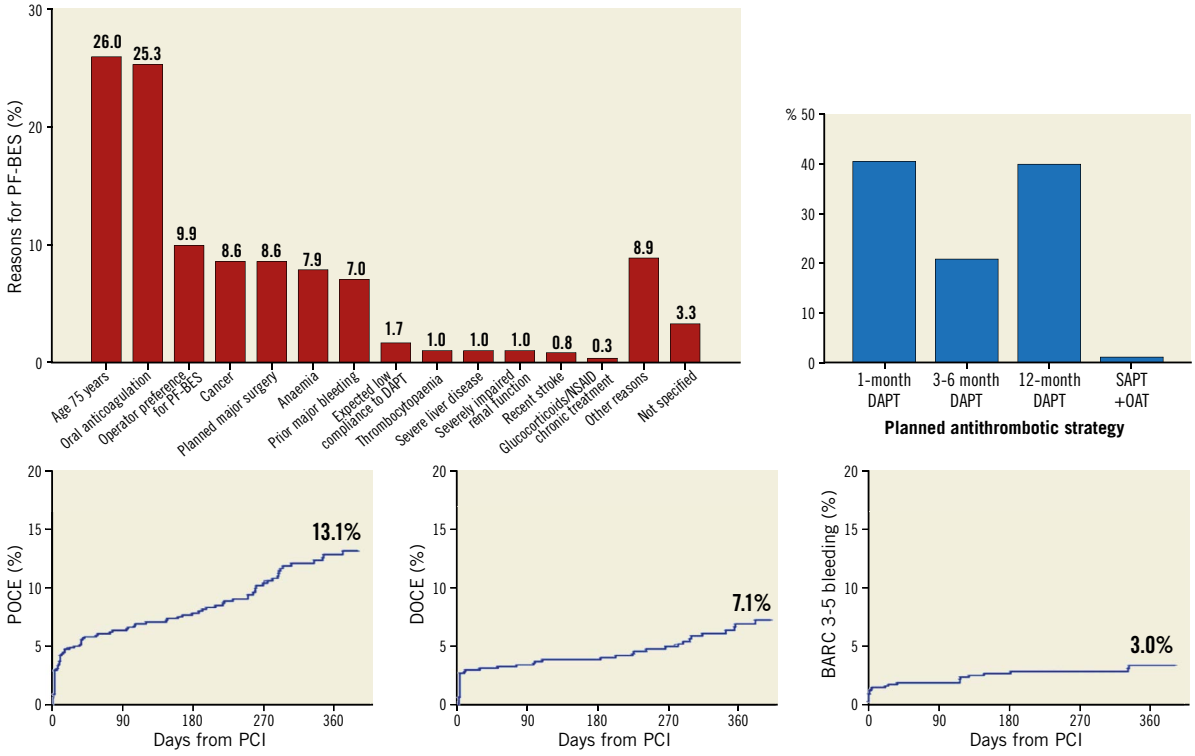

Figure 1. *Contemporary reasons, dual antiplatelet therapy strategies and clinical outcomes for a polymer-free biolimus A9-coated stent. In the real-world setting, reasons for PF-BES implantation reflected in most cases the operator-perceived high bleeding risk of the patient (top left). Following PF-BES PCI, a very short DAPT strategy was frequently implemented (top right). Despite the baseline high-risk features, the observed cardiovascular outcomes suggest a favourable safety and efficacy profile for the PF-BES in this all-comer real-world population (bottom). Reported reasons are not mutually exclusive.*

Table 2. Lesions (n=1,127) and procedural characteristics (n=858 patients).

		Patient-level characteristics (n=858)
Number of treated lesions per patient		1.32±0.47 (n=854)
Multivessel disease		384/698 (55.0)
Diffuse disease		179/613 (29.2)
Lesion-level characteristics (n=1,127)		
Treated vessel	Left main trunk	61/1,123 (5.4)
	Left anterior descending artery	476/1,123 (42.4)
	Left circumflex artery	274/1,123 (24.4)
	Right coronary artery	303/1,127 (27.0)
	Other	9/1,123 (0.9)
Bifurcation lesion		222/1,127 (19.7)
AHA/ACC type C lesion		434/1,120 (38.8)
Severely calcified lesion		147/1,127 (13.0)
Number of stents per lesion		1.03±0.19 (n=1,126)
Max stent diameter per lesion		3.14±0.70 (n=1,021)
Total stent length per lesion		20.92±8.43 (n=1,021)
Predilation		912/1,119 (81.5)
Post-dilation		802/1,119 (71.6)
Rotablation		23/1,120 (2.1)
Procedural outcomes		
Angiographic success		844/858 (98.3)
Procedural success		832/858 (97.0)

Values are expressed as n/N of patients (%) or mean±standard deviation.

Table 3. Antithrombotic therapy at discharge.

ASA	822/824 (99.8)
$P2Y_{12}$ inhibitor	819/824 (99.4)
OAC	174/824 (21.2)
VKA	128/172 (14.9)
NOAC	44/172 (25.6)
DAPT indication at discharge	817/824 (99.2)
No DAPT*	7/824 (0.8)
1-month DAPT	328/813 (40.3)
3-month DAPT	57/813 (7.0)
6-month DAPT	112/813 (13.8)
12-month DAPT	315/813 (39.9)
Long-term DAPT	1/813 (0.1)
Triple therapy indication at discharge	167/824 (19.5)

Values are expressed as n/N of patients (%) or mean±standard deviation. *All patients discharged on OAC plus SAPT regimen. ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; NOAC: new oral anticoagulant; OAC: oral anticoagulant; SAPT: single antiplatelet therapy; VKA: vitamin K antagonist

CLINICAL OUTCOMES

Clinical outcomes are shown in **Table 4**. Out-of-hospital follow-up was available for 799 (93.1%) patients.

