Polymer-Free Biolimus A9-Coated Stents in the Treatment of *De Novo* Coronary Lesions: 4- and 12-Month Angiographic Follow-up and Final 5-Year Clinical Outcomes of the Prospective, Multicenter BioFreedom FIM Clinical Trial

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ABSTRACT

OBJECTIVES: To evaluate the efficacy and long-term outcomes of a novel polymer/carrier-free drug-coated stent (DCS) in patients with *de novo* coronary lesions.

BACKGROUND: The BioFreedom™ (BFD) DCS incorporates a low profile stainless steel platform, which's surface has been modified to create a selectively micro-structured abluminal surface that allows adhesion and further release of Biolimus A9™ (Biosensors Europe SA, Morges, Switzerland).

METHODS: 182 patients (183 lesions) were randomized into 1:1:1 ratio for treatment with BFD "standard dose" (BFD) or BFD "low dose" (BFD-LD) versus first-generation paclitaxel-eluting stents (PES) at 4 sites in Germany.

RESULTS: Baseline and procedural characteristics were well matched. At 4-month angiographic follow-up (FU) (Cohort-1, n=75), in-stent late lumen loss (LLL) was significantly lower with BFD and BFD-LD vs. PES (0.08mm and 0.12mm versus 0.37mm, respectively; $p<0.0001$ for BFD versus PES; and $p=0.002$ for BFD-LD versus PES); at 12 months (Cohort-2, n=107), in-stent LLL (primary endpoint) was 0.17mm in BFD versus 0.35mm in PES ($p=0.001$ for non-inferiority; $p=0.11$ for superiority); however, the BFD-LD (0.22mm) did not reach non-inferiority ($p=0.21$). At 5 years (175/182), there were no significant differences in major adverse cardiac events (23.8%, 26.4% and 20.3%) and clinically-indicated target lesion revascularization (10.8%, 13.4%, and 10.2%); for BFD, BFD-LD and PES, respectively; also, there was no definite/probable stent thrombosis reported.

CONCLUSIONS: The BFD, but not the BFD-LD, demonstrated non-inferiority versus PES in terms of in-stent LLL, a surrogate of neointimal hyperplasia, at 12-month FU. At 5 years, clinical event rates were similar, without occurrence of stent thrombosis in all groups.

KEY WORDS: Drug-coated stents, Biolimus, percutaneous coronary intervention, coronary artery disease, polymer-free, carrier-free.

CONDENSED ABSTRACT

The BioFreedom™ (BFD) drug-coated stent incorporates a low profile stainless steel platform, which's surface has been modified to create a selectively micro-structured abluminal surface that allows adhesion and further release of Biolimus A9™ (Biosensors Europe SA, Morges, Switzerland). 182 patients were randomized (1:1:1) for treatment with BFD "standard" dose (BFD) or BFD "low" dose (BFD-LD) versus first-generation paclitaxel-eluting stents (PES). At 12 months, in-stent LLL (primary endpoint) was 0.17mm in BFD versus 0.35mm in PES (p=0.001 for non-inferiority); however, BFD-LD (0.22mm) did not reach non-inferiority. At 5-years, major adverse cardiac events were similar; also, there was no definite/probable stent thrombosis reported.

ABBREVIATIONS

BFD = BioFreedom "standard-dose"

BFD-LD = BioFreedom "low-dose"

DCS = drug-coated stents

DES = drug-eluting stents

FU = follow-up

LLL = late lumen loss

MACE = major adverse cardiac events

NIH = neointimal hyperplasia

PES = paclitaxel-eluting stents

TLR = target lesion revascularization

INTRODUCTION

Non-polymeric drug-coated stents (DCS) have been introduced as an alternative to polymeric drug-eluting stents (DES), as previous studies investigating the biocompatibility of drug-carriers – particularly durable polymers used in first-generation DES, had demonstrated negative effects of these components on vessel healing due to chronic inflammation and local toxicity, which could lead to proliferative and thrombogenic responses overtime (1-6). In addition, the safety of current DES systems appears to be dependent on relatively long (≥6 months) dual antiplatelet therapy (DAPT) (7,8), a fact that may limit their use on a significant proportion of patients with adherence restraints, such as those with high risk for bleeding (9). However, the absence of a drug-carrier has also been associated with lesser efficacy at inhibiting neointimal hyperplasia (NIH), most probably due to insufficient and/or uncontrolled drug delivery at the target coronary site (10-13).

BA9^{TM} (Biolimus) – a 31-membered triene macrolide lactone derivative of sirolimus, is a potent antiproliferative agent that has been developed for vascular applications, specifically for DES (14). Overall, Biolimus has consistently demonstrated high efficacy at inhibiting NIH, as well as sustained safety, when delivered via a biodegradable polymer DES in multiple clinical scenarios (15-17). Still, the impact of Biolimus released from a polymer/carrier-free DCS system in human coronary arteries is yet to be determined. Hence, the purpose of this analysis was to report the first-in-man (FIM) evaluation of a new polymer-free Biolimus-coated stent in the treatment of *de novo* coronary lesions. The study hypothesis was that a polymer-free Biolimus release via a micro-structured stent surface (18) could be as effective in reducing NIH as compared to a first-generation paclitaxel-eluting stent (PES) in diseased coronary vessels.

METHODS

Study Design and Patient Population

The BioFreedom FIM clinical trial was a prospective, randomized, single-blinded, multicenter feasibility study designed to investigate the performance, safety and efficacy of the novel polymer-free BioFreedom™ Biolimus-coated stents (Biosensors Europe SA, Morges, Switzerland) versus the Taxus® Liberté® PES (Boston Scientific, Natick, MA, USA) in the treatment of coronary lesions. The BioFreedom device was tested with 2 drug formulations: "standard-dose" (BFD) and "low-dose" (BFD-LD). Inclusion criteria were: ≥18-years-old; symptoms of stable or unstable angina, and/or presence of a positive functional test for ischemia; single *de novo* target lesion ≤14 mm in length, with stenosis 50-99%, in native coronary vessel 2.5-3.0mm in diameter; acceptable candidate for coronary artery bypass graft surgery; and agreement to undergo all protocol follow-ups (FUs) including one angiographic re-evaluation. Key exclusion criteria were: myocardial infarction (MI) <72 hours; left main, ostial location; moderate or severe calcification, as visible by fluoroscopy; target lesion involving a side branch >2.0 mm in diameter; thrombus; documented left ventricular ejection fraction <30% assessed within 6 months prior to procedure by echocardiography, during previous angiography or as measured during preprocedure angiography; known hypersensitivity or contra-indication to antithrombotic therapy; and concurrent medical condition with life expectancy <18 months.

The study complied with the Declaration of Helsinki regarding investigation in humans, followed ISO-14155:2003, and was approved by the local Ethics Committee at the participant institutions. All patients provided written informed consent prior to procedure. The BioFreedom FIM trial was registered at *www.ClinicalTrials.gov*: **NCT01172119**.

Study Device

The study device has been detailed elsewhere (18). In brief, it incorporates a 316L stainless steel platform, which has been modified with a proprietary surface treatment resulting in a selectively micro-structured abluminal surface (**Figure 1**). The selectively micro-structured surface allows adhesion of the antiproliferative agent (Biolimus) to the abluminal surface of the stent without a polymer or binder. The drug dose for the BFD device was 15.6µg per mm of stent length, whereas a half-dose (7.8µg per mm of stent length) was used for BFD-LD. As for release kinetics, approximately 90% of Biolimus was released from the stent <48 hours after implant, irrespectively of dose formulation, with the remaining being released in up to 28 days.

Randomization and Procedure

Eligible patients were randomized in a 1:1:1 ratio for treatment with BFD, BFD-LD and PES. The first subset of randomized patients (Cohort 1) was assigned for 4-month angiographic FU, as the intention was to have an early assessment of efficacy for a novel DCS with boost drug release. The second subset of randomized patients (Cohort 2) was assigned for 12-month angiographic FU. Percutaneous coronary intervention (PCI) was performed according to standard guidelines. Lesion predilatation was recommended by protocol; only one stent was allowed per target lesion, even though additional stent(s) (same as group allocation) could be used in bailout situations. The BioFreedom stents were available in 2.5 and 3.0mm in diameter, and 14 and 18mm in length; PES were disposed in 2.5, 2.75 and 3.0mm in diameter, and 12, 16 and 20mm in length. Multivessel PCI at index procedure including treatment of a non-target lesion in a non-target vessel was allowed, given that the non-target lesion had to be successfully treated first, with any non-study device, at operator's discretion. At postprocedure, DAPT was prescribed for at least 6 months.

Endpoints and Data Management

The primary endpoint was in-stent late lumen loss (LLL), as determined by independent quantitative coronary angiography (QCA) analysis, at 12-month angiographic FU (Cohort 2). Key secondary endpoints included: in-stent LLL at 4 months (Cohort 1); major adverse cardiac events (MACE), definite or probable stent thrombosis (ST) (19); clinically-driven target-lesion revascularization (TLR) and clinically-driven target-vessel revascularization (TVR) at hospital discharge, 30-day, 4- and 12-month, and yearly up to 5-year FU; angiographic binary restenosis at 4-month (Cohort 1) and 12-month (Cohort 2) FU; and lesion and procedural success. Data coordination and management, statistical analysis and unblinding of the data were performed by an independent Data Coordinating Center (Cardiovascular Research Foundation, New York, NY). Primary data collection was performed at each clinical site following standard procedures including source verification, electronic completion of individual Case Report Forms, physical monitoring and remittance of proper source-documentation. By protocol, clinical FU consisting of medical visits were scheduled at 1, 4 and 12-month, and yearly up to 5-year FU. Full definitions and details of the study organization are provided in the **Online Appendix**.

Angiographic Analysis

Serial coronary angiographic studies were obtained after intracoronary administration of nitroglycerin (100-200µg, unless contra-indicated) in 2 orthogonal matching views at preprocedure, postprocedure and FU. Angiographic analysis was performed *offline* by experienced operators blinded to group allocation, procedural data and clinical outcomes, at an independent core laboratory (Cardiovascular Research Center, São Paulo, Brazil). Quantitative analysis was performed with validated 2D software for QCA analysis (QAngio XA® version 7.2, Medis, Leiden, the Netherlands) (**Online Appendix**). LLL was the change in minimum lumen

diameter (MLD) from the post-stent implantation angiogram to FU; binary restenosis was defined as stenosis ≥50% at angiographic FU. QCA measurements were reported: “in-stent”, within the stented segment; “in-segment”, spanning the stented segment plus the 5mm proximal and distal peri-stent areas; and at 5mm proximal and distal peri-stent edges (outside the stent).

