Safety and efficacy of polymer-free biolimus-eluting stents versus ultrathin stents in unprotected left main or coronary bifurcation: A propensity score analysis from the RAIN and CHANCE registries

Dual antiplatelet therapy strategies and clinical outcomes for a polymer-free biolimus A9-coated stent

Running title: the all-comers CHANCE registry

Fabrizio D'Ascenzo[1] MD, Guglielmo Gallone[1] MD, Giacomo Boccuzzi[2] MD, Bernardo Cortese[3] MD, Maurizio Di Biasi[4] MD, Paolo Vicinelli[6] MD, Vincenzo Infantino[7] MD, Ferdinando Varbella[10] Arnaldo Poli[8] MD, Giulietta Grigis[9] MD, Davide Capodanno[5] MD;, Gaetano Maria De Ferrari[11] Prof and Alfonso Ielasi[12] MD.

1 Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, Torino
2 Division of Cardiology, San Giovanni Bosco, Torino
3 U.O.C. Cardiologia, Ospedale Fatebenefratelli, ASST Fatebenefratelli/Sacco, Milano
4 U.O.C. Cardiologia, Ospedale Sacco, ASST Fatebenefratelli/Sacco, Milano
5 Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania
6 U.O.C. Cardiologia, Ospedale di Magenta, ASST Milanese Ovest
7 Division of Cardiology, Ospedale Civile, Ciriè
8 U.O.C. Cardiologia, Ospedale di Legnano, ASST Milanese Ovest
9 U.O.C. Cardiologia, Ospedale di Seriate, ASST Bergamo Est
10 Department of Cardiology, Infermi Hospital, Rivoli
11 Division of Cardiology, University of Pavia, Pavia
12 U.O. Cardiologia Clinica ed Interventistica, Istitito Clinico S. Ambrogio Milano

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A list of study collaborators can be found in the appendix

Corresponding author:

Guglielmo Gallone, MD
Division of Cardiology, Città della Salute e della Scienza, Torino, Italy
Corso Bramante 88/90, 10126, Turin, Italy
Email: guglielmo.gallone@gmail.com Phone: +390116335443

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ABSTRACT

Aims

A large trial established the favorable clinical profile of a new polymer-free biolimus-A9-eluting stent (PF-BES) with a 1-month dual antiplatelet therapy (DAPT) regimen in patients at high bleeding risk (HBR). We evaluated the real-word patterns of indications, DAPT strategies and outcomes for the PF-BES following this evidence.

Methods and Results

CHANCE is a multicenter registry including all patients who underwent percutaneous coronary intervention (PCI) with at least one PF-BES. Reasons for PF-BES PCI and planned antithrombotic regimens were collected. Primary outcomes were the 390-day Kaplan Meier estimates of a patient-oriented and a device-oriented composite endpoints (POCE: death, myocardial infarction [MI] or target vessel revascularization [TVR]; DOCE: cardiac death, target vessel-MI or ischemia-driven target lesion revascularization [ID-TLR]).

Between January 2016 and July 2018, 858 patients (age: 74 ±10 years, 64.6% males, 58.7% acute coronary syndrome presentation) underwent PF-BES PCI. Main reasons for PF-BES physician's choice 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 incident estimate 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 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 mostly used in HBR patients, frequently followed by very-short DAPT regimen. The reported outcomes suggest a favorable safety

and efficacy profile for the PF-BES in a real-world clinical setting. (ClinicalTrials.gov identifier: NCT03622203)

CLASSIFICATIONS

Drug eluting stent, polymer-free biolimus-eluting stent, dual antiplatelet therapy, bleeding

CONDENSED ABSTRACT

CHANCE is the first registry to investigate real-world use of the PF-BES following demonstration of its favorable clinical profile in patients at high bleeding risk when combined with 1-month DAPT, an evidence currently lacking for any other drug-eluting stent. We found that PF-BES preference reflected in most cases the operator-perceived high bleeding risk of the patient, that a 1-month DAPT strategy was frequently implemented, and that PF-BES was associated with a favorable safety and efficacy profile across a wide range or real-world patients. Future studies should provide direct comparative evidence of the PF-BES performance in respect to other new-generation DESs across different patient subsets.

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
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

ID-TLR: ischemia-driven target lesion revascularization

TVR: target vessel revascularization

INTRODUCTION

Successfully developed to overcome the high rates of bare metal stent (BMS) restenosis, drug-eluting stent (DES) initially faced 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 partly caused by the persistence of the polymer coating, which may triggers chronic inflammation compromising arterial healing in the treated coronary segment [3–5].