Table 4. Clinical events at follow-up.

Outcome	30-day follow-up	180-day follow-up	390-day follow-up*
POCE	41/768 (5.3)	61/645 (9.5)	86 (13.1)
DOCE	25/768 (3.3)	31/645 (4.8)	44 (7.1)
All-cause death	23/768 (3.0)	38/645 (5.9)	49 (7.2)
Cardiac death	12/768 (1.6)	16/645 (2.5)	16 (2.1)
Any MI	20/768 (2.9)	24/645 (3.7)	28 (3.7)
Target vessel MI	20/768 (2.9)	22/645 (3.4)	25 (3.6)
Any ST	4/768 (0.5)	5/645 (0.8)	6 (0.9)
Definite or probable ST	4/768 (0.5)	5/645 (0.8)	6 (0.9)
TVR	3/768 (0.4)	8/645 (1.2)	19 (3.4)
TLR	2/768 (0.2)	5/645 (0.8)	10 (1.9)
ID-TLR	2/768 (0.2)	5/645 (0.8)	9 (1.4)
Any bleeding	31/768 (4.0)	45/645 (7.0)	63 (11.1)
BARC 3-5 bleeding	14/768 (1.8)	21/645 (3.3)	20 (3.0)

Values are expressed as n/N of patients (%). *Kaplan-Meier rates. BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoint; ID: ischaemia-driven; MI: myocardial infarction; POCE: patient-oriented composite endpoint; ST: stent thrombosis; TLR: target lesion revascularisation; TVR: target vessel revascularisation

Kaplan-Meier estimates at 390 days (median follow-up 340 days, interquartile range: 187-390 days) for the occurrence of the primary endpoints were as follows: POCE 13.1% (any MI 3.7%, any TVR 3.4%), DOCE 7.1% (TV-MI 3.6%, ID-TLR 1.4%), while the 390-day any ST estimate was 0.9%. The 390-day estimate of the any bleeding outcome was 11.1% (BARC 3-5 bleeding 3.0%).

Supplementary Table 3-**Supplementary Table 5** provide univariate and multivariate analysis for predictors of the primary outcomes. At multivariate analysis, independent predictors of 390-day POCE were eGFR ≤60 ml/min (HR 1.81, 95% CI: 1.09-3.04, p=0.028), a history of cancer (HR 2.62, 95% CI: 1.43-4.81, p=0.002) and severely calcified lesions (HR 2.05, 95% CI: 1.09-3.85, p=0.025). Independent predictors of 390-day DOCE were a previous MI (HR 2.06, 95% CI: 1.03-4.15, p=0.041), a history of cancer (HR 2.69, 95% CI: 1.18-6.13, p=0.019) and bifurcation lesions (HR 2.66, 95% CI: 1.38-5.13, p=0.004).

CLINICAL OUTCOMES ACCORDING TO CLINICAL PRESENTATION

Baseline clinical, lesion and procedural characteristics of patients undergoing PF-BES PCI following an ACS (n=491, 58.7%) as compared to those of patients with a stable presentation (n=346, 41.3%) are detailed in **Supplementary Table 5** and **Supplementary Table 6**.

In patients with ACS as compared to SCAD presentation, a potent $P2Y_{12}$ inhibitor (20.6% vs 16.0%, p<0.001) and a longer DAPT duration (12 months [IQR 1-12 months] vs 1 month [IQR 1-6 months], p<0.001) were most frequently prescribed **(Supplementary Table 7)**.

Clinical outcomes stratified by clinical presentation are reported in **Figure 2** and **Supplementary Table 8**. Patients presenting with an ACS had a higher 390-day estimated incidence of the POCE, also after adjustment for confounding variables (ACS vs SCAD: 16.7% vs 8.1%, log-rank p=0.002; adj. HR 1.69 [1.01-2.82]), while no difference in the 390-day estimated incidence of DOCE was observed (ACS vs SCAD: 8.4% vs 5.2%; p=0.168, adj. HR 1.21 [0.62-2.34]). The estimates of any ST at 390 days for ACS vs SCAD patients were 1.3% and 0.3% (p=0.193).

Discussion

The LEADERS FREE trial established the better clinical profile of a DES, the PF-BES, over a BMS in patients at high bleeding risk when combined with a very short (one-month) DAPT regimen. CHANCE is the first registry providing insights into real-world patterns of indications, DAPT strategies and outcomes for the PF-BES, following publication of the LEADERS-FREE trial. The main findings of this study can be summarised as follows **(Figure 1)**.

1) In a large, contemporary all-comers registry, the main reasons for PF-BES use in most cases reflected the operator-perceived HBR of the patient.
2) The real-life population for which PF-BES implantation was selected shows a high overall prognostic risk as established by the observed elevated all-cause death rate.
3) Following PF-BES PCI, a very short DAPT strategy was frequently implemented.
4) Despite the high-risk features of the study population, the cardiovascular outcomes observed in CHANCE suggest a favourable safety and efficacy profile for the PF-BES in a real-world setting.

For an overview of PF-BES development rationale, technological characteristics, preclinical and surrogate clinical outcomes, please see **Supplementary Appendix 2**.