Statistical Analysis

The sample size calculation for the BioFreedom FIM trial was based on the expected in-stent LLL results at 12-month angiographic FU (Cohort 2), given that this randomized trial would measure the non-inferiority of the BFD (“standard-dose") group compared to the PES group. The null hypothesis (Ho) for the primary endpoint was that the BFD group would have a mean in-stent LLL at 12 months that exceeds that of the PES group by at least a pre-specified margin of δ (delta), i.e., 0.24mm. The alternative hypothesis (Ha) was that the BFD group would have in-stent LLL at 12 months that is lower than the PES group plus δ. Therefore, rejection of the null hypothesis would indicate that the BFD group is non-inferior to the PES group in regard to 12-month in-stent LLL. The null and alternative hypotheses of interest are the following:

- Ho: μ BFD ≥ μ Taxus + δ;
- Ha: μ BFD < μ Taxus + δ;

where μ BFD is the mean in-stent LLL for the BFD arm, and μ PES is the mean in-stent LLL for the PES active control arm. The pre-specified margin (delta of 0.24mm) was considered because it yields less than half of the estimated standard deviation (SD) of in-stent LLL (0.5mm), as estimated from prior studies (20). In addition, because previous data suggest that Biolimus-eluting stents performs better than PES, it was assumed that the in-stent LLL at 12-month FU for the BFD group would be at least 0.12mm lower than the PES group (15,16,18,20). Hence, a minimum sample size of 32 patients in each study arm of Cohort 2 would give >80% power, at

one-sided α (alpha) of 0.025, to reject the null hypothesis in favor of non-inferiority of the BFD arm relative to the PES arm. Considering lost to angiographic FU up to 10%, the minimal sample size per randomized group in Cohort 2 was increased by approximately 10% (35 patients). As for Cohort 1, there were no formal statistical assumptions as the intention was to have an early evaluation of efficacy, at 4-month angiographic FU.

Categorical variables are expressed as numbers and percentages (or frequencies) of the total. Continuous variables are expressed as mean±standard deviation (SD) or median (interquartile range) when appropriate, based on the distribution pattern. Statistical comparisons were conducted between BFD versus PES and between BFD-LD versus PES. Categorical variables were compared with Chi-Square or Fischer's exact tests. Continuous variables were compared for superiority with Student's T test if normality was present or Wilcoxon rank sum test in case of non-normality. Kaplan-Meier event rates were compared using the log-rank test. Hazard ratios (HR) with 95% confidence interval were calculated using Cox proportional hazards regression. All statistical analyses were performed using SAS software version 8.2 or higher (SAS Institute Inc., Cary, NC, USA). A p value <0.05 was considered significant.

RESULTS

A total of 182 patients were enrolled between September/2008-June/2009 at 4 sites in Germany; the first 75 randomized patients were allocated in Cohort 1, and the subsequent 107 randomized patients were allocated in Cohort 2. The majority of patients (92%) underwent angiographic FU at their pre-assigned timeframe – either 4 or 12 months, and 98.9% (180/182) completed 12-month clinical FU (**Figure 2**). Considering the overall population, baseline characteristics were well matched between the groups (**Table 1** and **Table 2**). All lesions were

successfully treated, and procedural success was achieved in all but one patient in BFD-LD group **(Online Table 1)**.

QCA Analysis

Pre- and postprocedure QCA results were similar in the overall study population (**Table 2**), as well as in Cohorts 1 and 2 (**Online Table 2)**. At 4-month FU (Cohort 1), in-stent LLL (secondary endpoint) was significantly lower with BFD and BFD-LD versus PES (0.08mm and 0.12mm versus 0.37mm, respectively; p<0.0001 for BFD versus PES; p=0.002 for BFD-LD versus PES), **Table 3**. There were no cases of in-stent restenosis in both BFD and BFD-LD groups; conversely, 9.1% (2/22) presented with in-stent restenosis in PES. Moreover, focal edge restenosis was found in 1 case in each group. The primary outcome was assessed in Cohort 2 (**Table 3**), and in-stent LLL was 0.17mm in BFD versus 0.35mm in PES (p=0.001 for non-inferiority; p=0.11 for superiority); however, in-stent LLL with BFD-LD (0.22mm) did not reach significance in terms of non-inferiority against PES (p=0.21), **Figure 3**. Cumulative frequency distribution curves for in-stent MLD are shown in **Figure 4**. In addition, in-stent restenosis rates were 6.7% (2/30), 8.6% (3/35) versus 3.2% (1/31), whereas in-segment restenosis was 6.7% (2/30), 14.3% (5/35) versus 9.7% (3/31), for BFD, BFD-LD and PES groups, respectively (all p=not significant).

Clinical Outcomes

Kaplan-Meier estimates and occurrence curves for the composite and individual clinical endpoints are reported in **Table 4** and **Figure 5**. Between 1 and 5 years **(Online Table 3)**, clinically-driven TLR, associated with angiographic restenosis within the treated segment, was found in 2/5 cases in BFD, 2/4 in BFD-LD, and 1/3 in PES. The other cases of TLR evidenced patent stents, but significant stenoses within the coronary segments adjacent to the target lesion

site (stent +5 mm proximal/distal edges). Considering any TLR, event rates were 10.8% (n=6) in BFD, 15.1% (n=9) in BFD-LD versus 11.9% (n=7) in PES (all p=not significant). Overall, there were no cases of (ARC) definite or probable ST in any group.

DISCUSSION

In the current analysis, we tested the proof of concept that a polymer/carrier-free Biolimus release via a micro-structured stent surface could be effective in reducing NIH at least as compared to PES, and results were positive with BFD, but not with BFD-LD; in addition, there were similar event rates up to 5 years and no safety concerns, including absence of (ARC) definite or probable ST in all groups. Most of the rationale for developing non-polymeric DCS has been based on previous observations that linked synthetic polymers used in first-generation DES with persistent local inflammatory and toxic responses, which could lead to delayed (or lack of) vascular healing, hypersensitivity reactions, endothelial dysfunction, and even neoatherosclerosis; all phenomenon that have been associated with late and very late recurrences including ST (1-6,21-23). Overall, durable polymers used in first-generation DES were associated with suboptimal biocompatibility and mechanical complications, consequently, second-generation DES have incorporated lower profile components with thrombus-resistant properties; also, DES with biodegradable polymers have shown to improved long-term safety compared to DES with durable polymers (1-6,17,21-26). Nonetheless, despite clinical superiority of new generation DES over first-generation DES, late and very late events may still occur (17,27). Hence, non-polymer based DCS could offer, at least theoretically, additional advantages such as: avoid problems related to temporary or permanent polymeric residue; optimize vascular healing; maintain stent surface integrity (as opposed to webbing/delamination phenomenon seen with polymeric devices); and shorten DAPT post-stent implantation, reducing bleeding (without

compromising safety), while maintaining efficacy at inhibiting NIH. The BioFreedom DCS technology was primarily conceived with a dose of Biolimus identical to the reference dose applied in the BioMatrix^{TM} Biolimus-eluting stent (Biosensors Europe SA, Morges, Switzerland) with a biodegradable polymer, as this device has demonstrated high efficacy and sustained safety in multiple clinical scenarios (15-17). Yet, due to the high lipophilicity property of Biolimus (~10 times greater than sirolimus) (14), it was rationalized that a "lower dose" of Biolimus could be as efficacious and safe as the "standard drug dose", with potential additional advantages in terms of minimizing local inflammatory response (due to less drug load) and providing faster and enhanced vessel healing. Such assumptions were supported by prior pharmacokinetics analysis with Biolimus (14) and preclinical studies with BioFreedom stents (18), which demonstrated high efficacy in reducing NIH, optimal vessel healing and minimal local inflammatory response with both BFD and BFD-LD. In the current analysis, the BFD group met the primary outcome of non-inferiority in terms of in-stent LLL at 12-month angiographic FU ($p<0.001$), with a statistically non-significant trend towards superiority ($p=0.11$) versus the PES group. As for clinical events, there were no significant differences, and most recurrences after 1 year appeared to be related to coronary artery disease progression occurring in coronary segments other than the treated site. Of note is the fact that the BioFreedom FIM trial was not designed, sized or statistically powered to demonstrate superiority of the study groups versus the active control group in terms of LLL or any other angiographic or clinical endpoint. Nevertheless, 12-month in-stent LLL with BFD was relatively low (0.17mm), and comparable to the most effective DES systems tested to date (15,24,25,28). Interestingly, the BFD-LD group did not meet the primary endpoint of non-inferiority versus PES ($p=0.21$); in addition, it showed numerically higher rates of angiographic and clinical restenosis (**Table 3** and **Table 4**), thus, suggesting inferior efficacy

at inhibiting NIH. Based on these results, the BioFreedom clinical program was continued with the BFD stent only, as proof of concept was not demonstrated with BFD-LD.

Uncontrolled or boost drug release have been associated with poor efficacy and DCS failure (10-13); however, drug dose and pharmacodynamics may play an important role. In the DELIVER trial, only a marginal benefit in terms of in-stent LLL was observed at 8-month FU with the polymer-free paclitaxel-coated stent versus the uncoated control stent (0.81mm vs. 0.98mm, p=0.003, respectively); however, such difference did not translate into significant reductions in binary restenosis or TLR rates. By that time, it was estimated that up to 40% of drug was lost during stent delivery; also, release kinetics was considered "too fast" (within days to weeks) (10). On the contrary, the Taxus PES with durable polymer (used as active control group in our study) had a much slower drug release (<10% in 30 days), with approximately 67% less drug compared to the DCS used in DELIVER; yet, in-stent LLL in the TAXUS-IV trial was considerably lower (0.37mm), despite identical drug (paclitaxel) (20). Similarly, polymer-free sirolimus-eluting stents seem to perform worse in terms of efficacy compared to polymer-based sirolimus-eluting stents (12). Both BFD and BFD-LD shared identical stent design and release kinetics, but differed on drug dosage (BFD-LD with half dose of BFD). Therefore, we may speculate that the main mechanism associated with the negative results in terms of efficacy found with BFD-LD is insufficient drug amount, rather than release kinetics. Furthermore, the BFD DCS and the BioMatrix DES have completely different drug release kinetics (BioMatrix: ~70% in 30 days; BioFreedom: ~90% in 48 hours); still, in-stent LLL appears to be similar, despite boost release with BFD (15,16,18). There are a few possibilities to explain these findings. The innovative modified surface technology creating a selectively micro-structured textile reservoir in BioFreedom appears to be effective on holding and carrying the drug to the target site, where

it dissolves (18). Moreover, Biolimus may offer significant advantages compared to other "limus" agents, as it may improve pharmacokinetics due to its high lipophilicity and, consequently, optimize bioavailability, with rapid distribution into the arterial wall during the initial hours after stent implant, allowing achievement of faster therapeutic concentrations and extended duration of treatment effect (14,18), which may counterbalance the potentially negative effects of boost release.