The BioFreedom stent (BioFreedom™, 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 a month [6]. The absence of a polymer-coat 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 DESs [1,7,8].

While the safety of early dual antiplatelet therapy (DAPT) cessation with polymer-coated DES is still a matter of debate [9], the large scale LEADERS-FREE trial established the favourable clinical profile of the PF-BES when used with a 1-month DAPT strategy in high bleeding risk (HBR) patients [10]. This evidence, along with current guidance recommending BMS avoidance across any clinical scenario [11,12], might have favoured the operator choice for PF-BES in patients with high risk for bleeding, a constantly growing subset of patients requiring percutaneous coronary intervention (PCI) [13]. However, most of the features related to risk of bleedings like diabetes mellitus or renal failure increase in parallel incidence of restenosis and of ST, stressing the need of data from a real-world scenario which is currently limited to a single all-comers, enrolling most patients before LEADERS FREE trial publication [14]. Thus, no data exists on the contemporary indications and outcomes for the PF-BES following demonstration of the safety of a 1-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 multicenter 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. All patients gave written informed consent before the procedure, and all studies were performed in compliance with the Declaration of Helsinki.

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 revascularization [TVR]) and of the device-oriented composite endpoint (DOCE: a composite of cardiac death, TV-MI, and ischemia-driven target lesion revascularization [ID-TLR]). Other outcomes included the cumulative incidence at 390 days of ST, any bleeding (defined according to the Bleeding Academic Research Consortium [BARC] definition),

BARC 3-5 bleedings, and the individual components of the composite endpoints. Indexes of technical procedural success were also evaluated. Endpoint definitions and statistical methods are detailed in the **Online Supplementary Material**.

RESULTS

Study population

Between January 2016 and April 2018, 858 patients were enrolled across 10 Italian sites. **Table 1** presents the baseline characteristics of included patients. Mean age was 74 ±10 years, 64.6% of patients were males. At admission, 26.5% of patients were on OAC, 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 ACS and 41.3% with 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%), anemia (7.9%), recent bleeding (7.0%), expected low compliance to DAPT (1.7%), thrombocytopenia (1.0%), severe liver disease (1.0%), severely impaired renal function (1.0%), recent stroke (0.8%) and glucocorticoids or non-steroidal anti-inflammatory drugs chronic treatment (0.3%). Overall, the operator choice to implant a PF-BES reflected a perceived high bleeding risk or need for a short DAPT regimen in 77.7% of the population, as defined by the presence of at least one inclusion criteria of the LEADERS FREE trial [10].

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 1127 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 ACC/AHA type C features, 13.0% were severely calcified, and19.7% were bifurcation. Pre-dilation 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**. Aspirin and P2Y12 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 1-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 1-month.

Clinical outcomes

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

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 follow: POCE 13.1% (any MI 3.7%, any TVR 3.4%), DOCE 7.1% (TV-MI 3.6%, ID-TLR 1.4%), while 390-day any ST estimate was 0.9%. 390-day estimate of the any bleeding outcome was 11.1% (BARC 3-5 bleeding 3.0%).

Supplementary Tables 1S to 3S 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 **Tables 3S** and **4S** (Supplementary material).

In patients with ACS as compared to SCAD presentation, a potent P2Y12 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 (**Table 5S**, supplementary material).

Clinical outcomes stratified by clinical presentation are reported in **Figure 2** and **Table 6S** (supplementary material). Patients presenting with an ACS had a higher 390-day estimated incidence of the POCE endpoint, also after adjustment for confounding variables (ACS vs. SCAD: 16.7% vs 8.1%, log-rank=0.002; adj-HR 1.69 [1.01-2.82]), while no difference in 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-day for ACS vs. SCAD patients were 1.3% and 0.3% (p=0.193).

DISCUSSION

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 (1-month) DAPT regimen. CHANCE is the first registry providing insights on real-world patterns of

indications, DAPT strategies and outcomes for the PF-BES, following LEADERS-FREE trial publication. The main findings of this study can be summarized as follow (**Figure 1**):

1) In a large, contemporary all-comers registry, the main reasons for PF-BES use reflected in most cases the operator-perceived high bleeding risk 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) The cardiovascular outcomes observed in CHANCE despite the high-risk features of the study population suggest a favorable safety and efficacy profile for the PF-BES in the real-world clinical setting.