The favourable clinical profile of the PF-BES in a wide real-world population was assessed for the first time in the RUDI-FREE registry. In this study, comprising mainly patients with non-HBR features (83.7%), the PF-BES was associated with a high one-year safety and efficacy performance, with outcomes in the lower range of cardiovascular adverse event rates observed with contemporary new-generation DES[12].

Concurrently, the LEADERS FREE trial, comparing PF-BES with BMS in HBR patients followed by one-month DAPT, demonstrated superior safety and efficacy in this setting with this new technology[9]. No such evidence currently exists for any other commercially available DESs, hampering evidence-based recommendation on a one-month DAPT strategy in HBR patients undergoing non-PF-BES DES PCI. This recognition may have favoured the implementation of PF-BES across real-world cath labs with a specific indication for patients with adherence restraints, such as HBR patients.

Of note, a prospective randomised comparison of the BioFreedom PF-BES with the Resolute Onyx™ zotarolimus-eluting stent (Medtronic, Minneapolis, MN, USA) followed by one-month DAPT in HBR patients (Onyx ONE trial, NCT03344653) and a comparison of different DAPT durations (1-month vs >1-month) following Ultimaster® biodegradable polymer sirolimus-eluting stent (Terumo Corp., Tokyo, Japan) implantation in HBR patients (MASTER DAPT trial, NCT03023020) are currently ongoing and will provide insights on the potential use of other stent platforms in this setting.

In CHANCE, the first all-comers registry evaluating real-world use of PF-BES following LEADERS FREE, we found that roughly three out of four patients were implanted with PF-BES due to the operator-perceived high bleeding risk, which was the driver of the operator preference for PF-BES. This proportion is markedly different from the 16.3% of patients displaying HBR features (as defined by a CRUSADE score >40) of the RUDI-FREE registry, where most of the enrolment period was prior to LEADERS FREE publication. Even if the reasons driving the operator choice for PF-BES were not reported in the RUDI-FREE study and despite

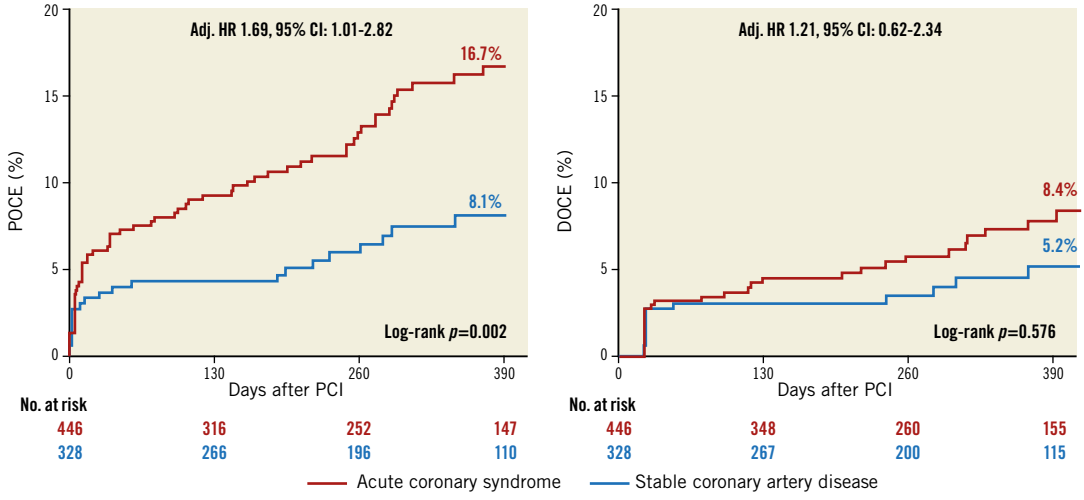

Figure 2. *Kaplan-Meier estimates of primary endpoints at 390-day follow-up stratified by clinical presentation.*

the different criteria used to define the bleeding risk status, this observation may suggest a changing pattern of indications for PF-BES in real practice, reflecting the evidence base for the use of this sole stent with a very short DAPT strategy. This is further substantiated by the striking increase in the one-month planned DAPT rates as compared to RUDI-FREE (40.3% vs 4.9% of patients).

Beyond high bleeding risk, the baseline features observed in CHANCE reflect an overall high prognostic risk: 56.5% of patients were older than 75 years, 23.1% had at least stage 3a chronic kidney disease, 10.4% had a cancer (81.4% active) and 14.7% had a planned surgery (24.1% cardiac). This is likely to have translated into the 7.2% estimated 390-day all-cause mortality (5.1% non-cardiovascular death) as well as the 3.0% estimated 390-day BARC 3-5 bleedings found in the study. This is consistent with data from the three available randomised controlled trials evaluating DESs in patients with HBR features[9,13,14], showing only slightly higher all-cause mortality and BARC bleeding rates than CHANCE (**Supplementary Table 9**, columns one to three).

As high bleeding predictors largely overlap with risk factors for ischaemic complications, high bleeding risk *per se* is an overall marker of the ischaemic risk[13,15]. This recognition, together with the observed anatomical presentation (29.2% diffuse disease, 19.7% bifurcation lesions, 38.8% type C lesions), establishes the concurrent high ischaemic risk of the CHANCE population. Notwithstanding this, we found acceptable rates of 390-day cardiovascular outcomes, reflecting the good clinical profile of the PF-BES in a contemporary real-world setting. For comparison, the safety outcomes of cardiac death, ST and MI were only slightly increased above the superior IQR reference limit of adverse event rates in a randomised controlled trial of well-selected non-HBR patients undergoing contemporary DES PCI reported by the ESC/EAPCI Task Force for coronary stent evaluation[12] (**Supplementary Table 9**, far right column). Conversely, the efficacy endpoint of TLR was well below the median reference value of the same analysis, possibly reflecting the optimal antirestenotic profile of biolimus, which remains in the coronary tissues until 180 days after stent implantation, with less than 1% of the original amount on the PF-BES following the first four weeks[5].

