Comparative Effectiveness and Safety of Polymer-Free Biolimus-Eluting Stent and Durable Polymer Everolimus-Eluting Stent in All-Comer Patients Undergoing Percutaneous Coronary Interventions

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Running head: ***PF-BES vs DP-EES in a real-world setting***

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DISCLOSURES

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

ABSTRACT

We aim to compare Polymer-Free Biolimus-Eluting Stent (PF-BES) with Durable Polymer-Everolimus-Eluting stent (DP-EES) in unselected patients. PF-BES showed a favorable profile in high bleeding risk patients undergoing PCI. Limited data are available on PF-BES compared with second generation durable polymer-coated drug-eluting stents in patients eligible for standard dual antiplatelet therapy. A total of 848 consecutive patients were enrolled: 306 patients were treated with PF-BES and 542 with DP-EES. Stent performance was tested in a propensity score-matched population and in a CHIP (Complex Higher-Risk and Indicated Patients) subpopulation. A per-lesion analysis on 1204 lesions (PF-BES= 424 vs DP-EES=780) was also performed. At a medium follow-up of 18.5±5.0 months, no differences in the matched population were found in terms of major adverse cardiac events (PF-BES 9.0% vs DP-EES 4.5%; p 0.091), myocardial infarction (PF-BES 6.2% vs DP-EES 2.3%; p 0.111), stent restenosis (PF-BES 2.3% vs DP-EES 0.0%; p 0.123), definite or probable stent thrombosis (PF-BES 2.8% vs DP-EES 1.1%; p 0.448). A significant inferior rate of restenosis was observed in the DP-EES arm in the whole (PF-BES 2.3% vs DP-EES 0.6%; p 0.041) and CHIP populations (PF-BES 4.3% vs DP-EES 0.5%; p 0.023), as well as in the per-lesion analysis (DP-EES 0.4% vs PF-BES 1.7%; p 0.039). In conclusion, in a real-world cohort PF-BES performed similarly to DP-EES in terms of restenosis and stent thrombosis in the matched population. Nonetheless, in the whole and CHIP populations, as well as in the per-lesion analysis, restenosis occurrence resulted higher in the PF-BES group.

KEYWORDS

Polymer-free biolimus-eluting stent; Durable polymer everolimus-eluting stent; Percutaneous Coronary Intervention; Coronary Artery Disease; Stent thrombosis.

TEXT

Drug-eluting stents (DES), firstly made of a metal platform and a durable polymer, have improved clinical outcomes of patients undergoing percutaneous coronary interventions (PCI) through a significant reduction of restenosis and revascularizations, as compared to bare metal stents (BMS) (1,2). However, first-generation DES raised a concern about late stent thrombosis (ST) and justified a longer dual antiplatelet therapy (DAPT) (3-5). The durable polymer (DP) coating has been addressed as one possible cause of delayed arterial healing, chronic inflammation, and impaired endothelialization of the struts (6-8). Second generation DP-DES, with a more favourable biocompatibility, have been shown to reduce the risk of thrombotic events (9). Among these new devices, DP everolimus-eluting stent (DP-EES) demonstrated an excellent safety and efficacy profile and is regarded as the "best in class" (5,10,11).

Evolving technology, through the intermediate step of biodegradable polymers, led nowadays to the introduction of a polymer-free biolimus-eluting stent (PF-BES). This device consists in a stainless steel platform from which the antirestenotic agent is directly released over a period of approximately 1 month without the need for a polymeric carrier; the stent has been thought for high bleeding risk (HBR) patients not compliant with long-term DAPT (12). In the large-scale LEADERS FREE study PF-BES showed to be safer and more effective than BMS in HBR patients treated with 1 month DAPT (13). Limited data are conversely available on the clinical outcomes of PF-BES in comparison with second generation DP-DES in all-comer patients. Aim of this study was to compare PF-BES and DP-EES in a prospective, all-comers, single center registry; stent performance was also tested in the Complex Higher-Risk and Indicated Patients (CHIP) population.

METHODS

All consecutive patients who underwent PCI with implantation of PF-BES (BioFreedom stent, Biosensors Europe SA, Morges, Switzerland) or DP-EES (Xience, Abbott Vascular, Santa Clara, CA, USA) at the coronary intervention center of Pineta Grande Hospital between June 2015 and November 2016 were enrolled in this prospective, single-center registry. All enrolled patients provided a written informed consent and the work has been carried out in accordance with the Declaration of Helsinki.

Exclusion criteria were admission diagnosis of ST-segment elevation myocardial infarction (STEMI), cardiogenic shock at presentation, cardiac arrest at presentation, DAPT prescription at discharge for less than 1 year, treatment of the same lesion with different stent types, age younger than 18 years old; no restrictions related to number, location, size and length of both the treated lesions and implanted stents were settled. The above mentioned criteria were matched by 896 patients; the patients treated with implantation of both DP-EES and PF-BES (48 patients) during the index hospital stay were excluded from the patients level analysis. A total of 306 patients who received one or more PF-BES during the index procedure and the subsequent hospital stay constituted the PF-BES group, while 542 patients treated with one or more DP-EES implantation the DP-EES group. The per-lesion analysis was performed on a total of 1204 coronary de novo and saphenous vein graft (SVG) lesions from 896 patients treated with either one or more PF-BES or DP-EES. Basal clinical, angiographic and follow up data were collected into a dedicated registry.

The DP-EES is a cobalt-chromium alloy stent coated with a nonadhesive, durable, biocompatible fluoropolymer loaded with the antiproliferative drug everolimus. The thickness of the metallic struts and coating combined is approximately 90 μm (81 μm for the stent and 7.8 μm for the polymer). The PF-BES consists in a stainless-steel platform, with a strut thickness of 112 μm. The stent is characterized by a modified microstructured abluminal surface, that allows adhesion of the antiproliferative agent biolimus A9 (a highly lipophilic sirolimus analog) without the use of a polymer coating. As for release kinetics, approximately 90% of biolimus A9 is released from the stent to the vessel wall during the first 48 hours after implantation, while the remaining during the following 28 days. By leaving a bare metal stent luminal surface, it promotes rapid re-endothelization and improves the healing process, allowing for ultra-short 1 month DAPT.