The ongoing evolution of coronary stents have led to thinner struts and more biocompatible polymers, (compared to first generation) in order to decrease the risk of vascular injury which increases inflammation and to improve the stent endothelization which is inversely related to neo-atherosclerosis and thrombosis

While polymer free stents, although promising, did not clearly showed a clinical benefit, .recently, ultrathin strut DES have been introduced and a meta-analysis of RCTs on this topis showed a reduction of target lesion failure compared to first generation[15,16]. I

Biolimus is a sirolimus derivative with potent antiproliferative properties consistently proven to inhibit neointimal hyperplasia when applied together with biodegradable polymer coating technologies[17-22]. 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 [6].

Although no powered comparative evidence of clinical outcomes with the PF-BES versus polymer-coated DESs is available, there is initial promise of improved reduction of late intimal proliferation and local inflammation with the PF-BES [5,6,8]. The favorable clinical

counterpart of these biological phenomena has been suggested by the RUDI FREE all-comers registry of patients undergoing PF-BES in real-word practice [14]. In this study, mainly comprising patients with non-HBR features (83.7%), the PF-BES was associated with a high 1-year safety and efficacy performance, with outcomes in the lower range of cardiovascular adverse event rates observed with contemporary new-generation DES, as reported by the ESC/EAPCI Task Force for coronary stent evaluation[23,24] . Regarding the comparison in particular with ultrathin stents, rates of TLR (about 2% at 1 year) and of ST (about 1% at 1 year) in our registry were similar to those of BIORESORT trial, which however enrolled fewer patients with high risk lesions like unprotected left main[25-27].

Concurrently, the LEADERS FREE trial, comparing PF-BES with BMS in HBR patients followed by 1-month DAPT, demonstrated superior safety and efficacy in this setting with this new technology [10]. No such evidence currently exists for any other commercially available DES, hampering evidence-based recommendation on a 1-month DAPT strategy in HBR patients undergoing non-PF-BES DES-PCI. This recognition may have favored the implementation of PF-BES across real-world cath-labs with a specific indication for patients with adherence restraints, such as HBR ones.

Of note, a prospective randomized comparison of the Biofreedom PF-BES with the Resolute Onyx Zotarolimus-Eluting Stent (Medtronic, Minneapolis, Minnesota, USA) followed by 1-month DAPT in HBR patients (Onyx ONE trial, NCT03344653) and a comparison of different DAPT durations (1 vs >1-month) following Ultimaster biodegradable-polymer sirolimus-eluting stent (Terumo, Tokyo, Japan) 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-word 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 RUDI-FREE study and despite 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 1-month planned DAPT rates as compared to RUDI-FREE (40.3% vs 4.9% 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 in 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 randomized controlled trials evaluating DESs in patients with HBR features [10,28,29], showing only slightly higher all-cause mortality and BARC bleeding rates than CHANCE (**Table 5**, columns one to three).

As high bleeding predictors largely overlap with risk factors for ischemic complications, high bleeding risk per se is an overall marker of the ischemic risk. 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 ischemic risk of the CHANCE population. This notwithstanding, 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 randomized controlled trial of well-selected non-HBR patients undergoing contemporary DES PCI reported by the ESC/EAPCI Task Force for coronary stent evaluation [25.] (**Table 5**, far right column). Conversely, the efficacy endpoint of TLR was well below the median reference value of the same analysis, possibly reflecting the optimal anti-restenotic 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 4 weeks [6].

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 (**Table 5**). This finding, suggesting a favorable 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. In this sense, a recent propensity-match analysis comparing RUDI-FREE with patients undergoing implantation of a new polymer-free Cre8 amphilimus-eluting stents in a real-life setting, showed comparable efficacy of the two devices .

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, and 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 incidence observed in our study are anyhow reassuring regarding the favorable 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. This notwithstanding, indirect comparison of the PF-BES outcomes of both our high-risk and a more benign population [14] with new-generation DESs in either HBR or non-HBR settings (**Table 5**), suggest the performance of PF-BES to be 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 patients with a HBR, often followed by a very-short DAPT strategy. The outcomes observed in this registry, in the context of previously available data, suggest a favorable safety and efficacy profile for the PF-BES across a wide range or real-world patients.