As expected, CHANCE event rates appear higher than those observed in the RUDI-FREE registry, in line with the different baseline features of the two populations. Importantly, despite the higher rates of the outcomes reflecting the overall patient-level risk, those more closely reflecting device-level performance (i.e., ST and TLR) were similar between studies **(Supplementary Table 9)**. This finding, suggesting a favourable PF-BES performance irrespective of the patient baseline characteristics, supports the feasibility of this stent across a wide range of real-life patients. Comparative evidence with new-generation DESs is needed to support this observation.

Limitations

The findings of this observational study should be interpreted in the context of some limitations. First, we abstracted clinical variables on the basis of documentation in medical records; the completeness of that documentation may not have been consistent either across hospitals or over time. Second, the study was not powered to evaluate rare events such as TLR and ST. With this premise, the low TLR and ST incidences observed in our study are nevertheless reassuring regarding the favourable profile of PF-BES in this setting. Third, the observational nature of this study, with the absence of a control arm, does not allow providing direct comparative evidence of the PF-BES performance in respect to other new-generation DESs. Notwithstanding this, indirect comparison of the PF-BES outcomes of both our high-risk and a more benign population[11] with new-generation DESs in either HBR or non-HBR settings **(Supplementary Table 9)** suggests that the performance of PF-BES is comparable with new-generation DESs across a wide range of real-world patients.

Conclusions

In this large, contemporary all-comers registry, PF-BES use was frequently adopted in HBR patients, often followed by a very short DAPT strategy. The observed outcomes, in the context of previously available data, suggest a favourable safety and efficacy profile for the PF-BES across a wide range of real-world patients.

Impact on daily practice

A new polymer-free biolimus A9-eluting stent (PF-BES) showed a favourable clinical profile in a large clinical trial, when used with a one-month DAPT regimen in HBR patients. Our results show that the PF-BES is associated with a favourable clinical profile across a wide range of real-world patients when a one-month DAPT duration is deemed necessary by the treating physician.

Appendix. Study collaborators

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Guest Editor

This paper was guest edited by Alec Vahanian, MD, PhD; Department of Cardiology, Hôpital Bichat-Claude Bernard, and University Paris VII, Paris, France.

Conflict of interest statement

The authors and the collaborators have no conflicts of interest to declare. The Guest Editor is a consultant for Edwards Lifesciences.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. Discussion.

Supplementary Table 1. Additional baseline patient characteristics.

Supplementary Table 2. Additional details on antithrombotic therapy at discharge.

Supplementary Table 3. Univariate and multivariate analysis for predictors of 390-day POCE.

Supplementary Table 4. Univariate and multivariate analysis for predictors of 390-day DOCE.

Supplementary Table 5. Distribution of baseline characteristics in patients presenting with an acute coronary syndrome as compared to stable coronary artery disease presentation.

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Supplementary Table 8. Kaplan-Meier estimates of clinical events at 390-day follow-up stratified by clinical presentation.

Supplementary Table 9. Comparison of CHANCE cardiovascular and bleeding outcomes with PF-BES and other DESs across different clinical and study settings.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-19-00450

Supplementary data

Supplementary Appendix 1. Methods

Patient consent

All patients gave written informed consent before the procedure, and all studies were performed in compliance with the Declaration of Helsinki.

Outcome definitions

Death, ST, TVR and ID-TLR were adjudicated using the Academic Research Consortium definitions [15]. MI was defined using the third universal definition [16]. Angiographic success was calculated as the percentage of patients with successful delivery and deployment of the PF-BES to the target lesion, with final diameter stenosis ≤10% by visual assessment and final TIMI 3 flow. Procedural success was calculated as successful stent implantation without any periprocedural complication. Indices of technical procedural success were also evaluated.

Statistical analysis

Categorical variables are expressed as numbers and percentages, continuous variables are expressed as mean±standard deviation or median (interquartile range) as appropriate. An unpaired t-test or non-parametric Mann-Whitney U test was used for comparisons of continuous variables and the chi-square test was used for categorical variables.

Kaplan-Meier analysis was performed to evaluate cumulative event rates at follow-up. To produce meaningful outcome estimates according to the observed number of patients at risk in the registry, maximum follow-up length was truncated at 390 days (corresponding to the 75^{th} percentile of available follow-up length in the study population).

A multivariate Cox proportional hazards analysis was performed to assess the independent determinants of the primary endpoints. All the variables with a univariate $p<0.05$ or having clinical relevance were entered into the model. The proportional hazards assumption of the Cox regression model was checked by using time-dependent Cox models. Results are presented as hazard ratio (HR) with 95% confidence interval (CI).

The impact of clinical presentation (acute coronary syndrome [ACS] versus stable coronary artery disease [SCAD]) on PF-BES outcomes was evaluated. Cumulative incidence rates come from the Kaplan-Meier estimator with log-rank p-value to test if the plots differ over time. Incidence rates of

the primary endpoints are presented both unadjusted and adjusted for clinically relevant factors (for the primary endpoints: oral anticoagulation therapy [OAT] at discharge, DAPT duration; for bleeding events: estimated glomerular filtration rate [eGFR] ≤60 ml/min, cancer, anaemia or thrombocytopaenia at presentation, OAT therapy at discharge, planned surgery) and for significant predictors of the outcome at the multivariate analysis.