All interventions were performed according to the standard clinical guidelines at the moment of enrollment; the decision to use a specific stent type was left to the interventional cardiologist. In absence of contraindications, DAPT regimen was based on aspirin and an oral P2Y12 inhibitor: clopidogrel, prasugrel or ticagrelor based on patients' clinical presentation and physicians' preference. Use of GP

IIb/IIIa receptor inhibitors was at the operators' discretion. At the moment of discharge DAPT was recommended for at least 1 year and aspirin lifelong, if not contraindicated.

Due to the observatory nature of the study no preliminary hypotheses were generated. The clinical endpoints of the study were: major adverse cardiac events (MACE), defined as a composite of death/acute myocardial infarction (AMI)/target vessel revascularization (TVR)/target lesion revascularization (TLR)/stent restenosis/definite or probable ST (14); cardiovascular (CV) MACE, defined as a composite of CV death/AMI/TVR/TLR/stent restenosis/definite or probable ST; death, intended as all cause death; CV death, defined as any death of cardiac origin; AMI, defined according to the Fourth Universal Definition of Myocardial Infarction (15); TVR, defined as any repeated revascularization procedure (PCI or surgical bypass) performed on the target vessel (14); TLR, defined as any repeated revascularization procedure (PCI or surgical bypass) performed on the target lesion (14); stent restenosis, defined as >50% luminal loss at the segment site (stent and 5 mm proximal and distal) that was demonstrated angiographically (14); definite or probable ST, assessed according to the definition of the Academic Research Consortium (ARC) (16); stent failure, defined as a composite of stent restenosis/definite or probable ST (17).

Complex PCI was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length >60 mm, chronic total occlusion (CTO) (18).

The CHIP population identify a subgroup of patients at both high ischemic and high surgical/interventional risk including patients with at least one of the following clinical or angiographic characteristics: age >85 years, previous Coronary Artery Bypass Graft (CABG) surgery, previous stroke, severe chronic kidney disease (CKD) (eGFR<30 ml/min), carotid artery disease, left main coronary artery (LMA) or SVG disease, CTO lesions, calcified and complex bifurcated lesions (19).

Each enrolled patient was included in a prospectively designed data collection scheme. The database was built up by Excel software (Microsoft Corporation, Redmond, Washington, USA); data were analyzed by STATA MP15 software (StataCorp LLC, College Station, Texas, USA). Continuous

variables were described as means±standard deviations and ranges, categorical variables as numbers with percentages. For continuous variables the normality analysis was performed and, where consistent, a normalization model was set. Normal and normalized continuous variables were compared by student's T test for independent data (parametric); the non-normalizable continuous variables were compared by Wilcoxon Rank-Sum test (non-parametric). The categorical variables were compared by Chi-square test or Fisher exact test, in case of small sample. For each of the following outcomes - stent failure, AMI, CV MACE - the association with gender, age, arterial hypertension, diabetes mellitus, previous AMI, previous stroke, severe CKD, acute coronary syndrome (ACS) at presentation, multivessel PCI, complex PCI, total stent length, minimum stent diameter, average stent diameter, bifurcations treated with 2-stents technique strategy has been tested with an univariate linear regression model; the Odd Ratio (OR) values were calculated with CI 95% and test Z score. For each of the previous outcomes a multivariate linear regression model was built, using as determinants the parameters associated with the single outcome in the simple linear regression. The adjusted Odd Ratio (aOR) values were calculated with CI 95% and test Z score. Chi-square was used to determine the goodness of fit test of the regression models. Because of the non-randomized nature of the study, Propensity Score (PS) analysis was then used to adjust for differences in patients' baseline and angiographic/procedural characteristics, balancing them for age, gender, diabetes mellitus, arterial hypertension, dyslipidemia, severe CKD, smoking habit, previous stroke, previous AMI, previous myocardial revascularization, ACS at presentation, left anterior descending artery (LAD) lesion, LMA lesion, number of stents per patient, total stent length per patient, average stent diameter, multivessel PCI, complex PCI. The 1:1 nearest neighbor matching without replacement method was used, performed by STATA MP15 software. For all tests significance was set for a 2-tailed value of $p<0.05$.

RESULTS

DP-EES group and PF-BES group included 542 and 306 patients respectively. Mean age of the whole population was 65.9±10.6 years; baseline clinical characteristics of patients, globally intended and by groups, are described in Table 1. Patients treated with DP-EES were older, more frequently presented

with ACS, and had higher prevalence of previous AMI and previous myocardial revascularization; PF-BES group conversely showed higher prevalence of arterial hypertension and dyslipidemia. Angiographic and procedural characteristics are described in Table 1 and differ between groups in terms of target vessel vascularization and of number and length of per-patient stents deployment.

Discharge therapy is shown in Table I in the Supplementary Data: in terms of DAPT the use of the "new" and more potent oral $P2Y_{12}$ inhibitor (Ticagrelor or Prasugrel) was more frequent in the DP-EES group, while treatment with Clopidogrel in the PF-BES group.

After PS matching a population of 354 patients was selected (Figure I in the Supplementary Data); baseline clinical and angiographic/procedural characteristics, as well as discharge therapy information, are shown in Table 2 and Table II in the Supplementary Data. Moreover, using the CHIP criteria, a subpopulation of 325 patients was detected; CHIP patients resulted equally distributed between the 2 groups: 209 in the DP-EES and 116 in the PF-BES group (38.6% vs 37.9%, p 0.851).