A few limitations must be acknowledged in our study. First, it comprised relatively simple and discrete lesions; thus, caution should be used before generalizing our results to patients with more complex disease. Second, PES represents a somewhat outdated DES technology, which had demonstrated to be inferior to current generation DES (27); however, the reasons for have chosen this active comparator were that: a) it was still largely used at the time of protocol design and enrollment start (29,30); b) there was robust evidence, without major concerns in terms of safety and clinical efficacy by that time (29-31); c) it had been used as control therapy in multiple other studies; and d) based on its historical LLL (0.37 mm) (20), it was thought to be the right comparator considering a non-inferiority study design and the assumptions made for the primary endpoint. Third, even though there were no significant differences in clinical outcomes and absence of definite/probable ST up to 5 years, no conclusions regarding safety and efficacy can be made, as the BioFreedom FIM trial was not statistically powered to demonstrate non-inferiority or superiority in clinical endpoints; therefore, future large-scale studies are needed to demonstrate the clinical implications of the BFD stent, particularly in comparison to newer generation DES. Specifically, due to its design and concept, the BFD stent may offer less dependence on prolonged DAPT than polymer-coated DES (18) and, in order to test this hypothesis, the 2,456 patient randomized LEADERS FREE trial

(**NCT01623180**) is currently ongoing (32). Based on our findings, we may speculate that BFD is likely to improve clinical efficacy against uncoated stents, but the implications regarding safety in such complex populations as expected in this trial are yet to be determined.

CONCLUSIONS

The polymer-free BioFreedom Biolimus-coated stents with a standard-dose (BFD) demonstrated high efficacy in inhibiting NIH at 4- and 12-month angiographic re-evaluations, and was non-inferior to the PES in terms of in-stent LLL, a surrogate of NIH, a 12-month FU. In addition, there were no safety concerns up to 5 years, including similar rates of MACE and absence of definite or probable ST in all groups.

CLINICAL PERSPECTIVES

What is Known?

Non-polymeric drug-coated stents have been introduced as an alternative to polymeric drug-eluting stents (DES) in order to avoid problems related to temporary or permanent polymeric residue that could lead to chronic inflammation and local toxicity; however, the absence of a drug-carrier had been associated with lesser efficacy a inhibiting neointimal hyperplasia (NIH).

What is New?

In the BioFreedom first-in-man trial, the proof of concept that "a polymer-free BA9 (Biolimus) release via a micro-structured stent surface could be as effective in reducing NIH as compared to a first generation paclitaxel-eluting stent (PES)" was demonstrated, as the BioFreedom drug-coated stent with a "standard dose" of Biolimus (15.6µg per mm of stent length) was significantly non-inferior in terms of in-stent late lumen loss, a surrogate of NIH, as compared to the PES active control group at 12-month angiographic follow-up (0.17mm versus 0.35mm,

respectively, p<0.001).

What is Next?

Due to its design and concept, the BioFreedom drug-coated stent may offer less dependence on prolonged dual antiplatelet therapy than polymer-coated DES, while maintaining efficacy; thus, it may be suitable for those at high risk for bleeding. The ongoing LEADERS FREE trial is investigating the clinical impact of the BioFreedom technology versus uncoated stents in complex patients with high-risk for bleeding receiving short-term (1-month) dual antiplatelet therapy; furthermore, future large-scale studies are needed to investigate its clinical implications in comparison to newer generation DES.

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FIGURE LEGEND

FIGURE 1: Polymer-Free BioFreedom Biolimus A9-Coated Stent – Illustration of the stent platform showing selectively micro-structured porous surface in the abluminal (outer) side, and luminal polished surface in the luminal (inner) side.

FIGURE 2: Study Flow – Group allocation in the BioFreedom FIM trial, were patients were randomized in a 1:1:1 ratio to treatment with the BFD and the BFD-LD stents versus PES. The first 75 patients enrolled were assigned to 4-month angiographic FU (Cohort 1); the subsequent 107 patients were assigned to 12-month angiographic FU (Cohort 2). Long-term FU for clinical endpoints available in 175 of 182 patients.

FIGURE 3: Late Lumen Loss at Angiographic Follow-up – Median (SD bars) in-stent LLL at 4-month (Cohort 1) and 12-month (Cohort 2) angiographic follow-up.

FIGURE 4: Distribution of MLD at Preprocedure, Postprocedure and Follow-up – Cumulative frequency distribution curves for in-stent MLD for Cohort 1 (4-month angiographic follow-up) and Cohort 2 (12-month angiographic follow-up).

FIGURE 5: Kaplan-Meier Curves Showing Event Rates Stratified by Group Allocation – Major adverse cardiac events **(A)**, cardiac death **(B)**, myocardial infarction **(C)**, any target-lesion revascularization **(D)**, clinically-driven target-lesion revascularization **(E)**, and clinically-driven target-vessel revascularization **(F)**.

TABLE 1: Baseline Clinical Characteristics of the Overall Study Population Comparing BFD and BFD-LD versus PES

Variable	BFD (a)	BFD-LD (b)	PES (c)	p value (a) vs. (c)	p value (b) vs. (c)
n	60	62	60		
Age, yrs	68.6 ± 9.0	65.0 ± 9.4	67.9 ± 8.0	0.55	0.13
Male	40 (66.7)	47 (75.8)	40 (66.7)	>0.99	0.27
Diabetes mellitus	17 (28.3)	18 (29.0)	15 (25.0)	0.68	0.62
Hypertension	54 (90.0)	50 (80.6)	51 (85.0)	0.41	0.52
Dyslipidemia	41 (68.3)	45 (73.8)	45 (75.0)	0.42	0.88
Smoking (current)	10 (16.9)	12 (20.3)	7 (12.3)	0.48	0.24
Family history of CAD	16 (32.7)	21 (38.2)	18 (38.3)	0.56	0.99
Prior MI	12 (20.0)	13 (21.3)	11 (18.3)	0.82	0.68
Prior PCI	19 (31.7)	27 (44.3)	27 (45.8)	0.11	0.87
Renal insufficiency*	5 (8.3)	3 (4.8)	1 (1.7)	0.09	0.33
Clinical presentation					
Stable angina	49 (81.7)	47 (75.8)	46 (76.7)	0.50	0.91

Unstable angina	7 (11.7)	8 (12.9)	4 (6.7)	0.34	0.25
Silent ischemia	2 (3.3)	6 (9.7)	6 (10.0)	0.14	0.95

Values are mean ± SD or n (%). *Defined as baseline serum creatinine ≥2.0mg/dL.
BFD = BioFreedom "standard dose" stents; BFD-LD = BioFreedom "low dose" stents; CAD = coronary artery disease; MI = myocardial infarction; PES = Taxus paclitaxel-eluting stents; PCI = percutaneous coronary intervention.

TABLE 2: Angiographic Data of the Overall Study Population Comparing BFD and BFD-LD versus PES

Variable	BFD (a)	BFD-LD (b)	PES (c)	p value (a) vs. (c)	p value (b) vs. (c)
n (patients/lesions)	60/60	62/63*	60/60		
Target coronary vessel					
Left anterior descending	21 (35.0)	30 (48.4)	18 (30.0)	0.56	0.04
Left circumflex	15 (25.0)	12 (19.4)	17 (28.3)	0.68	0.24
Right coronary artery	24 (40.0)	20 (32.3)	25 (41.7)	0.85	0.28
Calcium (moderate/severe)	13 (22.0)	13 (20.6)	18 (30.0)	0.32	0.23
Lesion class B2/C†	26 (44.1)	28 (44.4)	34 (56.7)	0.17	0.18
Preprocedural TIMI flow 3	54 (90.0)	53 (85.5)	54 (90.0)	>0.99	0.45
QCA					
Preprocedure					
Lesion length, mm	10.6 (9.3-13.9)	11.3 (9.8-13.6)	11.2 (9.5-14.0)	0.41	0.72
RD, mm	2.8 (2.5-3.0)	2.8 (2.5-3.0)	2.8 (2.5-3.0)	0.99	0.92
MLD, mm	0.6 (0.3-0.9)	0.6 (0.4-0.9)	0.7 (0.5-0.9)	0.53	0.59

% DS	76.0 (64.3-87.6)	77.2 (67.0-85.8)	75.9 (67.2-83.6)	0.66	0.58
Postprocedure					
RD, mm	2.9 (2.6-3.0)	2.8 (2.5-3.0)	2.8 (2.6-2.9)	0.90	0.85
In-stent					
Mean diameter, mm	2.9 (2.6-3.0)	2.9 (2.6-3.0)	2.9 (2.6-3.0)	0.92	0.88
MLD, mm	2.7 (2.3-2.8)	2.6 (2.3-2.8)	2.6 (2.4-2.8)	0.40	0.47
% DS	6.2 (3.9-11.5)	7.4 (4.5-9.9)	6.1 (3.6-9.4)	0.68	0.38
Acute gain, mm	2.0 (1.6-2.2)	1.9 (1.7-2.2)	1.9 (1.7-2.2)	>0.99	0.71
In-segment					
MLD, mm	2.3 (2.0-2.5)	2.2 (2.1-2.5)	2.2 (2.0-2.6)	0.71	0.81
% DS	17.2 (9.4-24.3)	16.9 (12.0-23.0)	19.1 (12.0-24.0)	0.98	0.89
Acute gain, mm	1.6 (1.3-2.0)	1.6 (1.4-1.8)	1.6 (1.3-2.0)	0.78	0.97
Proximal edge					
MLD, mm	2.6 (2.3-2.8)	2.5 (2.2-2.9)	2.5 (2.3-2.8)	0.88	0.74
% DS	8.6 (5.7-16.1)	9.4 (4.8-16.6)	12.5 (5.8-18.3)	0.38	0.47
Distal edge					

MLD, mm	2.3 (2.0-2.6)	2.3 (2.1-2.6)	2.2 (2.0-2.5)	0.92	0.35
% DS	11.9 (8.3-18.9)	11.0 (6.1-15.9)	11.8 (8.0-17.6)	0.43	0.38
Balloon-artery ratio	1.2 (1.1-1.2)	1.1 (1.1-1.2)	1.1 (1.1-1.2)	0.66	0.99

Values are n (%) or median (interquartile range). * One patient in BFD-LD had 2 target lesions treated within the same target vessel. †Only type B, according to the modified American College of Cardiology/American Heart Association lesion classification.
DS = diameter stenosis; MLD = minimum lumen diameter; QCA = quantitative coronary angiography; RD = reference diameter; TIMI = Thrombolysis In Myocardial. Infarction; other abbreviations as in **Table 1**.