A $p<0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS, Version 20.0 (IBM Corp., Armonk, NY, USA).

Supplementary Appendix 2. Discussion

Durable polymers, highly effective in preventing in-stent restenosis, have been implicated in chronic inflammation and local toxicity of the treated vessel, possibly leading to delayed vascular healing, hypersensitivity reactions, endothelial dysfunction and neoatherosclerosis [1–4]. These phenomena may all trigger late and very late ST, which is the basis for the requirement of prolonged DAPT following DES implantation [10].

These limitations with durable polymers fostered the development of DES technology with biodegradable polymer coatings [16]. More recently, the evolution of a stent platform allowing drug binding and release directly from the stent surface led to polymer-free DES, with the potential of abolishing the inflammatory stimuli related to the polymer coating [5]. However, initial experience with paclitaxel- and rapamycin-eluting polymer-free stents suggested lesser efficacy at inhibiting neointimal hyperplasia, most probably due to insufficient and/or uncontrolled drug delivery at the target coronary site [17,18].

Biolimus is a sirolimus derivative with potent antiproliferative properties consistently proven to inhibit neointimal hyperplasia when applied together with biodegradable polymer coating technologies [16,19,20]. The PF-BES combines the excellent pharmacokynetic and pharmacodynamic properties of biolimus with a selectively micro-structured, abluminal stent surface allowing adhesion and highly controlled release of the drug, which is absorbed by the vessel wall within a period of a month, without the need for a polymer [5]. Of note, the parallel evolution of polymer coatings leading to more biocompatible durable polymers (compared to first-generation ones) along with thinner stent struts translated into favourable healing patterns and low rates of (very late) ST for durable-polymer DESs, comparable with those of biodegradable-polymer DESs [21,22]. Direct evaluations between the PF-BES and new-generation polymer-coated DESs, and safety evidence of short DAPT treatment following new-generation durable-polymer-coated DESs are currently lacking. Concerning comparative data of the PF-BES versus first-generation durable-polymer-coated DESs, although not powered for clinical outcomes, there is initial evidence hinting at improved reduction of late intimal proliferation and local inflammation with the PF-BES [5,7]. The favourable clinical counterpart of these biological phenomena has been suggested by the RUDI-FREE all-comers registry of patients undergoing PF-BES in real-world practice [11,23].

Supplementary Table 1. Additional baseline patient characteristics (N=858 patients).

OAC	225/849 (26.5)
Indication	
Atrial fibrillation	146/167 (87.4)
Valvular	5/167 (3.0)
VTE	14/167 (8.4)
Cardiac thrombus	2/167 (1.2)
Drug	
VKA	145/216 (67.1)
Dabigatran	27/216 (12.5)
Rivaroxaban	17/216 (7.9)
Edoxaban	9/216 (4.2)
Apixaban	18/216 (8.3)
Presentation	
ACS	491/837 (58.7)
STEMI	155/837 (18.5)
NSTEMI	221/837 (26.4)
Unstable angina	115/837 (13.7)
SCAD	346/837 (41.3)
Stable angina	214/837 (25.6)
Positive ischaemia test	84/837 (10.0)
Planned angiographic FU	22/837 (2.6)
Other	26/837 (3.1)

Values are expressed as n/N of patients (%) or mean±standard deviation.
ACS: acute coronary syndrome; FU: follow-up; NSTEMI: non-ST-elevation myocardial infarction; SCAD: stable coronary artery disease; STEMI: ST-elevation myocardial infarction; VKA: vitamin K antagonists; VTE: venous thromboembolism

Supplementary Table 2. Additional details on antithrombotic therapy at discharge.

ASA	822/824 (99.8)
$P2Y_{12}$ inhibitor	819/824 (99.4)
Clopidogrel	634/747 (84.9)
Ticagrelor	101/747 (13.5)
Prasugrel	6/747 (0.8)
OAC	174/824 (21.2)
VKA	128/172 (14.9)
NOAC	44/172 (25.6)
Dabigatran	23/172 (13.4)
Rivaroxaban	11/172 (6.4)
Apixaban	7/172 (4.1)
Edoxaban	3/172 (1.7)
DAPT indication at discharge	817/824 (99.2)
No DAPT*	7/824 (0.8)
1-month DAPT	328/813 (40.3)
3-month DAPT	57/813 (7.0)
6-month DAPT	112/813 (13.8)
12-month DAPT	315/813 (39.9)
Long-term DAPT	1/813 (0.1)
Triple therapy indication at discharge	167/824 (19.5)
1-month triple therapy	111/167 (66.5)
3-month triple therapy	17/167 (10.2)
6-month triple therapy	24/167 (14.3)
12-month triple therapy	15/167 (9.0)

Values are expressed as n/N of patients (%) or mean ± standard deviation.
*All patients discharged on OAC plus SAPT regimen.
ASA: acetylsalicylic acid; DAPT: dual antiplatelet therapy; NOAC: new oral anticoagulant; OAC: oral anticoagulant; SAPT: single antiplatelet therapy; VKA: vitamin K antagonists

Supplementary Table 3. Univariate and multivariate analysis for predictors of 390-day POCE.