The lesion-level comparison was performed on 1204 lesions: 780 lesions were treated with DP-EES and 424 with PF-BES (Figure II in the Supplementary Data). Angiographic and procedural characteristics of the treated lesions are described in Table 3. The PF-BES group had a higher number of longer, bifurcated and LAD located lesions, while lesions treated with DP-EES were more often heavily calcified and located in the right coronary artery (RCA). PF-BES treated lesions were also characterized by a lower number of stents per lesion and a lower postdilation rate. As shown in Table III in the Supplementary Data, the 24 LMA lesions were prevalently treated with DP-EES; when the bifurcation was involved provisional stenting was the prevalent strategy and the final kissing balloon was basically reserved to the procedures in which 2 stents were deployed, the setting in which was recently proved to be maximally beneficial (20).

The medium follow-up was 18.5±5.0 months. Adherence to DAPT therapy was similar in the 2 groups: at 1 year DAPT was ongoing in the 92.8% and 91.5% of patients in the DP-EES and PF-BES group respectively (Table IV in the Supplementary Data). Similar results were also found in the PS-matched population (92.1% vs 91.5%, p 0.846) (Table V in the Supplementary Data).

The clinical outcomes of the unmatched population, the PS-matched population, and the CHIP subpopulation are summarized in Table 4. No statistically significant differences between the 2 arms in all the analyzed populations were found in terms of MACE, CV MACE, death, CV death, AMI. Nonetheless, in divergence with the results of the unmatched and CHIP population, the differences between the 2 groups in the propensity matching analysis in terms of MACE (4.5% vs 9.0%, p 0.091) nearly approach statistical significance. In addition, it seems noteworthy to highlight that the rate of MACE and CV MACE in the CHIP subpopulation is higher than in the total population, in agreement with the higher risk profile of these patients. Divergently from the above-mentioned clinical endpoints, significant differences in terms of TVR and TLR have been detected between the 2 arms in both the unmatched and PS-matched population, as well as in the CHIP subpopulation. In the total population TVR occurred in 16 patients treated with PF-BES and in 5 patients treated with DP-EES (5.2% vs 0.9%, p <0.001), TLR in 15 patients treated with PF-BES and in 5 patients treated with DP-EES (4.9% vs 0.9%, p <0.001); in the PS-matched population TVR and TLR occurred in 8 patients treated with PF-BES, but in none of the DP-EES group (4.5% vs 0.0%, p<0.001). As expected the difference between the 2 groups in terms of TVR and TLR kept significant also in the CHIP subpopulation: 8 subjects treated with PF-BES underwent both TVR and TLR, but only 1 in the DP-EES group (6.9% vs 0.5%, p<0.001). The very low rate of TVR and TLR in the DP-EES can be explained by the large quote of AMI that in the same group did not undergo coronary angiography: among 542 DP-EES patients, out of the 20 patients suffering from AMI during the follow up, only 5 underwent coronary angiography and myocardial revascularization with PCI on the same lesion treated during the index procedure (in 3 cases because of stent restenosis, in 2 cases because of ST). The remaining 15 patients suffered cardiac death due to myocardial infarction (without angiographic confirmation, but recognized with ECG and/or echocardiogram); in particular, 7 deaths occurred within 30 days from the index procedure and were attributed to probable ST. On the other side, in the PF-BES group, among the 18 patients who suffered from AMI, only 2 patients did not undergo coronary angiography, since 1 was medically treated and 1 died before any other procedure

could be performed; in the remaining cases angiography revealed the occurrence of 7 restenoses and 9 thromboses, and all these patients underwent myocardial revascularization.

With reference to device performance endpoints, a significant higher rate of stent restenosis was observed in the PF-BES arm in both the whole population (p 0.041) and the CHIP subgroups (p 0.023). On the other side, stent restenosis in the matched population was not statistically different between groups (p 0.123), nevertheless it deserves to be mentioned that in this selected population no restenosis occurred in the DP-EES (Figure 1). The higher rates of restenosis in PF-BES group drove to a statistically significant difference between the 2 arms in the unmatched population in terms of stent failure (2.2% vs 5.2%, p 0.018). Conversely, the differences between the 2 arms in the PS-matched (1.1% vs 5.1%, p 0.061) and CHIP population (2.9% vs 6.9%, p 0.087) in terms of stent failure, despite reflecting the same trend, only approached threshold for statistical significance. With reference to definite or probable ST the differences between the groups resulted non significant at both 1 month and full length follow up in all the analyzed populations; nevertheless short term definite or probable ST occurred more frequently in the DP-EES group (Figure 2).

In the lesion-level analysis TLR, stent failure, stent restenosis, definite or probable ST were considered. DP-EES and PF-BES, compared on the ground of the single treated lesion, showed significant differences in favor of DP-EES in terms of TLR (p<0.001), stent failure (p 0.014), stent restenosis (p 0.039) (Table 5 and Figure 3).

At the linear regression analysis: diabetes mellitus, severe CKD, total stent length, multivessel PCI, complex PCI resulted predictors of stent failure (Table VI in the Supplementary Data); age, severe CKD, previous AMI, total stent length, complex PCI resulted predictors of AMI (Table VII in the Supplementary Data); age, diabetes mellitus, severe CKD, previous AMI, multivessel PCI, total stent length of CV MACE (Table VIII in the Supplementary Data).

DISCUSSION

This study is, to the best of authors' knowledge, the first report providing a comparison between the performances of DP-EES and PF-BES. To this aim we analyzed the clinical outcomes of both stents in

real-world, all-comer, no HBR patients undergoing PCI; the evaluation was performed in both the whole and PS-matched population. All clinical endpoints were also tested in the CHIP population, that represents a frail, higher risk and enlarging subgroup of patients undergoing PCI (19). The main findings can be summarized as follows:

- in the PS-matched population at a medium follow up time of 18.5±5.0 months DP-EES and PF-BES showed similar efficacy in terms of MACE, CV MACE, death, CV death, AMI;
- stent restenosis in both the whole and CHIP populations showed a significant inferior rate in the DP-EES group as compared to the PF-BES one; in the PS-matched population, despite the same trend was noticed, threshold for significance was not reached;
- definite or probable ST did not differ between the 2 groups in all the studied populations (whole, PS-matched, CHIP);
- in the per lesion-analysis the rate of stent failure was higher in the PF-BES group compared to DP-EES, as it was the stent restenosis rate; differences in terms of definite or probable ST resulted conversely non-significant;
- the analysis of the clinical, angiographic and procedural characteristics of the whole population highlighted that some high risk categories of patients, such as previous AMI or previously revascularized patients, were preferentially treated with DP-EES, probably because of the higher operator confidence in the device.