TABLE 3: QCA Results at 4-Month (Cohort 1) and 12-Month (Cohort 2) Follow-up Comparing BFD and BFD-LD versus PES

Variable	BFD (a)	BFD-LD (b)	PES (c)	p value (a) vs. (c)	p value (b) vs. (c)
4-Month FU (Cohort 1)					
n (lesions)	23	25	22		
RD, mm	2.8 (2.5-2.9)	2.7 (2.5-2.9)	2.7 (2.4-3.0)	0.96	0.83
In-stent					
Mean diameter, mm	2.7 (2.6-2.9)	2.8 (2.4-3.0)	2.6 (2.2-3.0)	0.32	0.31
MLD, mm	2.5 (2.1-2.7)	2.5 (2.0-2.7)	2.2 (1.6-2.6)	0.09	0.17
% DS	7.6 (4.0-13.6)	10.1 (7.3-17.3)	18.0 (11.3-22.9)	0.002	0.02
LLL, mm	0.08 (0.02-0.14)	0.12 (0.07-0.25)	0.37 (0.14-0.50)	<0.0001	0.002
LLL index	0.05 (0.01-0.09)	0.06 (0.04-0.14)	0.19 (0.09-0.31)	0.0002	0.003
In-segment					
MLD, mm	2.0 (1.7-2.3)	2.1 (1.9-2.3)	2.0 (1.5-2.3)	0.80	0.44
% DS	25.2 (16.8-33.0)	24.3 (18.8-27.9)	24.6 (20.4-29.8)	0.65	0.50
LLL, mm	0.12 (0.02-0.20)	0.12 (0.06-0.25)	0.18 (0.09-0.42)	0.09	0.35

LLL index	0.06 (0.02-0.17)	0.08 (0.04-0.15)	0.12 (0.07-0.29)	0.15	0.32
Proximal edge					
MLD, mm	2.3 (2.0-2.5)	2.4 (2.2-2.6)	2.3 (2.2-2.7)	0.13	0.95
% DS	18.6 (13.3-24.1)	12.0 (8.7-17.1)	16.7 (11.1-24.2)	0.31	0.34
LLL, mm	0.13 (0.04-0.32)	0.13 (0.04-0.26)	0.15 (0.05-0.25)	0.77	0.99
Distal edge					
MLD, mm	2.0 (1.8-2.4)	2.2 (1.9-2.4)	2.1 (1.9-2.3)	0.75	0.95
% DS	16.2 (8.2-21.9)	15.3 (11.8-20.1)	12.6 (8.1-19.0)	0.30	0.42
LLL, mm	0.06 (0.01-0.16)	0.11 (0.04-0.31)	0.09 (0.01-0.24)	0.71	0.37
12-Month FU (Cohort 2)					
n (lesions)	31	35	31		
RD, mm	2.8 (2.5-2.9)	2.8 (2.4-2.9)	2.8 (2.7-2.9)	0.97	0.87
In-stent					
Mean diameter, mm	2.8 (2.5-2.8)	2.6 (2.3-2.9)	2.6 (2.5-2.9)	0.76	0.33
MLD, mm	2.4 (2.0-2.6)	2.2 (1.8-2.6)	2.3 (2.0-2.4)	0.49	0.83
% DS	13.8 (9.4-21.3)	13.6 (9.0-39.5)	19.3 (10.0-25.0)	0.21	0.30

LLL, mm	0.17 (0.09-0.39)	0.22 (0.17-0.66)	0.35 (0.22-0.57)	0.11	0.55
LLL index	0.10 (0.05-0.22)	0.12 (0.09-0.35)	0.20 (0.11-0.30)	0.11	0.63
In-segment					
MLD, mm	2.0 (1.9-2.4)	2.0 (1.6-2.3)	2.0 (1.9-2.3)	0.85	0.36
% DS	21.8 (14.6-30.9)	23.7 (15.0-45.0)	22.9 (17.1-32.9)	0.60	0.75
LLL, mm	0.17 (0.12-0.35)	0.19 (0.07-0.58)	0.27 (0.08-0.57)	0.52	0.93
LLL index	0.11 (0.06-0.22)	0.12 (0.04-0.33)	0.17 (0.05-0.30)	0.56	0.94
Proximal edge					
MLD, mm	2.5 (2.2-2.8)	2.2 (1.8-2.7)	2.5 (2.2-2.8)	0.78	0.09
% DS	11.1 (6.3-18.5)	18.1 (7.8-31.1)	12.4 (6.0-24.1)	0.62	0.16
LLL, mm	0.10 (0.03-0.20)	0.17 (0.06-0.48)	0.07 (0.01-0.25)	0.60	0.01
Distal edge					
MLD, mm	2.3 (2.0-2.5)	2.3 (2.0-2.5)	2.2 (1.9-2.5)	0.93	0.72
% DS	12.1 (7.7-21.3)	12.0 (10.2-17.0)	10.1 (7.6-16.7)	0.70	0.56
LLL, mm	0.14 (0.05-0.19)	0.10 (0.05-0.34)	0.10 (0.06-0.19)	0.61	0.91

Values are median (interquartile range).
LLL = late lumen loss; other abbreviations as in **Tables 1 and 2**.

TABLE 4. Clinical Outcomes of the Overall Study Population Comparing BFD and BFD-LD versus PES

Cumulative events	BFD	BFD-LD	PES	HR (95% CI)		p value	
	(a)	(b)	(c)	(a) vs. (c)	(b) vs. (c)	(a) vs. (c)	(b) vs. (c)
0-30 days							
MACE	0 (0)	1 (1.6)	0 (0)	-	-	-	0.33
All-cause death	0 (0)	0 (0)	0 (0)	-	-	-	-
Cardiac	0 (0)	0 (0)	0 (0)	-	-	-	-
Non-cardiac	0 (0)	0 (0)	0 (0)	-	-	-	-
MI	0 (0)	1 (1.6)	0 (0)	-	-	-	0.33
Clinically-driven TLR	0 (0)	0 (0)	0 (0)	-	-	-	-
Clinically-driven TVR	0 (0)	0 (0)	0 (0)	-	-	-	-
ST (ARC definite/probable)	0 (0)	0 (0)	0 (0)	-	-	-	-
0-4 months							
MACE	0 (0)	2 (3.3)	1 (1.7)	0.00	1.96 (0.18-21.57)	0.32	0.58
All-cause death	0 (0)	0 (0)	0 (0)	-	-	-	-
Cardiac	0 (0)	0 (0)	0 (0)	-	-	-	-

Non-cardiac	0 (0)	0 (0)	0 (0)	-	-	-	-
MI	0 (0)	1 (1.6)	0 (0)	-	-	-	0.33
Clinically-driven TLR	0 (0)	0 (0)	1 (1.7)	0.00	0.00	0.32	0.31
Clinically-driven TVR	0 (0)	2 (3.3)	1 (1.7)	0.00	1.93 (0.18-21.34)	0.32	0.58
ST (ARC definite/probable)	0 (0)	0 (0)	0 (0)	-	-	-	-
0-12 months							
MACE	3 (6.1)	7 (11.6)	3 (5.5)	0.98 (0.20-4.83)	2.36 (0.61-9.12)	0.98	0.20
All-cause death	1 (1.8)	0 (0)	0 (0)	-	-	0.34	-
Cardiac	1 (1.8)	0 (0)	0 (0)	-	-	0.34	-
Non-cardiac	0 (0)	0 (0)	0 (0)	-	-	-	-
MI	1 (2.6)	1 (1.6)	0 (0)	-	-	0.32	0.33
Clinically-driven TLR	1 (1.7)	4 (6.7)	3 (5.5)	0.34 (0.03-3.22)	1.30 (0.29-5.80)	0.32	0.73
Clinically-driven TVR	3 (5.1)	8 (14.0)	3 (5.5)	1.02 (0.21-5.06)	2.70 (0.72-10.19)	0.98	0.13
ST (ARC definite/probable)	0 (0)	0 (0)	0 (0)	-	-	-	-
0-60 months							
MACE	14 (23.8)	16 (26.4)	12 (20.3)	1.18 (0.55-2.56)	1.41 (0.67-2.98)	0.67	0.37

All-cause death	5 (8.5)	7 (11.6)	4 (6.9)	1.27 (0.34-4.74)	1.75 (0.51-5.99)	0.72	0.36
Cardiac	3 (5.2)	2 (3.6)	0 (0)	-	-	0.08	0.16
Non-cardiac	2 (3.5)	5 (8.3)	4 (6.9)	0.51 (0.09-2.79)	1.25 (0.34-4.66)	0.43	0.74
MI	3 (5.3)	2 (3.3)	2 (3.5)	1.58 (0.26-9.44)	1.02 (0.14-7.21)	0.61	0.99
Clinically-driven TLR	6 (10.8)	8 (13.4)	6 (10.2)	1.00 (0.32-3.11)	1.35 (0.47-3.91)	>0.99	0.57
Clinically-driven TVR	11 (19.3)	13 (21.7)	9 (15.4)	1.27 (0.53-3.08)	1.54 (0.66-3.59)	0.59	0.32
ST (ARC definite/probable)	0 (0)	0 (0)	0 (0)	-	-	-	-