Variable	yes	no	Univariate analysis		Multivariate analysis	
	POCE (%)		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Clinical characteristics						
Age ≥75	20 (9.6)	66 (13.1)	0.70 (0.41-1.18)	0.114		
Male sex	72 (13.7)	28 (10.3)	1.39 (0.88-2.21)	0.096		
Smoker	31 (11.8)	69 (12.9)	0.90 (0.57-1.42)	0.370		
Arterial hypertension	81 (12.6)	19 (12.3)	1.02 (0.60-1.75)	0.527		
Dyslipidaemia	61 (13.6)	39 (11.2)	1.24 (0.81-1.90)	0.192		
Diabetes mellitus	39 (14.4)	61 (11.6)	1.23 (0.83-1.97)	0.155		
eGFR <60 ml/min	34 (18.2)	66 (10.8)	**1.83 (1.17-2.88)**	**0.007**	**1.81 (1.09-3.04)**	**0.028**
Prior MI	25 (16.8)	75 (11.6)	1.54 (0.94-2.51	0.059		
Prior PCI	31 (13.2)	69 /12.3)	1.10 (0.69-1.72)	0.390		
Prior CABG	7 (10.9)	93 (12.7)	0.85 (0.37-1.91)	0.433		
Prior bleeding	9 (13.0)	77 (12.0)	1.10 (0.52-2.31)	0.458		
OAT on admission	18 (8.8)	68 (13.4)	0.62 (0.36-1.08)	0.056		
Planned surgery	4 (5.6)	82 (12.8)	**0.40 (0.14-1.12)**	**0.046**	0.85 (0.30-2.38)	0.757
History of cancer	18 (26.1)	68 (10.6)	**2.98 (1.65-5.40)**	**0.001**	**2.62 (1.43-4.81)**	**0.002**
Thrombocytopaenia	2 (22.2)	84 (11.9)	2.11 (0.43-10.3)	0.298		
Anaemia	5 (9.3)	81 (12.3)	0.73 (0.28-1.88)	0.343		
Presentation – ACS (vs SCAD)	72 (16.1)	25 (7.6)	**2.33 (1.44-3.76)**	**0.000**	1.32 (0.75-2.33)	0.330
1-month DAPT duration at discharge	39 (12.5)	54 (12.0)	1.04 (0.67-1.62)	0.465		
Lesion and procedural characteristics						
Multivessel CAD	50 (13.8)	28 (9.8)	1.47 (0.90-2.40)	0.076		
Diffuse disease	23 (13.9)	43 (10.4)	1.40 (0.82-2.41)	0.141		
PCI on LM/LAD prox	27 (16.6)	61 (10.7)	**1.66 (1.01-2.71)**	**0.031**	1.37 (0.77-2.45)	0.284
Bifurcation lesion/s	29 (18.1)	71 (11.2)	**1.76 (1.10-2.82)**	**0.015**	1.47 (0.80-2.45)	0.221
AHA/ACC C lesion/s	39 (13.7)	60 (11.8)	1.18 (0.77-1.82)	0.255		
Severe calcification	19 (20.2)	81 (11.5)	**1.95 (1.11-3.39)**	**0.017**	**2.05 (1.09-3.85)**	**0.025**
Max. diameter stent per lesion	-	-	1.15 (0.85-1.57)	0.362		

Max. number of stents per lesion	-	-	2.01 (1.06-3.82)	0.061		
Total stent length per lesion	-	-	1.01 (0.96-1.05)	0.774		
Radial access (vs femoral)	60 (10.4)	27 (18.2)	**1.17 (1.10-3.16)**	**0.008**	0.93 (0.47-1.85)	0.850
Predilation	83 (13.1)	17 (10.6)	1.27 (0.73-2.21)	0.239		
Post-dilation	68 (12.3)	30 (12.8)	0.85 (0.60-1.51)	0.463		
Rotablator	3 (16.7)	96 (12.4)	1.41 (0.40-4.97)	0.395		

Values are expressed as n (%) and hazard ratio (HR) with 95% confidence interval (CI).
ACS: acute coronary syndrome; AHA/ACC: American Heart Association/American College of Cardiology; CABG: coronary artery bypass graft; DAPT: dual antiplatelet therapy; eGFR: estimated glomerular filtration rate; LAD: left anterior descending; LM: left main; MI: myocardial infarction; PCI: percutaneous coronary intervention; POCE: patient-oriented composite endpoint; SCAD: stable coronary artery disease

Supplementary Table 4. Univariate and multivariate analysis for predictors of 390-day DOCE.