As stated above, in the PS-matched population no significant differences were detected between patients treated with PF-BES and with DP-EES in terms of clinical outcomes as well as in terms of device performance. Though differences were not statistically significant and the cohort of 354 patients is relatively small, it seems noteworthy to mention the non-occurrence of stent restenosis in the DP-EES group. This advantage reached threshold for significance in both the whole population and CHIP population. Taking into the due account the bias deriving from the non-randomized nature of the analysis, it seems reasonable to explain this difference by the wider populations represented by the whole and CHIP cohorts, and also by the worse risk profile of these patients who present higher likelihood for

adverse events. As a confirmation, in the PS-matched, general and CHIP populations the rates of stent failure are indeed 3.1%, 3.3%, and 4.3% respectively. The CHIP population represents a frail, complex, and higher risk subgroup of patients towards which the interest of the interventional cardiology community is recently growing (19). CHIP patients present severe coronary artery disease (CAD) with clinical indication for complete revascularization, but are poor candidates for both surgical and interventional procedures for the extreme/inoperable surgical risk on the one side and for the demonstrated low success rates and high occurrence of adverse events at follow up on the other side (19,21).

With reference to ST no significant differences in the 3 populations were detected at follow up; nevertheless some considerations appear opportune because ST represents the target of PF-BES use. Over the last decades DES, firstly introduced to overcome the high rates of restenosis of BMS, carried long-term inhibition of neointimal growth and delayed vascular healing (also related to the permanent drug carrier coating) raising concerns about the increased risk of late-ST (1,2,3,4,22). This issue has been addressed by prolonging antithrombotic regimens at the expense of augmented rates of bleedings (23). Despite second-generation DES, as DP-EES, partly mitigated the long-term risk of ST, the need for more biocompatible stents has led to the development of PF-BES (9,11,14,24). The PF-BES "revolution" is mainly based on the idea of eliminating the inflammatory and pro-thrombotic trigger of polymer coatings (25). Despite, as stated above, no differences at the end of the follow up time were detected, it seems noteworthy to highlight a different trend of the definite or probable ST at 1 month in both the PS-matched and CHIP population: in the PS-matched cohort stent thromboses were almost halved in the PF-BES group and the difference in favor of PF-BES was also wider in the CHIP group. This advantage was later on dissipated from the first month to the full follow up period when the absolute occurrence of definite or probable ST was higher in the PF-BES in all the 3 analyzed populations, despite no significant differences were detected. Moreover, in this all-comers registry the 2 stents comparison was not biased by the patients' bleeding risk, so that adherence to DAPT was high and equal in the 2 arms, thus unable to influence ST. The size and non-randomized nature of the study does not allow any speculations on this

topic, nevertheless it is authors' opinion that larger studies with longer follow up should be advocated to clarify if this peculiar and unexpected trend is simply a matter of chance or underlies a different performance over time of PF-BES and DP-EES.

The stent failure, intended as the composite of definite or probable ST and stent restenosis, represents an indicator of the overall stent performance and resulted lower in the DP-EES group in all the 3 populations, with differences between groups very close to significance in both the PS-matched population (p 0.061) and CHIP population (p 0.087), and statistically significant in the whole population (p 0.018). Known as comparable the rates of definite or probable ST at full follow up, this result has been mainly carried by the lower occurrence of restenosis in the DP-EES groups. The lesion-level analysis confirmed a significant higher rate of stent restenosis in the PF-BES group, able to drive a significant difference also in terms of stent failure (p 0.014). These results allow the hypothesis of an inferior efficacy of PF-BES at inhibiting neointimal hyperplasia in the long course; this feature can be hypothetically due to the nature of the device itself that, in the absence of a carrier, provides a shorter drug delivery at the target coronary site.

The present analysis could not avoid certain limitations, associated with its observational nature. First, the non-randomized nature of the registry data would result in selection bias, even though we used a large, prospectively collected dataset from a high volume center. Indeed, we observed differences in baseline clinical and procedural characteristics between the 2 groups in the unmatched population. Although we sought to reduce potential confounding using PS matching analysis, we were not able to correct for the unmeasured variables. Second, the use of PF-BES and DP-EES was at the discretion of the physician. Third, no information about impaired ventricular function or the presence of concomitant valvular heart disease were collected. Eventually, our data could be applied only to patients with stable angina or non-ST-elevation ACS, due to the exclusion of STEMI patients.

As far as authors know, this is the first study comparing PF-BES with DP-EES in a large cohort of consecutive patients eligible for a standard DAPT regimen. Despite the non-significant differences found in the PS matching comparison, the higher rate of stent restenosis in the PF-BES group, as compared to

the DP-EES group, in both the whole and CHIP populations, as well as in the per-lesion analysis, allows to hypothesize a possible different performance over time of the 2 compared devices warranting further investigations.

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FIGURE LEGENDS

Figure 1. ***Stent restenosis****-Comparison between DP-EES and PF-BES in terms of stent restenosis in the propensity matched patients, Complex Higher-Risk and Indicated Patients (CHIP) and whole population.* *CHIP*= Complex Higher-Risk and Indicated Patients; *DP*-EES= Durable Polymer Everolimus-Eluting Stent; *PF-BES*= Polymer-Free Biolimus-Eluting Stent. *p<0.05