Values are n (%) or HR (95% CI).
ARC = Academic Research Consortium; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events (the composite of all-cause death, MI, emergent bypass surgery or TLR); MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in **Tables 1 to 3**.
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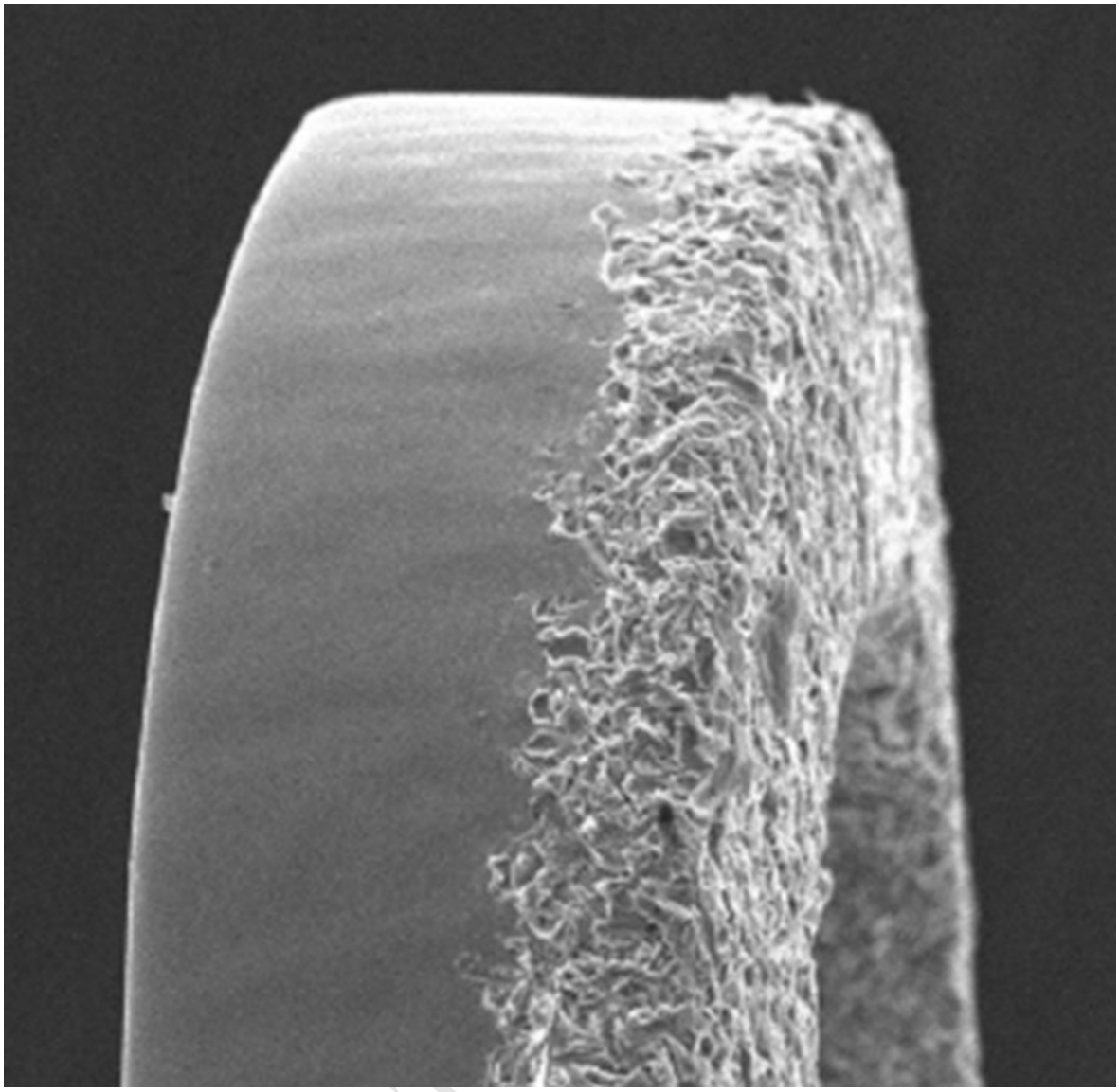
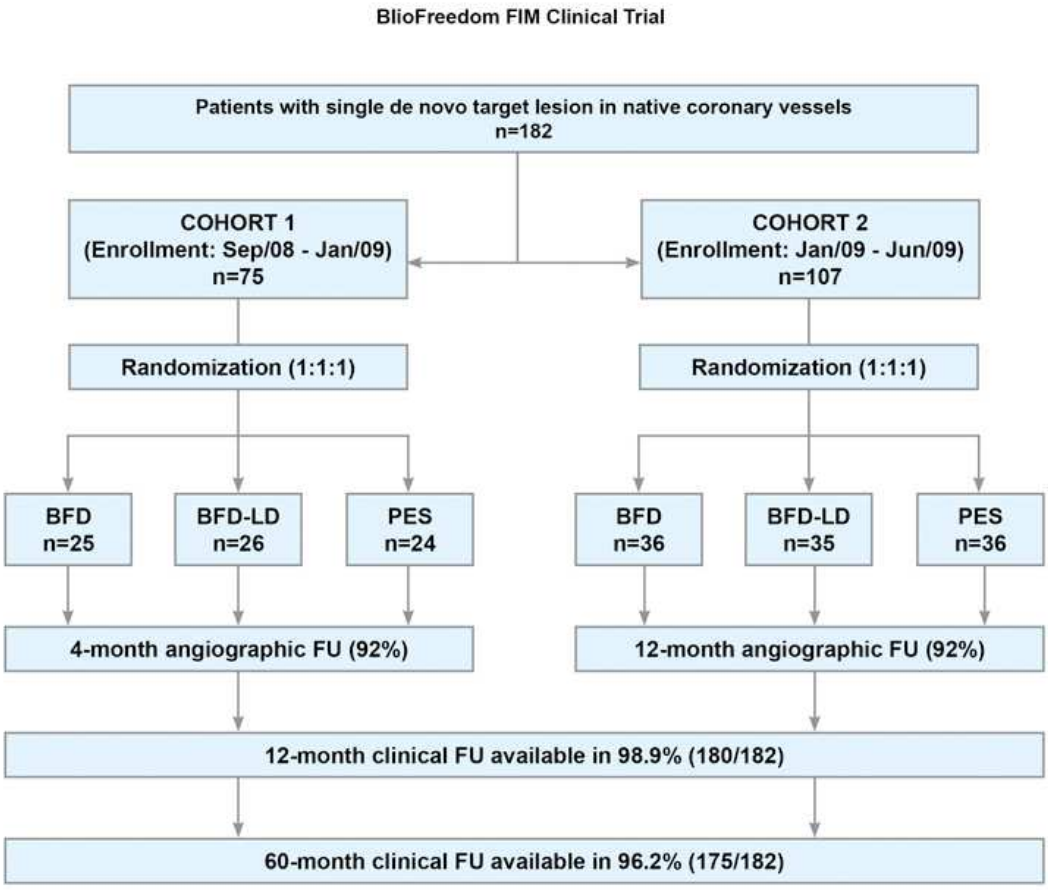
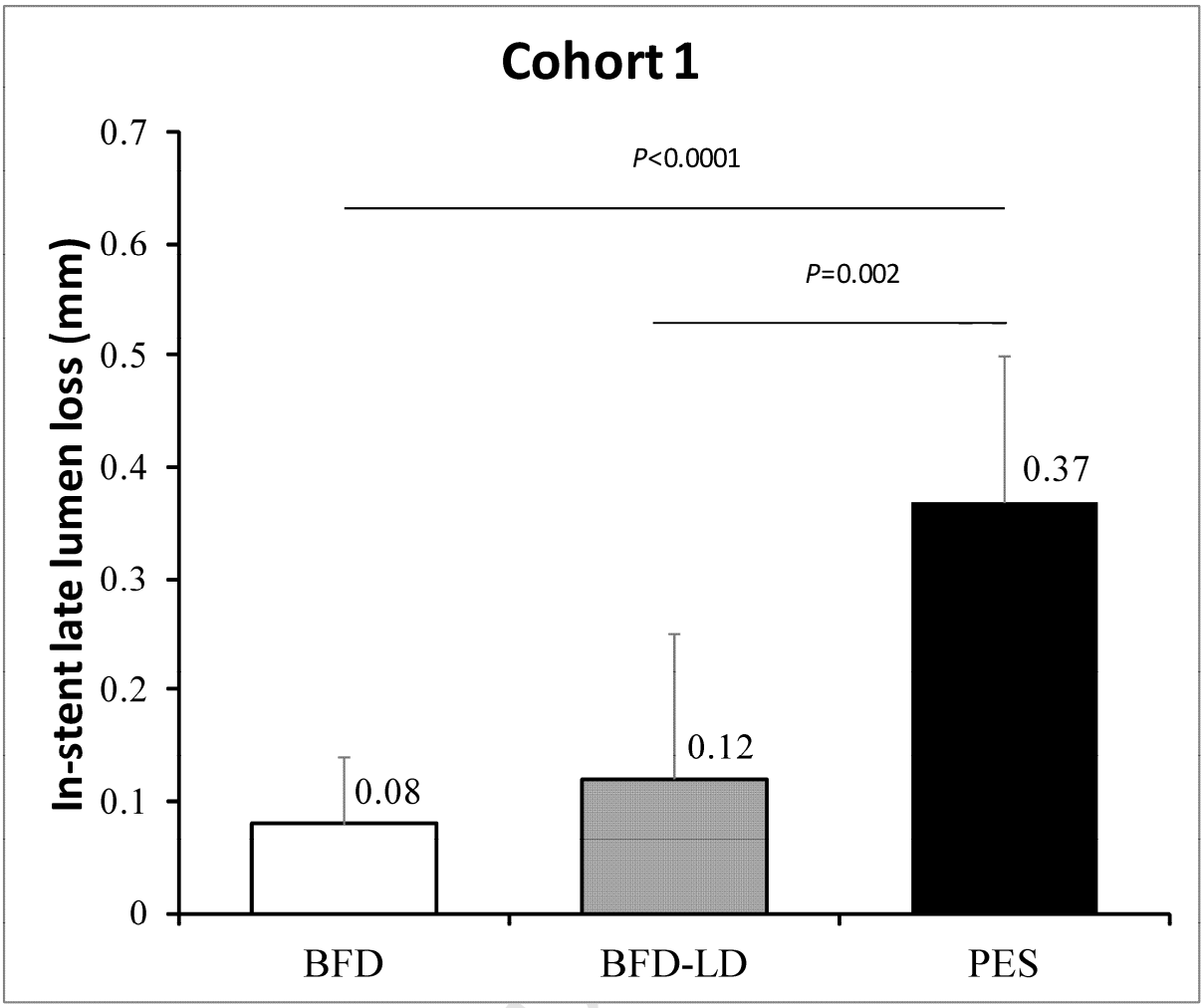



BlioFreedom FIM Clinical Trial
Patients with single de novo target lesion in native coronary vessels
n=182
COHORT 1
(Enrollment: Sep/08 - Jan/09)
n=75
COHORT 2
(Enrollment: Jan/09 - Jun/09)
n=107
Randomization (1:1:1)
Randomization (1:1:1)
BFD
n=25
BFD-LD
n=26
PES
n=24
BFD
n=36
BFD-LD
n=35
PES
n=36
4-month angiographic FU (92%)
12-month angiographic FU (92%)
12-month clinical FU available in 98.9% (180/182)
60-month clinical FU available in 96.2% (175/182)


Cohort 1
In-stent late lumen loss (mm)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
P<0.0001
P=0.002
0.08
0.12
0.37
BFD
BFD-LD
PES