IMPACT ON DAILY PRACTICE

A new polymer-free biolimus-A9-eluting stent (PF-BES) showed a favorable clinical profile in a large clinical trial, when used with a 1-month dual antiplatelet therapy (DAPT) regimen in patients at high bleeding risk (HBR). Our results show that the PF-BES is associated with a favorable safety and efficacy profile across a wide range or real-world patients, also when a very short (1-month) DAPT duration is deemed necessary by the treating physician.

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FIGURE LEGENDS

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**). The observed cardiovascular outcomes, despite the baseline high-risk features, suggest a favorable safety and efficacy profile for the PF-BES in this all-comers real-world population (**BOTTOM**).

Reported reasons are not mutually exclusive. Abbreviations as in Tables 1 and 3.

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

Abbreviations as in Tables 1 and 3.

TABLES

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

Age (years)	74 ± 10 (n=858)
Male	554/858 (64.6)
Smoke	
Prior smoker	217/856 (25.4)
Current smoker	67/856 (7.8)
Arterial hypertension	693/856 (81.0)
Dyslipidemia	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)
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 ischemia 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; AF, atrial fibrillation; ASA, acetylsalicylic acid; CABG, coronary artery bypass graft; eGFR, estimated glomerular filtration rate; FU, follow-up; ID, insulin-dependent; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; SCAD, stable coronary artery disease; STEMI, ST-elevation myocardial infarction; VTE, venous thromboembolism; VKA, Vitamin K antagonists.

Table 2. Lesions (n=1127) 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=1127)	
Treated vessel	
Left main trunk	61/1123 (5.4)
Left anterior descending artery	476/1123 (42.4)
Left circumflex artery	274/1123 (24.4)
Right coronary artery	303/1127 (27.0)
Other	9/1123 (0.9)
Bifurcation lesion	222/1127 (19.7)
AHA/ACC C type lesion	434/1120 (38.8)
Severely calcified lesion	147/1127 (13.0)
Number of stents per lesion	1.03±0.19 (n=1126)
Max stent diameter per lesion	3.14±0.70 (n=1021)
Total stent length per lesion	20.92±8.43 (n=1021)
Pre-dilation	912/1119 (81.5)
Post-dilation	802/1119 (71.6)
Rotablation	23/1120 (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 lesions (%) or mean ± standard deviation.
AHA/ACC, American Heart Association/American College of Cardiology.

Table 3. Antithrombotic therapy at discharge

ASA	822/824 (99.8)
P2Y12 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 (%). *All patients discharged on OAC plus SAPT regimen

DAPT, dual antiplatelet therapy; NOAC, new oral anticoagulant; OAC, oral anticoagulant. Other abbreviations as in Table 1.

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 grade 3-5 bleeding	14/768 (1.8)	21/645 (3.3)	20 (3.0)

Values are expressed as n/N of patients (%), or n (%). * Rates derived from the Kaplan-Meier analysis.
BARC, Bleeding Academic Research Consortium; DOCE, device-oriented composite endpoint; ID, ischemia-driven; POCE, patient-oriented composite endpoint; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization. Other abbreviations as in Table 1.

Table 5. 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 [10]	**ZEUS-HBR** [22]	**SENIOR** [23]	**HBR trials pooled** [26]	**CHANCE**	**RUDI-FREE** [14]	**EAPCI report** [21]
Study type	RCT	RCT subanalysis	RCT	Meta-analysis	Real-word registry	Real-word 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-month		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 grade 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 to CHANCE column); real-world outcomes following PF-BES (right to 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 DESs RCT populations. The favourable cardiovascular outcomes despite these features

observed in CHANCE may reflect the favourable clinical profile of the PF-BES in a contemporary real-world setting. *Refer to the original publications [10,22,23] for the specific HBR inclusion criteria of each RCT.

HBR, high bleeding risk; NA, not available; PF-BES, polymer-free biolimus-eluting stent; RCT, randomized controlled trial. Other abbreviations as in Table 1 and 3.