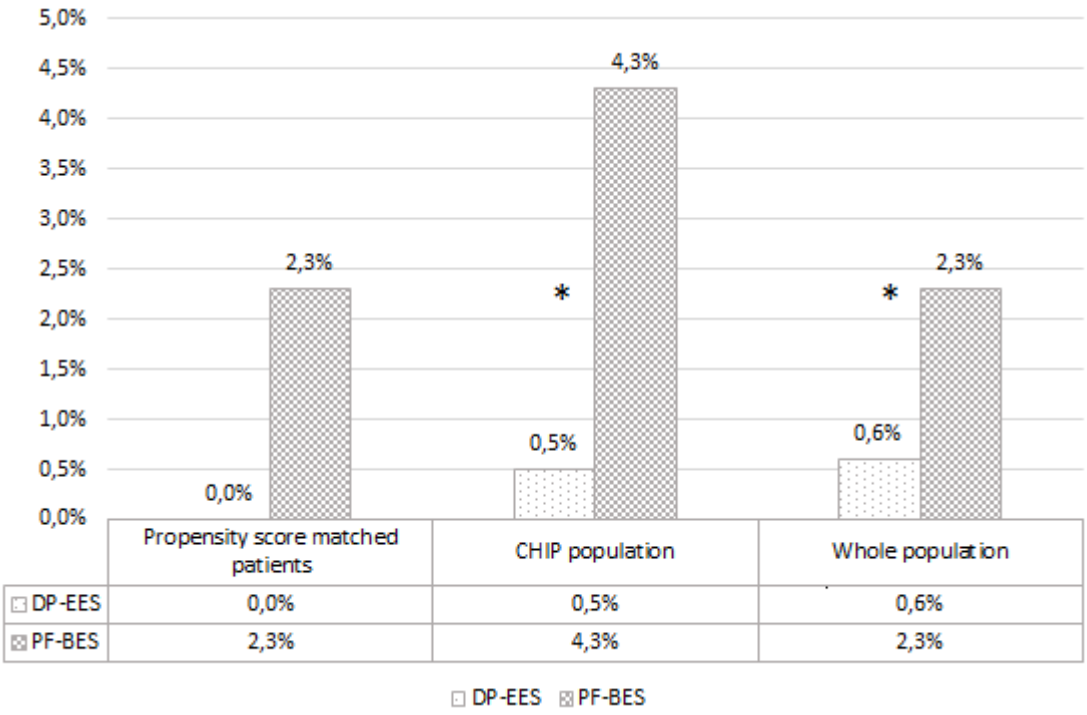

Figure 2. ***Definite or probable stent thrombosis****-Comparison between DP-EES and PF-BES in terms of definite or probable stent thrombosis at 1 month and at follow up time in the propensity matched patients, Complex Higher-Risk and Indicated Patients (CHIP) and whole population. CHIP*= Complex Higher-Risk and Indicated Patients. *DP-EES*= Durable Polymer Everolimus-Eluting Stent; *PF-BES*= Polymer-Free Biolimus-Eluting Stent. †= The medium follow-up was 18.5±5.0 months

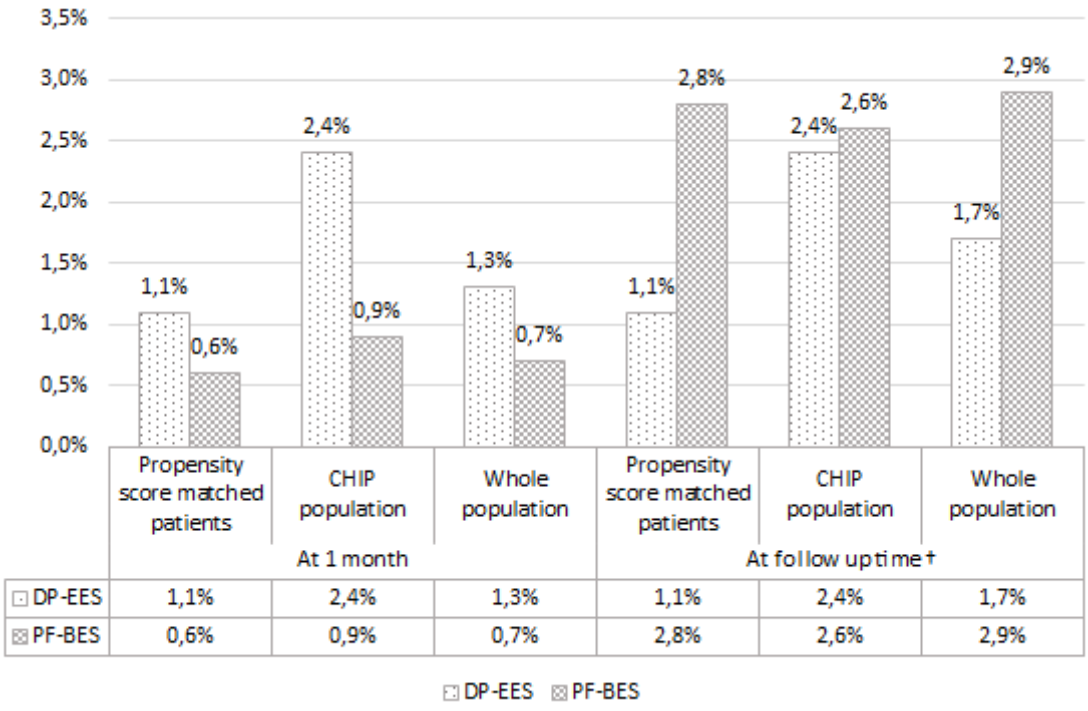

Figure 3. ***Per-lesion clinical outcomes***-*Comparison between DP-EES and PF-BES in terms of stent failure, stent restenosis, definite or probable stent thrombosis at 1 month and at follow up time in the per-lesion analysis*. *DP-EES*= Durable Polymer Everolimus-Eluting Stent; *PF-BES*= Polymer-Free Biolimus-Eluting Stent. *p<0.05