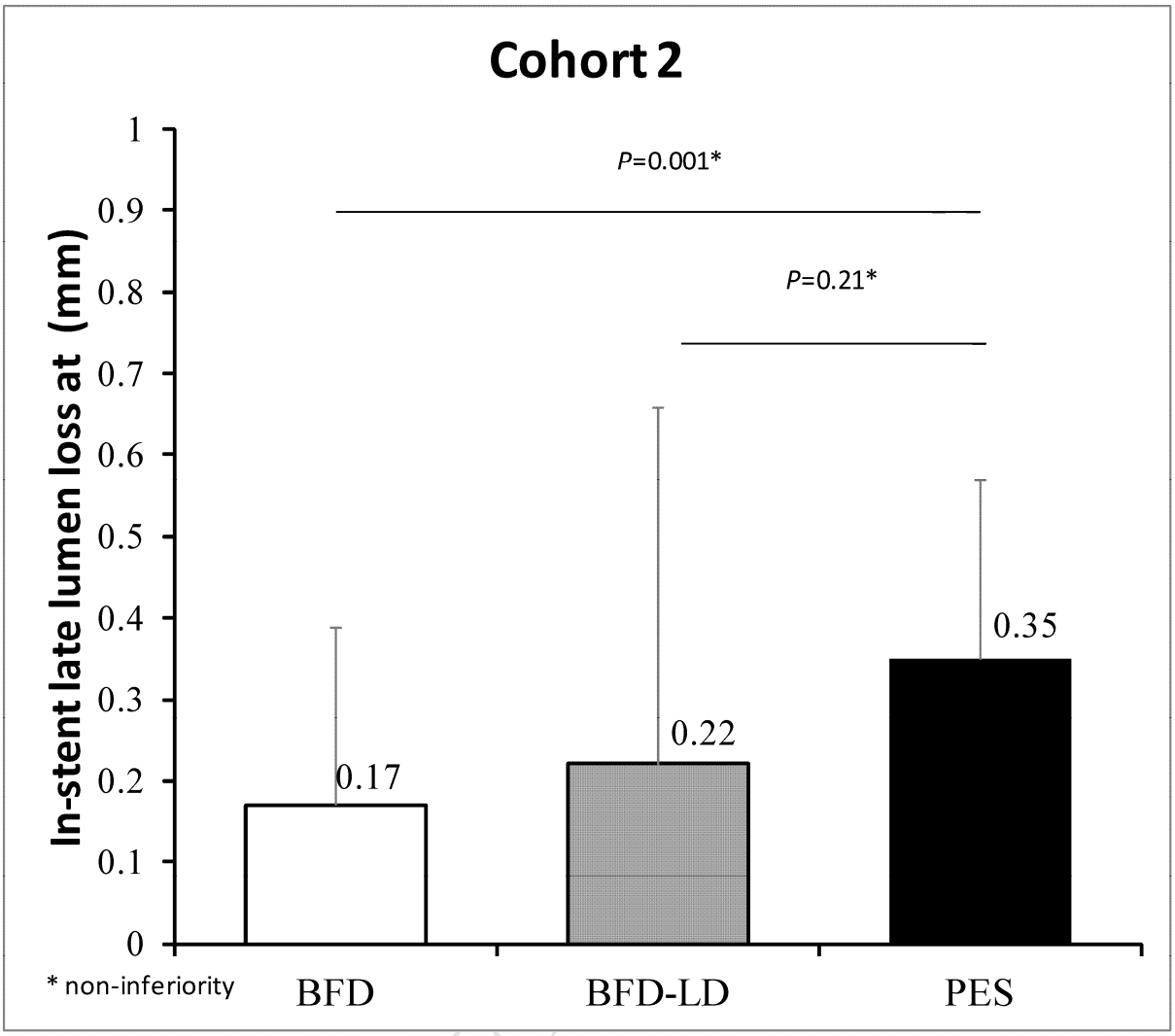


Figure 4: Cohort 1

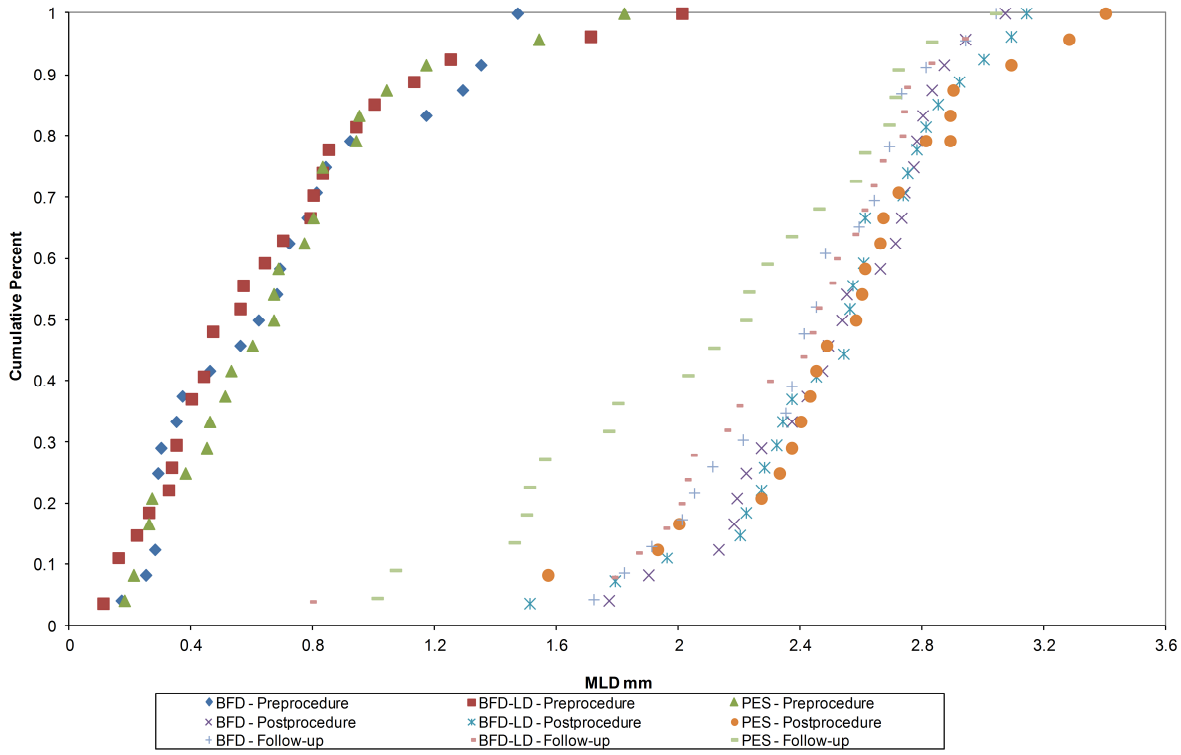
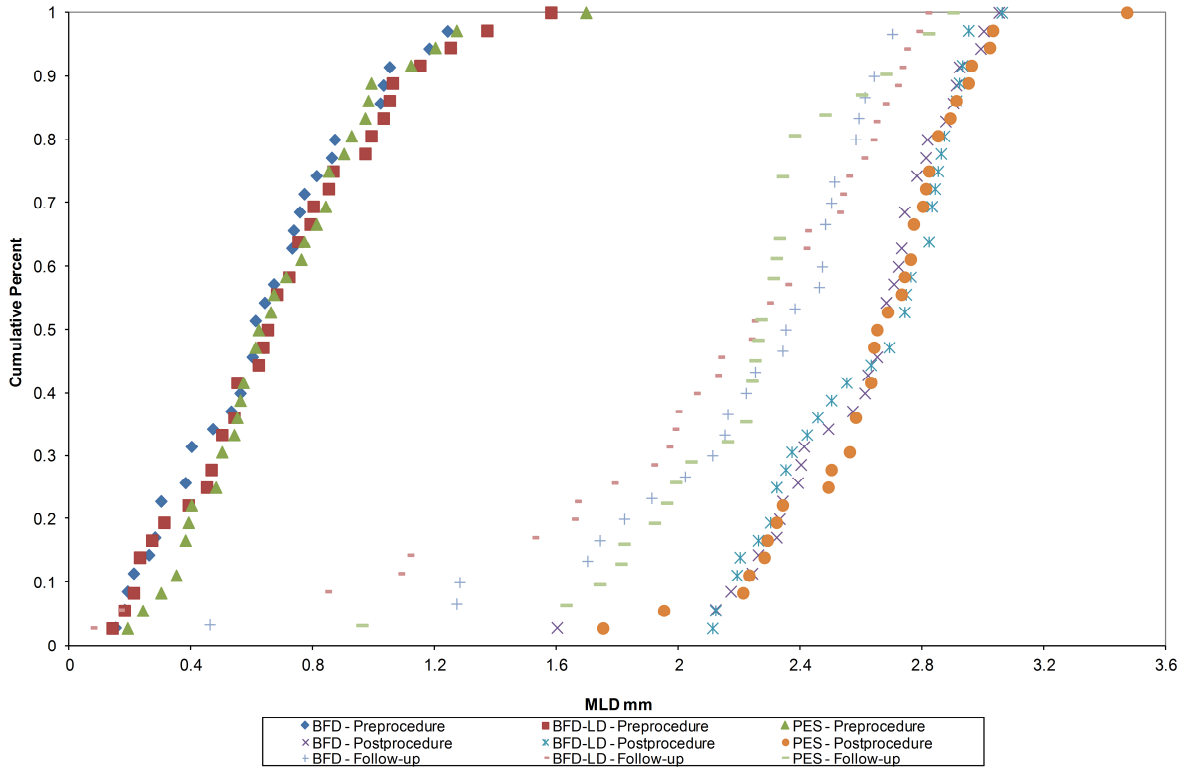
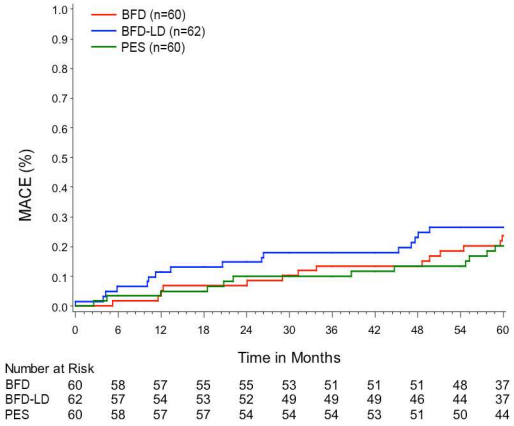