Figure 1

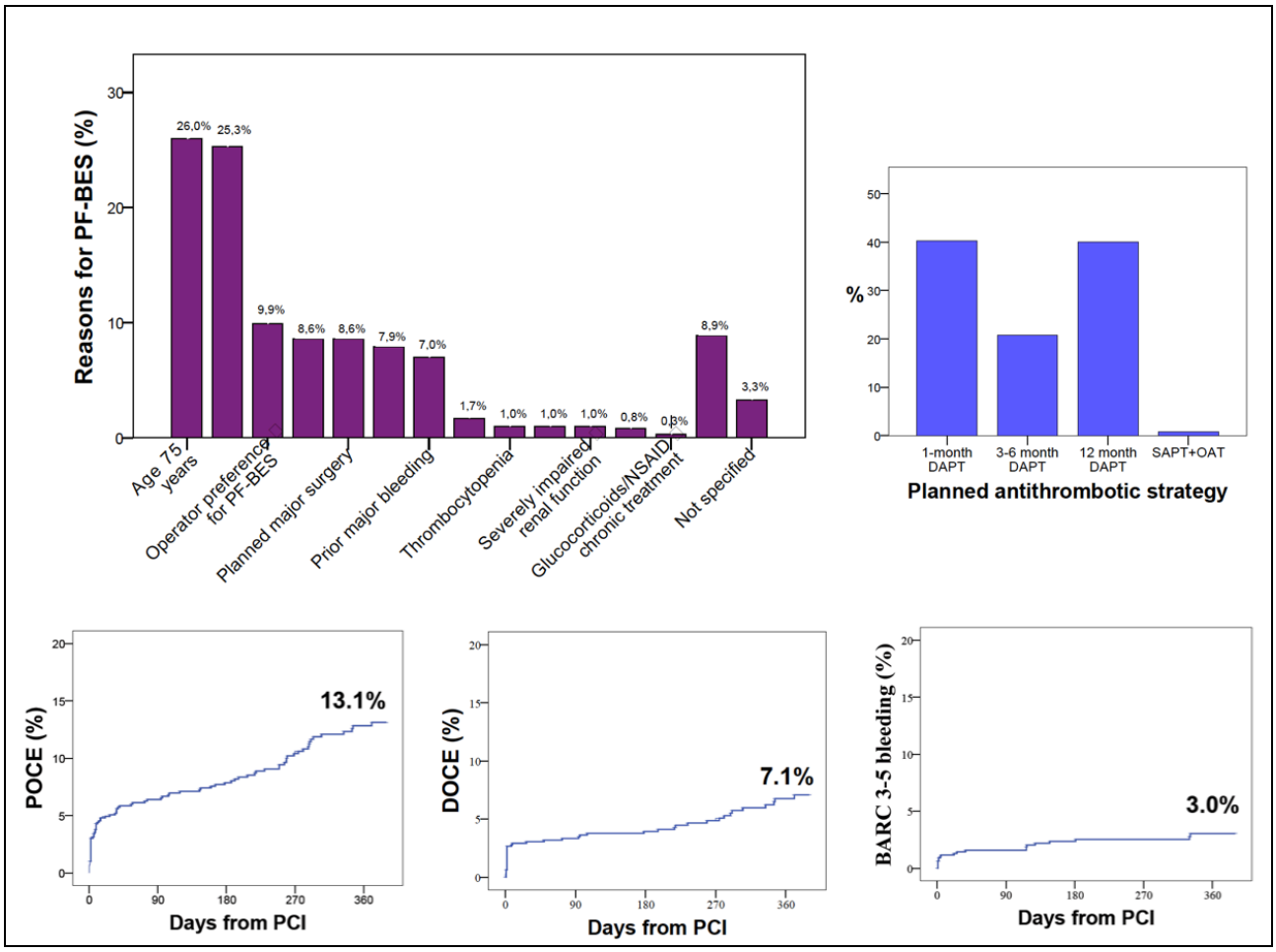
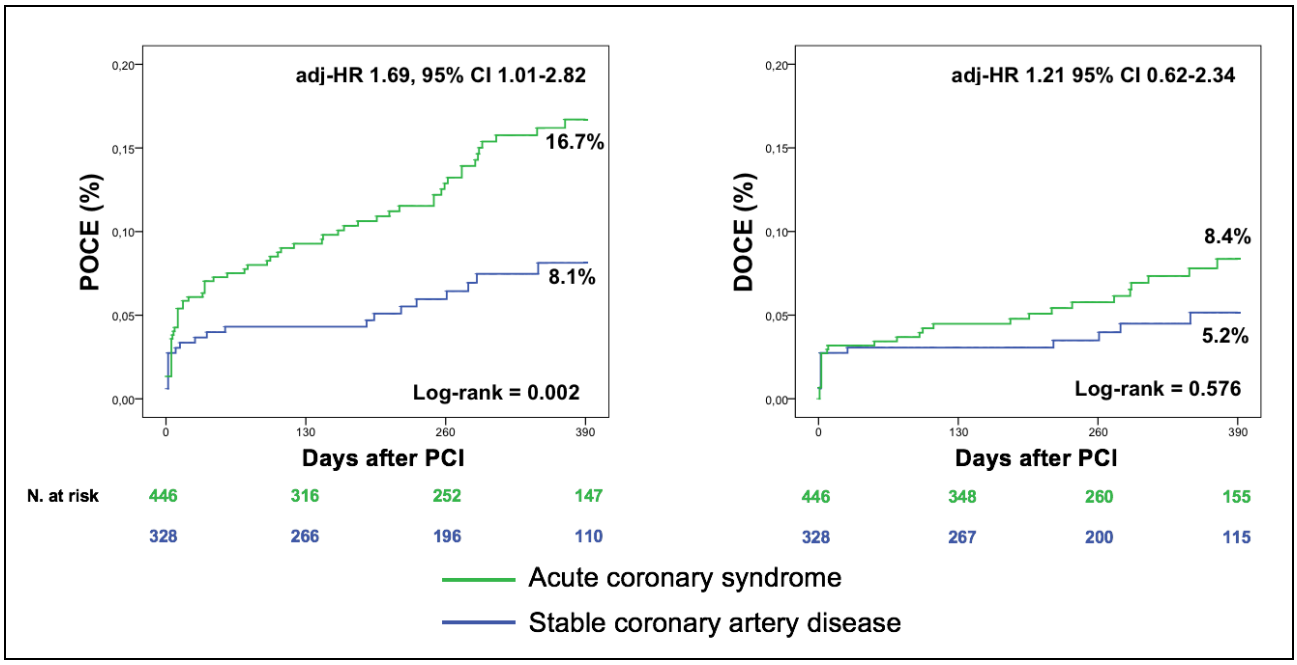