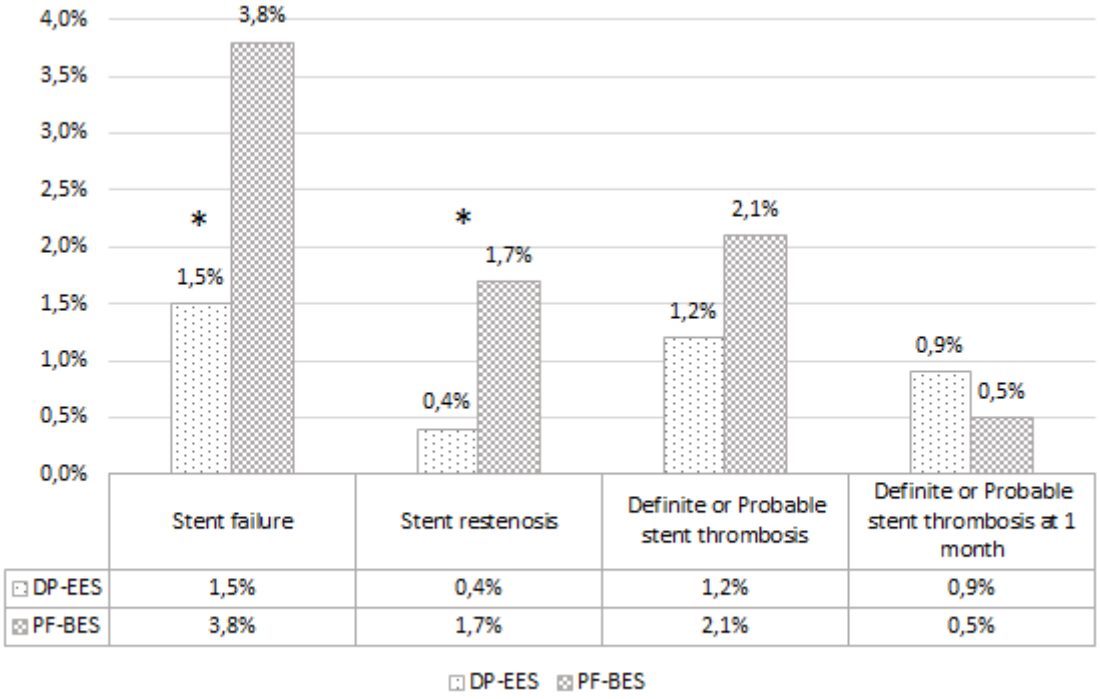

Table 1**. **Baseline, angiographic and procedural characteristics of the whole population.

Variable	***OVERALL*** (n=848)	***DP-EES*** (n=542)	***PF-BES*** (n=306)	***P***
Age (years)	65.9±10.6	66.7±10.4	64.4±10.8	0.001
Male	675 (79.6%)	436 (80.4%)	239 (78.1%)	0.417
Hypertension	671 (79.1%)	412 (76.0%)	259 (84.6%)	0.003
Current smoker	286 (33.7%)	186 (34.3%)	100 (32.7%)	0.628
Dyslipidemia	508 (59.9%)	292 (53.9%)	216 (70.6%)	<0.001
Diabetes mellitus	246 (29.0%)	158 (29.2%)	88 (28.8%)	0.904
eGFR<30 mL/min	46 (5.4%)	33 (6.1%)	13 (4.3%)	0.256
Prior coronary artery disease	140 (16.5%)	86 (15.9%)	54 (17.7%)	0.503
Previous myocardial infarction	252 (29.7%)	174 (32.1%)	78 (25.5%)	0.043
Previous PCI	299 (35.3%)	209 (38.6%)	90 (29.4%)	0.007
Previous Coronary Artery Bypass Graft	74 (8.7%)	61 (11.3%)	13 (4.3%)	0.001
Previous myocardial revascularization	338 (39.9%)	243 (44.8%)	95 (31.1%)	<0.001
Previous stroke	5 (0.6%)	4 (0.7%)	1 (0.3%)	0.659
Acute coronary syndrome	225 (26.5%)	171 (31.6%)	54 (17.7%)	<0.001
CHIP population*	325 (38.3%)	209 (38.6%)	116 (37.9%)	0.851
Number of coronary arteries narrowed				
1	747 (88.1%)	477 (88.0%)	270 (88.2%)	0.922
2	92 (10.9%)	59 (10.9%)	33 (10.8%)	0.964
3	9 (1.0%)	6 (1.1%)	3 (1.0%)	1.000
Number of lesions/patient	1.3±0.6	1.3±0.6	1.3±0.7	0.837
1 lesion PCI	639 (75.4%)	407 (75.2%)	232 (75.8%)	0.814
2 lesions PCI	163 (19.2%)	107 (19.7%)	56 (18.3%)	0.609
3 lesions PCI	37 (4.4%)	24 (4.4%)	13 (4.3%)	0.902
≥4 lesions PCI	9 (1.0%)	4 (0.7%)	5 (1.6%)	0.296

Treated vessel				
Left anterior descending artery	370 (43.6%)	209 (38.6%)	161 (52.6%)	<0.001
Left circumflex artery	269 (31.7%)	172 (31.7%)	97 (31.7%)	0.992
Right coronary artery	273 (32.2%)	204 (37.6%)	69 (22.6%)	<0.001
Left main coronary artery	24 (2.8%)	17 (3.1%)	7 (2.3%)	0.474
Saphenous vein graft	21 (2.5%)	15 (2.8%)	6 (2.0%)	0.468
Number of stents/patient	1.5±0.8	1.5±0.8	1.4±0.8	0.017
Total stent lenght/patient (mm)	30.5±19.7	31.4± 19.3	27.8 ±20.2	0.010
Minimum diameter/patient (mm)	2.76±0.47	2.76±0.49	2.75± 0.45	0.887
Medium diameter/patient (mm)	2.80±0.46	2.80±0.47	2.80±0.45	0.905
Complex PCI †	175 (20.6%)	115 (21.2%)	60 (19.6%)	0.578
3 vessels PCI	9 (1.1%)	6 (1.1%)	3 (1.0%)	1.000
≥3 stents implanted	87 (10.3%)	59 (10.9%)	28 (9.2%)	0.424
≥3 lesions treated	46 (5.4%)	28 (5.1%)	18 (5.9%)	0.658
>60 mm total stent length	27 (3.2%)	21 (3.9%)	6 (2.0%)	0.127
Chronic total occlusions	88 (10.4%)	54 (10.0%)	34 (11.1%)	0.599
Bifurcations treated with 2-stents technique strategy	4 (0.5%)	4 (0.7%)	0 (0.0%)	0.303
Complete revascularization	831 (98.0%)	530 (97.8%)	301 (98.4%)	0.621

**CHIP* (Complex Higher-Risk and Indicated Patients) population included patients with at least one of the following clinical or angiographic characteristics: age >85 years, previous coronary artery bypass graft, previous stroke, severe chronic kidney disease (eGFR<30 ml/min), carotid artery disease, left main coronary artery or saphenous vein graft disease, chronic total occlusion, calcified and complex bifurcated lesions.