Variable	yes	no	Univariate analysis		Multivariate analysis	
	DOCE (%)		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Clinical characteristics						
Age ≥75	13 (6.2)	33 (6.6)	0.95 (0.49-1.84)	0.511		
Male sex	38 (7.3)	15 (5.5)	1.35 (0.73-2.50)	0.211		
Smoker	19 (6.9)	35 (6.6)	**1.06 (0.59-1.90)**	**0.482**		
Arterial hypertension	9 (5.9)	44 (6.9)	1.17 (0.56-2.47)	0.412		
Dyslipidaemia	34 (7.6)	10 (5.5)	1.41 (0.79-2.51)	0.153		
Diabetes mellitus	20 (7.4)	33 (6.3)	1.18 (0.67-2.11)	0.330		
eGFR <60 ml/min	14 (7.5)	39 (6.4)	1.18 (0.63-2.23)	0.356		
Prior MI	17 (11.5)	36 (5.6)	2.20 (1.20-4.04)	0.011	**2.06 (1.03-4.15)**	**0.041**
Prior PCI	19 (8.2)	34 (6.0)	1.38 (0.77-2.47)	0.176		
Prior CABG	4 (6.2)	49 (6.7)	0.93 (0.32-2.66)	0.574		
Prior bleeding	5 (7.2)	41 (6.4)	1.14 (0.44-3.00)	0.469		
OAT on admission	7 (3.4)	39 (7.7)	0.43 (0.19-0.98)	0.024	0.58 (0.20-1.72)	0.325
Planned surgery	3 (4.2)	43 (6.7)	**0.60 (0.18-1.99)**	**0.292**		
History of cancer	9 (13.0)	37 (5.8)	**2.45 (1.13-5.32)**	**0.026**	**2.69 (1.18-6.13)**	**0.019**
Thrombocytopaenia	1 (11.1)	45 (6.4)	1.82 (0.22-14.89)	0.455		
Anaemia	5 (9.3)	41 (6.2)	1.53 (0.57-4.05)	0.266		
Presentation – ACS (vs SCAD)	35 (7.8)	17 (5.2)	**1.56 (0.37-2.15)**	**0.091**		
Lesion and procedural characteristics						
Multivessel CAD	29 (8.0)	15 (5.2)	1.58 (0.83-3.00)	0.106		
Diffuse disease	16 (9.8)	21 (5.1)	2.02 (1.03-3.98)	0.033		
PCI on LM/LAD prox	12 (7.4)	37 (6.5)	**1.15 (0.58-2.26)**	**0.397**		
Bifurcation lesion/s	20 (12.7)	33 (5.2)	**2.65 (1.48-4.75)**	**0.001**	**2.66 (1.38-5.13)**	**0.004**
AHA/ACC C lesion/s	28 (9.8)	25 (4.9)	**2.10 (1.20-3.67)**	**0.007**	1.98 (0.86-8.47)	0.108
Severe calcification	11 (11.7)	42 (6.0)	2.08 (1.03-4.20)	0.038	1.96 (0.92-4.13)	0.078
Max. diameter stent per lesion	-	-	0.94 (0.61-1.44)	0.758		
Max. number of stents per lesion	-	-	1.50 (0.53-4.28)	0.448		

Total stent length per lesion	-	-	1.056 (1.00-1.11)	0.052
Radial access (vs femoral)	10 (6.8)	35 (6.1)	**1.12 (0.54-2.31)**	**0.443**
Predilation	43 (6.8)	10 (6.2)	1.10 (0.54-2.24)	0.479
Post-dilation	40 (7.2)	13 (5.5)	1.33 (0.69-2.54)	0.240

Values are expressed as n (%) and hazard ratio (HR) with 95% confidence interval (CI).
ACS: acute coronary syndrome; AHA/ACC: American Heart Association/American College of Cardiology; CABG: coronary artery bypass graft; DOCE: device-oriented composite endpoint; eGFR: estimated glomerular filtration rate; LAD; left anterior descending; LM: left main; MI: myocardial infarction; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease

Supplementary Table 5. Distribution of baseline characteristics in patients presenting with an acute coronary syndrome as compared to stable coronary artery disease presentation (n=837 patients).

	ACS n=491	**SCAD n=346**	***p*-value**
Age (years)	76±7	76±7	0.395
Male	63.3%	67.3%	0.131
Smoke	33.2%	34.1%	0.421
Arterial hypertension	80.6%	81.5%	0.403
Dyslipidaemia	57.5%	56.4%	0.402
Diabetes mellitus	33.4%	35.0%	0.345
eGFR <60 mL/min/1.73 m^2	23.5%	23.1%	0.481
Prior MI	19.3%	18.9%	0.484
Prior PCI	29.7%	29.9%	0.505
Prior CABG	8.6%	7.8%	0.397
Prior OAT	25.3%	28.1%	0.210
Cancer	11.6%	9.2%	0.183
Planned surgery	10.4%	20.4%	**<0.001**

Values are expressed as n/N of patients (%) or mean±standard deviation.
ACS: acute coronary syndrome; CABG; coronary artery bypass graft; eGFR; estimated glomerular filtration rate; MI: myocardial infarction; OAT: oral anticoagulant therapy; PCI: percutaneous coronary intervention; SCAD: stable coronary artery disease

Supplementary Table 6. Distribution of lesion and procedural characteristics stratified by clinical presentation (n=837 patients, lesions=987).

	ACS lesions, n=514 patients, n=491	**SCAD** lesions, n=473 patients, n=346	***p*-value**
Number of treated lesions per patient	1.34±0.49	1.28±0.45	0.090
Multivessel disease	54.8%	55.1%	0.501
Diffuse disease	30.0%	28.1%	0.340
Radial access (vs femoral)	20.5%	17.8%	0.204
Lesion-level characteristics			
Treated vessel			
Left main trunk	6.5%	3.4%	
Left anterior descending artery	40.1%	43.4%	
Left circumflex artery	24.5%	24.2%	
Right coronary artery	27.6%	28.6%	
Other	1.4%	0.4%	0.747
Bifurcation lesion	17.3%	16.5%	0.403
AHA/ACC C type lesion	42.2%	30.9%	**<0.001**
Severely calcified lesion	17.5%	8.7%	**<0.001**
Number of stents per lesion	1.01±0.12	1.06±0.26	**<0.001**
Max. stent diameter per lesion	3.10±0.68	3.17±0.71	0.163
Total stent length per lesion	20.53±7.64	20.75±8.33	0.855
Predilation	78.8%	80.1%	0.329
Post-dilation	64.9%	72.7%	**0.005**
Procedural outcomes			
Angiographic success	98.4%	98.8%	0.400
Procedural success	96.9%	96.8%	0.745

Values are expressed as n/N of lesions (%) or mean±standard deviation.
ACS: acute coronary syndrome; AHA/ACC: American Heart Association/American College of Cardiology; SCAD: stable coronary artery disease

Supplementary Table 7. Antithrombotic therapy at discharge stratified by clinical presentation.