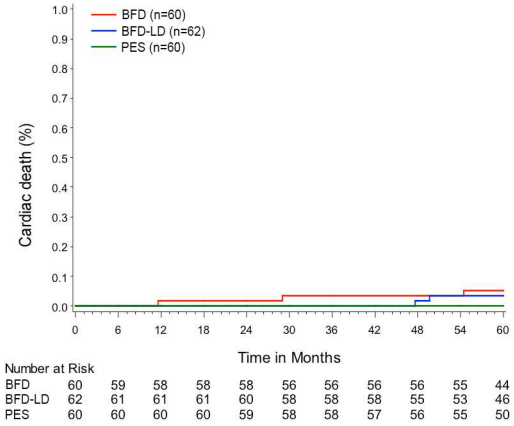
Figure 5: Cohort 2





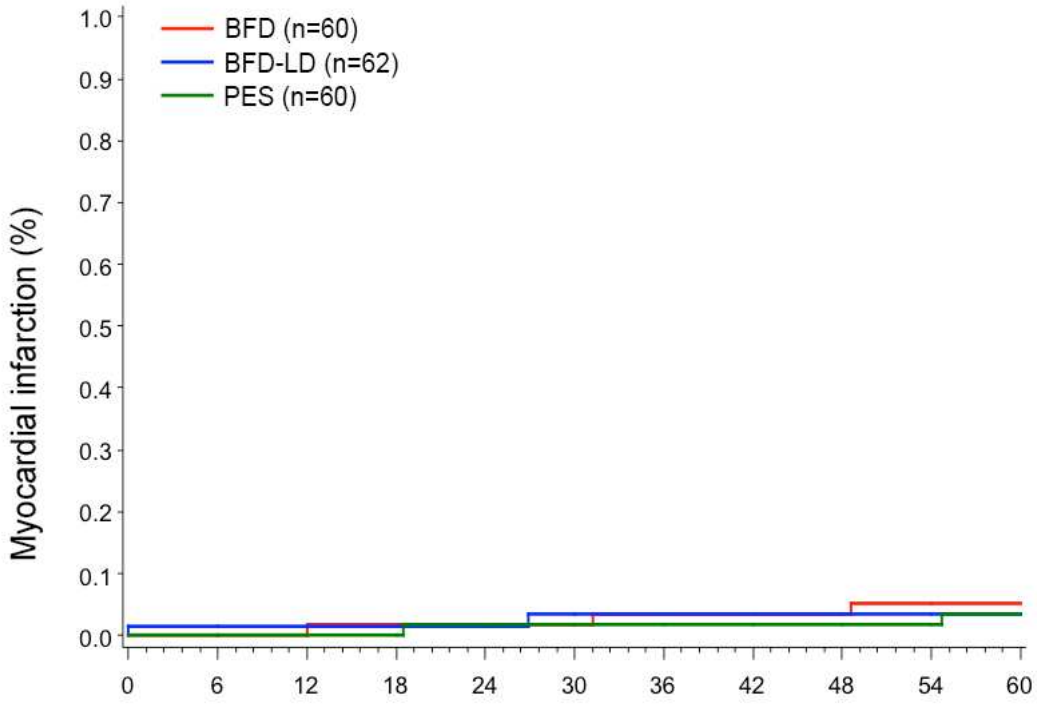
Number at Risk

BFD	60	58	57	55	55	53	51	51	51	48	37
BFD-LD	62	57	54	53	52	49	49	49	46	44	37
PES	60	58	57	57	54	54	54	53	51	50	44



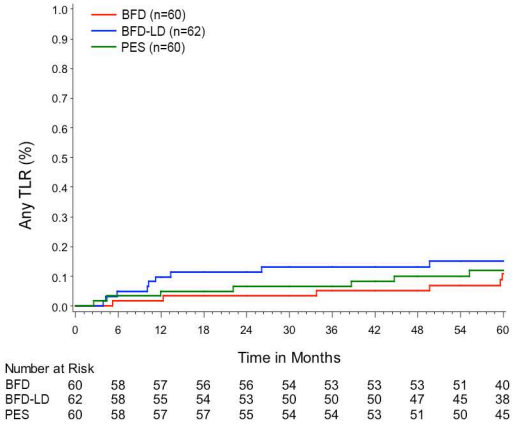
Number at Risk

BFD	60	59	58	58	58	56	56	56	56	55	44
BFD-LD	62	61	61	61	60	58	58	58	55	53	46
PES	60	60	60	60	59	58	58	57	56	55	50



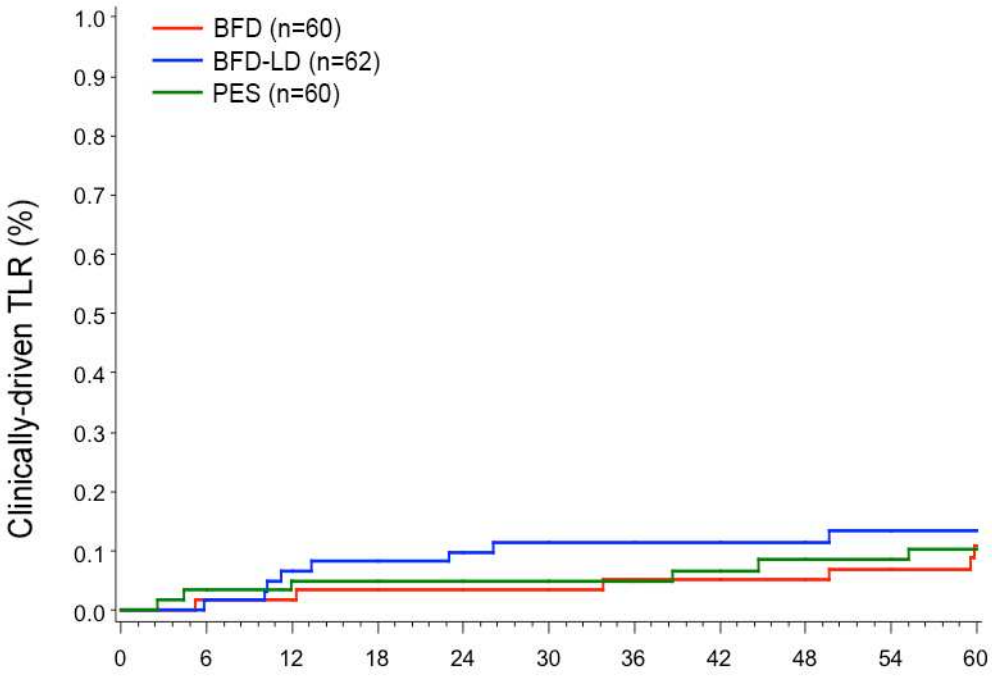
Number at Risk

BFD	60	59	58	57	57	55	54	54	54	52	41
BFD-LD	62	60	60	60	59	56	56	56	53	51	44
PES	60	60	60	60	58	58	58	57	56	55	49



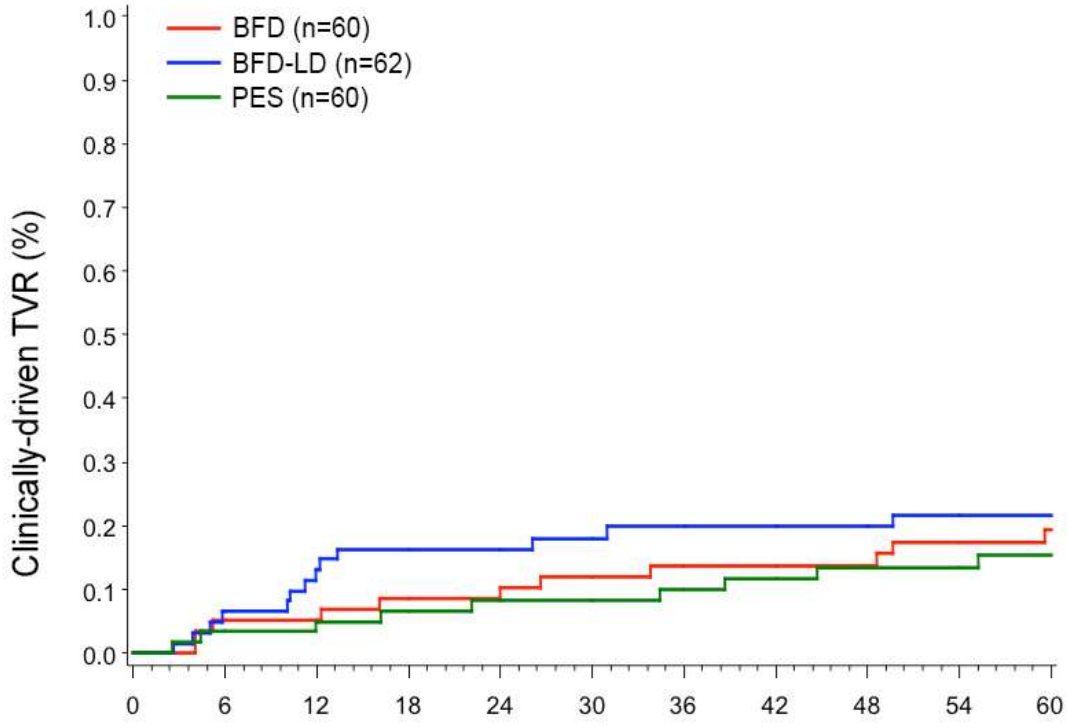
Number at Risk

BFD	60	58	57	56	56	54	53	53	53	51	40
BFD-LD	62	58	55	54	53	50	50	50	47	45	38
PES	60	58	57	57	55	54	54	53	51	50	45



Number at Risk

BFD	60	58	57	56	56	54	53	53	53	51	40
BFD-LD	62	60	57	56	54	51	51	51	48	46	39
PES	60	58	57	57	56	55	55	54	52	51	45



Number at Risk											
BFD	60	56	55	53	52	49	48	48	48	45	35
BFD-LD	62	57	53	51	50	47	46	46	43	41	35
PES	60	58	57	56	54	53	52	51	49	48	43

Online Appendix - A

BioFreedom FIM Trial Endpoints and Definitions

(Listed in alphabetical order)

Angiographic Binary Restenosis – Defined as >50% diameter stenosis at the follow-up angiogram, as determined by quantitative coronary angiography (QCA).

Late Lumen Loss – Post-procedure minimal lumen diameter (MLD) minus follow-up MLD as determined by QCA.

Major Adverse Cardiac Events (MACE) – Defined as a composite of death, MI (Q wave and non-Q wave), emergent bypass surgery, or TLR (repeat PTCA or CABG).

Minimum Lumen Diameter (MLD) – Defined as the mean minimum lumen diameter derived from two orthogonal views.

Myocardial Infarction (MI) – A positive diagnosis of MI was made when one of the following criteria was met:

- Q wave MI (QMI) required one of the following criteria:
  - Chest pain or other acute symptoms consistent with myocardial ischemia and new pathological Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC, in the absence of timely cardiac enzyme data.
  - New pathologic Q waves in two or more contiguous ECG leads as determined by an ECG core laboratory or independent review of the CEC and elevation of

cardiac enzymes. In the absence of ECG data the CEC may adjudicate Q wave MI based on the clinical scenario and appropriate cardiac enzyme data.

- Non-Q Wave MI (NQWMI) required the following (FDA) definition:
  - Elevated CK > 2X the upper laboratory normal with the presence of elevated CK-MB (any amount above the institution's upper limit of normal) in the absence of new pathological Q waves.

Target Lesion Revascularization (TLR) – Defined as any repeat percutaneous intervention of the target lesion or bypass surgery of the target vessel.

- Clinically-driven revascularizations are those in which the subject has a positive functional study, ischemic ECG changes at rest in a distribution consistent with the target vessel, or ischemic symptoms. Revascularization of a target lesion with an in-segment diameter stenosis 70% (by QCA) in the absence of the above-mentioned ischemic signs or symptoms is also considered clinically-driven. In the absence of QCA data for relevant follow-up angiograms, the clinical need for revascularization is adjudicated using the presence or absence of ischemic signs and symptoms.

Target Lesion Failure (TLF) – Cardiac death that cannot be clearly attributed to a non-cardiac event or non-target vessel, target vessel related MI or clinically-driven TLR.

Target Vessel Failure (TVF) – Defined as a composite of TVR, recurrent QMI or NQWMI, or cardiac death that could not be clearly attributed to a vessel other than the target vessel.

Target Vessel Revascularization (TVR) – Defined as any repeat percutaneous intervention of the target vessel whether PCI or bypass surgery. Clinically-driven TVR is defined the same as above for TLR.

Stent Thrombosis (ST) – Defined according to the Academic Research Consortium (ARC) definitions:

- ***Definite ST***: Definite stent thrombosis was considered to have occurred by either angiographic or pathologic confirmation:
    - Angiographic confirmation of stent thrombosis included Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 with occlusion originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus, or TIMI flow grade 1, 2, or 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of a thrombus; and,
    - At least one of the following criteria within a 48 hours time window: a) new acute onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes), b) new ischemic ECG changes suggestive of acute ischemia, and c) typical rise and fall in cardiac biomarkers (as defined for non-procedural related MI).
- ***Probable ST***: Clinical definition of probable stent thrombosis was considered to have occurred after intracoronary stenting in the following cases:
    - Any unexplained death within the first 30 days.
    - Irrespective of the time after the index procedure any MI (MI), which was related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

- ***Possible ST***: Clinical definition of possible stent thrombosis was considered to have occurred with any unexplained death from 30 days following intracoronary stenting until end of trial follow-up.
- ST was also classified according to the timing of its occurence:
    - Acute: 0 to 24 hours post stent implantation;
    - Subacute: > 24 hours to 30 days post stent implantation;
    - Late ST: > 30 days to 1 year post stent implantation;
    - Very late ST: > 1 year post stent implantation.

Success:

- ***Device*** **–** Attainment of <50% residual stenosis of the target lesion using the BioFreedom coronary stent and delivery system.
- ***Lesion*** **–** Attainment of <50% residual stenosis of the target lesion using any percutaneous method.
- ***Procedure*** **–** Attainment of <50% residual stenosis of the target lesion and no in-hospital MACE.

Vascular Complications – Vascular complications may include the following:

- Pseudoaneurysm;
- Arteriovenous fistula;
- Peripheral ischemia/nerve injury;
- Vascular event requiring transfusion or surgical repair.