†Complex PCI was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length >60 mm, chronic total occlusion.

Table 2. Baseline, angiographic and procedural characteristics of the propensity matched patients.

Variable	***OVERALL*** (n=354)	***DP-EES*** (n=177)	***PF-BES*** (n=177)	***P***
Age (years)	65.85±10.48	65.18±10.40	66.53±10.56	0.322
Male gender	283 (79.9%)	140 (79.1%)	143 (80.9%)	0.690
Hypertension	292 (82.5%)	149 (84.2%)	143 (80.8%)	0.401
Current smoker	117 (33.1%)	55 (31.1%)	62 (35.0%)	0.429
Dyslipidemia	234 (66.1%)	118 (66.7%)	116 (65.5%)	0.822
Diabetes mellitus	99 (28.0%)	46 (26.0%)	53 (29.9%)	0.407
eGFR<30ml/min	14 (4.0%)	5 (2.8%)	9 (5.1%)	0.414
Prior coronary artery disease	56 (15.8%)	28 (15.8%)	28 (15.8%)	1.000
Previous myocardial infarction	86 (24.3%)	44 (24.9%)	42 (23.7%)	0.804
Previous PCI	121 (34.2%)	61 (34.5%)	60 (33.9%)	0.911
Previous coronary artery bypass graft	26 (7.3%)	16 (9.0%)	10 (5.7%)	0.222
Previous myocardial revascularization	133 (37.6%)	69 (39.0%)	64 (36.2%)	0.583
Previous stroke	3 (0.9%)	2 (1.1%)	1 (0.6%)	1.000
Acute coronary syndrome	83 (23.5%)	44 (24.9%)	39 (22.0%)	0.530
Number of coronary arteries narrowed				
1	306 (86.4%)	152 (85.9%)	154 (87.0%)	0.756
2	45 (12.7%)	24 (13.6%)	21 (11.9%)	0.632
3	3 (0.9%)	1 (0.6%)	2 (1.1%)	1.000
Number of lesions/patient	1.3±0.6	1.2±0.5	1.3±0.7	0.202
1 lesion PCI	270 (76.3%)	140 (79.1%)	130 (73.5%)	0.212
2 lesions PCI	62 (17.5%)	30 (17.0%)	32 (18.1%)	0.780
3 lesions PCI	16 (4.5%)	5 (2.8%)	11 (6.2%)	0.200
≥4 lesions PCI	6 (1.7%)	2 (1.1%)	4 (2.3%)	0.685

Treated vessel				
Left anterior descending artery	172 (48.6%)	87 (49.2%)	85 (48.0%)	0.832
Left circumflex artery	124 (35.0%)	63 (35.6%)	61 (34.5%)	0.824
Right coronary artery	88 (24.9%)	43 (24.3%)	45 (25.4%)	0.806
Left *main* coronary artery	11 (3.1%)	7 (4.0%)	4 (2.3%)	0.542
Saphenous vein graft	7 (2.0%)	3 (1.7%)	4 (2.3%)	1.000
Number of stents/patient	1.45±0.79	1.44±0.77	1.47±0.81	0.886
Total stent lenght/patient (mm)	29.6±20.8	29.6±19.8	29.6±20.3	0.798
Minimum diameter/patient (mm)	2.74±0.47	2.75± 0.48	2.75±0.47	0.915
Medium diameter/patient (mm)	2.78±0.47	2.76±0.45	2.79±0.47	0.374
Complex PCI*	74 (20.9%)	36 (20.3%)	38 (21.5%)	0.794
3 vessels PCI	3 (0.9%)	1 (0.6%)	2 (1.1%)	1.000
≥3 stents implanted	38 (10.7%)	18 (10.2%)	20 (11.3%)	0.731
≥3 lesions treated	22 (6.2%)	7 (4.0%)	15 (8.4%)	0.078
>60 mm total stent length	10 (2.8%)	7 (4.0%)	3 (1.7%)	0.337
Chronic total occlusions	36 (10.2%)	18 (10.2%)	18 (10.2%)	1.000
Bifurcations treated with 2-stents technique strategy	1 (0.3%)	1 (0.6%)	0 (0.0%)	1.000
Complete revascularization	347 (98.0%)	174 (98.3%)	173 (97.7%)	1.000

**Complex PCI* was defined as a procedure with at least one of the following angiographic characteristics: 3 vessels treated, ≥3 stents implanted, ≥3 lesions treated, bifurcation with deployment of 2 stents, total stent length >60 mm, chronic total occlusion.

Table 3. Angiographic and procedural characteristics of all treated lesions.