	ACS patients, n=491	**SCAD** patients, n=346	***p*-value**
DAPT at discharge	98.9%	99.4%	0.404
Planned DAPT duration (months)	12 (1-12)	1 (1-6)	**<0.001**
Type of $P2Y_{12}$ inhibitor			
Clopidogrel	78.5%	93.5%	
Ticagrelor	20.6%	16.0%	
Prasugrel	1.2%	0.3%	**<0.001**
OAT at discharge	21.8%	19.3%	0.213
Planned triple therapy duration (months)	1 (1-6)	1 (1-1)	**<0.001**
Type of OAC			
VKA	76.9%	70.3%	
NOAC	23.1%	29.7%	0.094

Values are expressed as n/N of patients (%) and median (interquartile range).
ACS: acute coronary syndrome; DAPT: dual antiplatelet therapy; NOAC: new oral anticoagulant; OAT: oral anticoagulant; SCAD: stable coronary artery disease; VKA: vitamin K antagonists

Supplementary Table 8. Kaplan-Meier estimates of clinical events at 390-day follow-up stratified by clinical presentation.

	Presentation		
Outcome	**ACS (n=491)**	**SCAD (n=346)**	***p*-value**
POCE	62 (16.7)	22 (8.1)	**0.002**
DOCE	29 (8.4)	14 (5.2)	0.168
All-cause death	38 (9.9)	10 (3.7)	**0.002**
Cardiac death	12 (2.8)	3 (1.1)	0.069
Any MI	18 (4.9)	10 (3.2)	0.450
Target vessel MI	16 (4.4)	9 (2.8)	0.497
Any ST	5 (1.3)	1 (0.3)	0.193
Definite or probable ST	5 (1.3)	1 (0.3)	0.193
TVR	14 (4.7)	4 (1.9)	0.071
TLR	8 (2.7)	1 (0.3)	0.052
ID-TLR	7 (2.7)	1 (0.3)	0.078
Any bleeding	35 (9.8)	28 (11.2)	0.691
BARC 3-5 bleeding	10 (2.5)	10 (4.0)	0.471

Values are expressed as n (%).
ACS: acute coronary syndrome; BARC: Bleeding Academic Research Consortium; DOCE: device-oriented composite endpoint; ID: ischaemia-driven; MI: myocardial infarction; POCE: patient-oriented composite endpoint; SCAD: stable coronary artery disease; ST: stent thrombosis; TLR: target lesion revascularisation; TVR: target vessel revascularisation

Supplementary Table 9. Comparison of CHANCE cardiovascular and bleeding outcomes with PF-BES and other DESs across different clinical and study settings.

	HBR populations*				PF-BES all-comers populations		Non-HBR RCT populations
	LEADERS FREE [9]	**ZEUS-HBR[20]**	**SENIOR[21]**	**HBR trials pooled[23]**	**CHANCE**	**RUDI-FREE[11]**	**EAPCI report[19]**
Study type	RCT	RCT sub-analysis	RCT	Meta-analysis	Real-world registry	Real-world registry	Systematic review
DES stent	PF-BES	Zotarolimus durable-polymer DES	Everolimus bioresorbable-polymer DES	-	PF-BES	PF-BES	CE-marked contemporary DESs
DAPT strategy	1-month	1-month	SCAD: 1-month ACS: 6 months		12 months (IQR 1-12)	12 months (IQR 6-12)	NA
Follow-up	13 months	12 months	12 months	12-13 months	13 months	12 months	9-12 months
Outcomes							
All-cause death	8.0%	15.8%	6%	8.9%	7.2%	3.9%	1.92% (IQR 1.05–2.54)
Cardiac death	4.2%	11.8%	1%	-	2.1%	2.4%	1.00% (IQR 0.65–1.63)
MI	6.1%	3.5%	4%	4.8%	3.7%	1.8%	2.89% (IQR 1.45–4.21)
Any ST	-	6.6%	-		0.9%	-	-
Definite or probable ST	2.0%	2.6%	1.0%	1.7%	0.9%	1.1%	0.47% (IQR 0.28–0.72)
TVR	5.8%	5.9%	-		3.4%	1.8%	-
TLR	5.1%	5.2%	2%	4.1%	1.9%	1.4%	2.91% (IQR 1.67–5.94)
Any bleeding	18.1%	8.5%	5%	9.7%	11.1%	-	-
BARC 3-5 bleeding	7.2%	3.5%	3%	5.4%	3.0%	1.2%	-

Outcomes following PF-BES PCI in the CHANCE study (light blue column) are presented in comparison with several scenarios: outcomes in HBR patients undergoing DES PCI in RCTs (left of CHANCE column); real-world outcomes following PF-BES (right of CHANCE column); outcomes in non-HBR patients undergoing contemporary DESs PCI in RCTs (far right column). The high rates of all-cause death and BARC 3-5 bleedings observed in CHANCE reflect the overall high-risk features of the study population as compared to RUDI-FREE and contemporary DES RCT populations. The favourable cardiovascular outcomes observed in CHANCE despite these features may reflect the favourable clinical profile of the PF-BES in a contemporary real-world setting. *Refer to the original publications[9,20,21] for the specific HBR inclusion criteria of each RCT.
HBR: high bleeding risk; NA: not available; PF-BES: polymer-free biolimus-eluting stent; RCT: randomised controlled trial