Online Appendix - B

BioFreedom FIM Trial Study Organization

Investigators and Sites: Eberhard Grube, MD (Principal Investigator) – Helios Heart Center, Siegburg, Germany; Karl E. Hauptmann, MD – Krankenhaus der Barmherzigen Brüder, Trier, Germany; Joachim Schofer, MD – Medical Care Center, Hamburg University Cardiovascular Center, Hamburg, Germany; Gerhard C. Schuler – Herzzentrum Leipzig GmbH, Leipzig, Germany, MD.

Steering Committee: Eberhard Grube, MD (Principal Investigator) – Helios Heart Center, Siegburg, Germany; Alexandre Abizaid, MD, PhD – Institute Dante Pazzanese of Cardiology, São Paulo, SP, Brazil; Roxana Mehran, MD – Cardiovascular Research Foundation, New York, NY, USA; John Shulze – Biosensors Europe SA, Morges, Switzerland.

Data Coordinating Center (DCC): Cardiovascular Research Foundation, New York, NY, USA – Roxana Mehran, MD (Director).

Monitoring: Claudia Czub, Ulrike Gross, Kerstin Kupfer, Germany.

Clinical Events Committee (CEC): Cardiovascular Research Foundation, New York, NY, USA. Members: William Gray, MD – Columbia University Medical Center, New York, NY, USA; William Sherman, MD – Columbia University Medical Center, New York, NY, USA; Giora Weisz, MD – Columbia University Medical Center, New York, NY, USA.

Data Safety and Monitoring Board (DSMB): John A. Ambrose, MD – University of California, Fresno, CA, USA; Peter B. Berger, MD – Geisinger Health System, Danville, PA,

USA; Tim C. Clayton, MSc – Medical Statistics Unit, London School of Hygiene & Tropical Medicine, London, UK.

Angiographic Core Laboratory: Cardiovascular Research Center, São Paulo, SP, Brazil – Ricardo A. Costa, MD, PhD (Director).

Intravascular Ultrasound Core Laboratory: Stanford University Cardiovascular Core Analysis Laboratory, Stanford, CA, USA – Peter Fitzgerald, MD, PhD (Director).

Electrocardiogram Core Laboratory: Cardiovascular Research Foundation, New York, NY, USA – Alexandra J. Lansky, MD (Director).

Sponsor: Biosensors Europe SA, Morges, Switzerland.

Online Appendix - C

Angiographic Analysis

Serial coronary angiographic studies were obtained after intracoronary administration of nitroglyceryn (100-200µg, unless contra-indicated) in 2 orthogonal matching views at preprocedure, postprocedure and FU. Angiographic analysis was performed *offline* by experienced operators blinded to group allocation, procedural data and clinical outcomes, at an independent core laboratory (Cardiovascular Research Center, São Paulo, Brazil). Quantitative analysis was performed with validated 2D software for QCA analysis (QAngio XA® version 7.2, Medis, Leiden, the Netherlands), as previously reported (1). The minimal lumen diameter (MLD) and the mean reference diameter (RD), obtained from averaging 5mm proximal and distal segments to the target lesion, were used to calculate the diameter stenosis [DS=(1–MLD/RD)x100]. Acute gain was the change in MLD from baseline to post-stent implantation; LLL was the change in MLD from the post-stent implantation angiogram to FU; LLL index was LLL divided by acute gain. Binary restenosis was defined as stenosis ≥50% at angiographic FU, and was classified according to the Mehran classification (2). Overall, QCA measurements were reported “in-stent” within the stented segment, “in-segment”, spanning the stented segment plus the 5 mm proximal and distal peri-stent areas, and at 5mm proximal and distal peri-stent edges (outside the stent).

References:

1. Dani S, Costa RA, Joshi H, et al. First-in-human evaluation of the novel BioMime sirolimus-eluting coronary stent with bioabsorbable polymer for the treatment of single de novo lesions located in native coronary vessels - results from the meriT-1 trial. *EuroIntervention*. 2013;9:493-500.

2. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation*. 1999;100:1872-8.

Online Appendix D - Online Tables

ONLINE TABLE 1. Procedure Data of the Overall Population Comparing BFD and BFD-LD versus PES.

Variable	BFD (a)	BFD-LD (b)	PES (c)	*P* value	
				(a) vs. (c)	(b) vs. (c)
Patients/lesions, n	60/60	62/63	60/60		
Balloon Predilatation, n (%)	56 (94.9)	58 (92.1)	55 (91.7)	0.48	0.94
Study stent implanted, n (%)	60 (100)	62 (100)	60 (100)	-	-
Additional study stent implanted, n (%)	6 (10.2)	6 (9.5)	3 (5.0)	0.29	0.34
Stents per patient, n	1.1±0.3	1.1±0.3	1.1±0.2	0.30	0.33
Total stent length, mm	17.6±4.8	17.5±4.7	16.9±4.0	0.81	0.85
Maximum deployment pressure, atm	13.6±3.7	13.4±3.4	14.7±3.0	0.07	0.04
Balloon postdilatation, n (%)	11 (18.6)	18 (28.6)	14 (23.3)	0.53	0.51
Final TIMI 3 flow, n (%)	60 (100)	62 (100)	60 (100)	-	-
Lesion success, n (%)	60 (100)	62 (100)	60 (100)	-	-
Procedural success, n (%)	60 (100)	61 (98.4)*	60 (100)	-	0.32

Values are n (%). *One patient developed periprocedural non-Q wave myocardial infarction.

BFD = BioFreedom “standard dose" stents; BFD-LD = BioFreedom “low dose" stents; TIMI = Thrombolysis In Myocardial Infarction.

ONLINE TABLE 2B. QCA Results at Postprocedure for Cohorts 1 and 2 Comparing BFD and BFD-LD versus PES.

Variable	BFD (a)	BFD-LD (b)	PES (c)	p value	
				(a) vs. (c)	(b) vs. (c)
Cohort 1					
n	24	27	24		
RD, mm	2.8 (2.5-2.9)	2.8 (2.6-3.0)	2.8 (2.5-3.1)	0.67	0.81
In-stent					
Mean diameter, mm	2.8 (2.5-3.1)	2.9 (2.6-3.1)	2.8 (2.6-3.2)	0.48	0.76
MLD, mm	2.5 (2.2-2.8)	2.6 (2.3-2.8)	2.6 (2.4-2.9)	0.45	0.40
% DS	6.3 (3.8-9.9)	8.7 (4.7-13.0)	6.3 (3.5-9.9)	0.89	0.17
Acute gain, mm	1.7 (1.5-2.3)	1.8 (1.7-2.2)	1.9 (1.6-2.2)	0.70	0.81
In-segment					
MLD, mm	2.1 (2.0-2.5)	2.3 (1.9-2.4)	2.2 (2.0-2.5)	0.34	0.87
% DS	18.6 (14.2-29.2)	19.6 (12.8-24.4)	19.1 (13.2-22.2)	0.59	0.76
Acute gain, mm	1.4 (1.1-1.8)	1.6 (1.4-1.9)	1.5 (1.2-2.0)	0.33	0.88
Proximal edge					
MLD, mm	2.3 (2.0-2.6)	2.6 (2.4-2.8)	2.5 (2.3-2.9)	0.18	0.78

% DS	12.3 (6.0-22.1)	8.0 (4.9-13.6)	12.5 (7.9-20.9)	0.97	0.09
Distal edge					
MLD, mm	2.2 (2.0-2.5)	2.3 (2.1-2.8)	2.2 (2.0-2.4)	0.75	0.45
% DS	14.5 (11.0-18.9)	11.0 (6.1-15.0)	12.6 (8.3-17.2)	0.31	0.42
Balloon-artery ratio	1.2 (1.1-1.2)	1.1 (1.1-1.2)	1.1 (1.1-1.2)	0.51	0.73
Cohort 2					
n	35	36	36		
RD, mm	2.9 (2.6-3.0)	2.9 (2.5-3.0)	2.9 (2.6-2.9)	0.44	0.81
In-stent					
Mean diameter, mm	2.9 (2.7-3.0)	2.9 (2.5-3.0)	2.9 (2.6-3.0)	0.57	0.85
MLD, mm	2.7 (2.4-2.8)	2.7 (2.3-2.9)	2.7 (2.5-2.8)	0.68	0.95
% DS	6.2 (4.3-12.0)	6.2 (4.0-8.0)	5.9 (3.6-8.6)	0.52	0.84
Acute gain, mm	2.0 (1.6-2.2)	1.9 (1.7-2.2)	1.9 (1.7-2.2)	0.66	0.79
In-segment					
MLD, mm	2.3 (2.1-2.6)	2.2 (2.1-2.5)	2.2 (2.0-2.6)	0.67	>0.99
% DS	17.2 (8.0-23.6)	16.0 (11.9-22.6)	18.2 (10.6-24.3)	0.70	0.80
Acute gain, mm	1.6 (1.4-2.0)	1.6 (1.4-1.8)	1.6 (1.4-2.0)	0.73	0.80

Proximal edge					
MLD, mm	2.7 (2.4-2.9)	2.4 (2.2-3.0)	2.5 (2.3-2.8)	0.29	0.55
% DS	7.8 (4.7-11.7)	10.9 (4.8-20.3)	10.7 (5.7-17.1)	0.28	0.65
Distal edge					
MLD, mm	2.3 (2.1-2.6)	2.3 (2.1-2.6)	2.3 (2.0-2.6)	0.69	0.58
% DS	14.5 (11.0-18.9)	11.0 (6.1-15.0)	12.6 (8.3-17.2)	0.31	0.42
Balloon-artery ratio	1.1 (1.1-1.2)	1.1 (1.1-1.2)	1.1 (1.1-1.2)	0.94	0.85

Values are median (interquartile range).

DS = diameter stenosis; MLD = minimum lumen diameter; QCA = quantitative coronary angiography; RD = reference diameter; other abbreviations as in Online Table 1.

Online Table 3. Clinical Outcomes Occurring Between 1 and 5 Years for the Overall Study Population Comparing BFD and BFD-LD versus PES.

Events between 1 and 5 years	BFD	BFD-LD	PES	HR (95% CI)		p value	
	(a)	(b)	(c)	(a) vs. (c)	(b) vs. (c)	(a) vs. (c)	(b) vs. (c)
All-cause death	4 (6.7)	7 (11.3)	4 (6.7)	1.02 (0.23-4.10)	1.75 (0.51-6.00)	0.98	0.37
Cardiac	2 (3.3)	2 (3.2)	0 (0)	-	-	-	-
MI	2 (3.3)	1 (1.6)	2 (3.3)	1.04 (0.15-7.36)	0.51 (0.05-5.59)	0.97	0.58
Clinically-driven TLR	5 (8.3)	4 (6.4)	3 (5.0)	1.71 (0.41-7.17)	1.37 (0.31-6.14)	0.46	0.68
Clinically-driven TVR	8 (13.3)	5 (8.1)	6 (10.0)	1.39 (0.48-4.00)	0.84 (0.36-2.76)	0.54	0.77
ST (ARC definite/probable)	0 (0)	0 (0)	0 (0)	-	-	-	-

Values are n (%) or HR (95% CI).

ARC = Academic Research Consortium; CI = confidential interval; HR = hazard ratio; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.