Variable	***OVERALL*** (n=1204)	***DP-EES*** (n=780)	***PF-BES*** (n=424)	***P***
Lesion lenght (mm)	20.2±10.4	19.9 ±10.6	21.0±10.1	0.001
Vessel diameter (mm)	2.78±0.46	2.79±0.48	2.77±0.46	0.839
Target vessel				
Left anterior descending artery	464 (38.5%)	263 (33.7%)	201 (47.4%)	<0.001
Left *main* coronary artery	25 (2.1%)	18 (2.3%)	7 (1.7%)	0.445
Right coronary artery	364 (30.2%)	275 (35.3%)	89 (21.0%)	<0.001
Left circumflex artery	332 (27.6%)	210 (26.9%)	122 (28.8%)	0.493
Saphenous vein graft	19 (1.6%)	14 (1.8%)	5 (1.2%)	0.477
Bifurcations	82 (6.8%)	15 (1.9%)	67 (15.8%)	<0.001
Calcified lesions	77 (6.4%)	70 (9.0%)	7 (1.7%)	<0.001
Chronic total occlusions	101 (8.4%)	63 (8.1%)	38 (9.0%)	0.597
Lesion lenght> 20 mm	437 (36.3%)	258 (33.1%)	179 (43.3%)	0.001
AHA/ACC B2/C lesions*	822 (68.3%)	529 (67.8%)	293 (69.1%)	0.648
Number of stents/ lesion	1.1±0.4	1.2±0.4	1.1±0.3	<0.001
Total stent lenght/lesion (mm)	23.5±12.0	24.0±12.4	22.7±11.2	0.405
Medium stent diameter/lesion (mm)	2.77±0.46	2.77±0.48	2.77±0.42	0.504
Bifurcations treated with 2-stents technique strategy	4 (0.3%)	4 (0.5%)	0 (0.0%)	0.304
Overlap	178 (14.8%)	120 (15.4%)	58 (13.7%)	0.416
Balloon predilation	781 (65.0%)	501 (64.4%)	280 (66.0%)	0.569
Stent postdilation	580 (48.3%)	228 (53.8%)	352 (45.2%)	0.005

**ACC/AHA*= American College of Cardiology/American Heart Association classification.

Table 4. Clinical outcomes in the whole population, propensity matched patients and Complex Higher-Risk and Indicated patients.

WHOLE POPULATION

	OVERALL (n=848)	***DP-EES*** (n=542)	***PF-BES*** (n=306)	***P***
MACE	59 (7.0%)	32 (5.9%)	27 (8.8%)	0.109
Cardiovascular MACE	41 (4.8%)	21 (3.9%)	20 (6.5%)	0.083
Death	39 (4.6%)	27 (5.0%)	12 (3.9%)	0.479
Cardiovascular death	21 (2.5%)	16 (3.0%)	5 (1.6%)	0.357
Acute myocardial infarction	38 (4.5%)	20 (3.7%)	18 (5.9%)	0.138
Target vessel revascularization	21 (2.5%)	5 (0.9%)	16 (5.2%)	<0.001
Target lesion revascularization	20 (2.4%)	5 (0.9%)	15 (4.9%)	0.001
Stent failure	28 (3.3%)	12 (2.2%)	16 (5.2%)	0.018
Stent restenosis	10 (1.2%)	3 (0.6%)	7 (2.3%)	0.041
Definite or probable stent thrombosis	18 (2.1%)	9 (1.7%)	9 (2.9%)	0.214
Definite or probable stent thrombosis at 1 month	9 (1.1%)	7 (1.3%)	2 (0.7%)	0.501

PROPENSITY MATCHED PATIENTS

	OVERALL (n=354)	***DP-EES*** (n=177)	***PF-BES*** (n=177)	***P***
MACE	24 (6.8%)	8 (4.5%)	16 (9.0%)	0.091
Cardiovascular MACE	16 (4.5%)	5 (2.8%)	11 (6.2%)	0.200
Death	17 (4.8%)	8 (4.5%)	9 (5.1%)	0.804
Cardiovascular death	9 (2.5%)	5 (2.8%)	3 (2.3%)	1.000
Acute myocardial infarction	15 (4.2%)	4 (2.3%)	11 (6.2%)	0.111
Target vessel revascularization	8 (2.3%)	0 (0.0%)	8 (4.5%)	0.007
Target lesion revascularization	8 (2.3%)	0 (0.0%)	8 (4.5%)	0.007
Stent failure	11 (3.1%)	2 (1.1%)	9 (5.1%)	0.061
Stent restenosis	4 (1.1%)	0 (0.0%)	4 (2.3%)	0.123
Definite or probable stent	7 (2.0%)	2 (1.1%)	5 (2.8%)	0.448

thrombosis				
Definite or probable stent thrombosis at 1 month	3 (0.9%)	1 (1.1%)	1 (0.6%)	1.000

COMPLEX HIGHER-RISK AND INDICATED PATIENTS

	OVERALL (n=325)	***DP-EES*** (n=209)	***PF-BES*** (n=116)	***P***
MACE	31 (9.5%)	18 (8.6%)	13 (11.2%)	0.446
Cardiovascular MACE	22 (6.8%)	11 (5.3%)	11 (9.5%)	0.147
Death	24 (7.4%)	17 (8.1%)	7 (6.0%)	0.488
Cardiovascular death	15 (4.6%)	10 (4.8%)	5 (4.3%)	1.000
Acute myocardial infarction	21 (6.5%)	11 (5.3%)	10 (8.6%)	0.238
Target vessel revascularization	9 (2.8%)	1 (0.5%)	8 (6.9%)	0.001
Target lesion revascularization	9 (2.8%)	1 (0.5%)	8 (6.9%)	0.001
Stent failure	14 (4.3%)	6 (2.9%)	8 (6.9%)	0.087
Stent restenosis	6 (1.9%)	1 (0.5%)	5 (4.3%)	0.023
Definite or probable stent thrombosis	8 (2.5%)	5 (2.4%)	3 (2.6%)	1.000
Definite or probable stent thrombosis at 1 month	6 (1.9%)	5 (2.4%)	1 (0.9%)	0.427

Table 6**. **Per-lesion clinical outcomes.

	OVERALL (n=1204)	***DP-EES*** (n=780)	***PF-BES*** (n=424)	***P***
Target lesion revascularization	20 (1.7%)	5 (0.6%)	15 (3.5%)	<0.001
Stent failure	28 (2.3%)	12 (1.5%)	16 (3.8%)	0.014
Stent restenosis	10 (0.8%)	3 (0.4%)	7 (1.7%)	0.039
Definite or probable stent thrombosis	18 (1.5%)	9 (1.2%)	9 (2.1%)	0.186
Definite or probable stent thrombosis at 1 month	9 (0.8%)	7 (0.9%)	2 (0.5%)	0.506