Reasons for PF-BES (%)
26,0%
25,3%
9,9%
8,6%
8,6%
7,9%
7,0%
1,7%
1,0%
1,0%
1,0%
0,8%
0,3%
8,9%
3,3%
Age 75 years
Operator preference for PF-BES
Planned major surgery
Prior major bleeding
Thrombocytopenia
Severely impaired renal function
Glucocorticoids/NSAID chronic treatment
Not specified
%
1-month DAPT
3-6 month DAPT
12 month DAPT
SAPT+OAT
Planned antithrombotic strategy
POCE (%)
13.1%
Days from PCI
DOCE (%)
7.1%
Days from PCI
BARC 3-5 bleeding (%)
3.0%
Days from PCI

Figure 2


adj-HR 1.69, 95% CI 1.01-2.82
16.7%
8.1%
Log-rank = 0.002
POCE (%)
0,20
0,15
0,10
0,05
0,00
0
130
260
390
Days after PCI
adj-HR 1.21 95% CI 0.62-2.34
8.4%
5.2%
Log-rank = 0.576
DOCE (%)
Days after PCI
N. at risk
446 316 252 147
328 266 196 110
446 348 260 155
328 267 200 115
Acute coronary syndrome
Stable coronary artery disease

APPENDIX

COLLABORATORS

Enrico Cerrato[1] MD, Mauro Pennone[2] MD, Fabrizio Ugo[3] MD, Pierluigi Omedè[2] MD, Roberto Adriano Latini[4] MD, Maurizio D'Urbano[5] MD, Antonio Montefusco[1] MD, Andrea Montabone[3] MD, Gaetano Senatore[6] MD, Erika Ferrara[7] MD, Mauro Rinaldi[8] Prof, Maurizio D'Amico[1] MD.

1 Department of Cardiology, Infermi Hospital, Rivoli
2 Division of Cardiology, Department of Internal Medicine, Città della Salute e della Scienza, Torino
3 Division of Cardiology, San Giovanni Bosco, Torino
4 U.O.C. Cardiologia, Ospedale Fatebenefratelli, ASST Fatebenefratelli/Sacco, Milano
5 U.O.C. Cardiologia, Ospedale di Magenta, ASST Milanese Ovest
6 Division of Cardiology, Ospedale Civile, Ciriè
7 U.O.C. Cardiologia, Ospedale di Legnano, ASST Milanese Ovest
8 Division of Cardiac Surgery, Città della Salute e della Scienza, Torino