

CLINICAL RESEARCH

Interventional Cardiology

A Randomized Multicenter Study Comparing a Paclitaxel Drug-Eluting Balloon With a Paclitaxel-Eluting Stent in Small Coronary Vessels

The BELLO (Balloon Elution and Late Loss Optimization) Study

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Objectives

The aim of this study was to evaluate the efficacy of drug-eluting balloons (DEB) compared with paclitaxel-eluting stents (PES) for the reduction of restenosis in small vessels.

Background

DEB have been shown to be effective in the treatment of coronary in-stent restenosis, but data are limited regarding their efficacy in de novo disease.

Methods

BELLO (Balloon Elution and Late Loss Optimization) is a prospective, multicenter trial that randomized 182 patients with lesions located in small vessels (reference diameter <2.8 mm) to treatment with paclitaxel DEB and provisional bare-metal stenting (n = 90) or PES implantation (n = 92). The primary endpoint was noninferiority of angiographic in-stent (in-balloon) late loss with a delta of 0.25 mm. Secondary endpoints were angiographic restenosis, target lesion revascularization, and major adverse cardiac events (MACE; death, myocardial infarction, target vessel revascularization) at 6 months.

Results

Baseline characteristics were well matched, except for a smaller vessel size in the DEB group (2.15 ± 0.27 mm vs. 2.25 ± 0.24 mm; $p = 0.003$). The majority (89%) of lesions involved vessels with a diameter <2.5 mm. Bail-out stenting was required in 20% of lesions in the DEB group. The primary endpoint of in-stent (in-balloon) late loss was significantly less with DEB compared with PES (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; difference -0.21 ; 95% CI: -0.34 to -0.09 ; $p_{\text{noninferiority}} < 0.001$; $p_{\text{superiority}} = 0.001$). At 6 months, DEB and PES were associated with similar rates of angiographic restenosis (8.9% vs. 14.1%; $p = 0.25$), target lesion revascularization (4.4% vs. 7.6%; $p = 0.37$), and MACE (7.8% vs. 13.2%; $p = 0.77$).

Conclusions

Treatment of small-vessel disease with a paclitaxel DEB was associated with less angiographic late loss and similar rates of restenosis and revascularization as a PES. (Balloon Elution and Late Loss Optimization [BELLO]; Study NCT01086579) (J Am Coll Cardiol 2012;60:2473–80) © 2012 by the American College of Cardiology Foundation

Drug-eluting balloons (DEB) are emerging as an effective treatment for in-stent restenosis in both bare-metal stents

(BMS) (1,2) and drug-eluting stents (DES) (3,4). However, the efficacy of these devices in de novo lesions needs to be

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**Abbreviations
and Acronyms**

| | |
|-------------|-----------------------------------|
| BMS | = bare-metal stent(s) |
| CI | = confidence interval |
| DEB | = drug-eluting balloon(s) |
| DES | = drug-eluting stent(s) |
| ECG | = electrocardiogram |
| MACE | = major adverse cardiac event |
| MI | = myocardial infarction |
| MLD | = minimum lumen diameter |
| PES | = paclitaxel-eluting stents |
| RVD | = reference vessel diameter |
| TLR | = target lesion revascularization |
| TVR | = target vessel revascularization |

established. Small coronary vessels remain a lesion subset in which DES remain associated with relatively high restenosis rates, especially in real-world patients and registries (5,6). In some circumstances, the extent of the disease may demand implantation of long stents. Therefore, a suitable alternative to stent implantation to treat small-vessel disease is desirable. In addition, treatment of patients with multivessel disease could benefit from a strategy of DES implantation on the proximal major epicardial vessels and angioplasty with DEB of more distal lesions. DEB may also provide significant theoretical advantages over DES such as a lower risk of stent thrombosis, shorter durations, and less dependence on dual antiplatelet therapy.

Because limited and inconsistent data are available for DEB in small-vessel disease (7,8), we performed a randomized study to evaluate the efficacy and safety of DEB as compared with paclitaxel-eluting stent (PES) implantation for the reduction of restenosis in patients with coronary artery disease in small vessels.

Methods

The BELLO (Balloon Elution and Late Loss Optimization) trial was an investigator-initiated, prospective, multicenter, single-blinded, active-treatment controlled clinical trial in which 182 patients undergoing percutaneous revascularization of small coronary vessels (reference vessel diameter [RVD] <2.8 mm by visual estimation) were randomly assigned in a 1:1 ratio to treatment with: 1) IN.PACT Falcon paclitaxel DEB (Medtronic, Inc., Santa Rosa, California) dilation and provisional BMS; or 2) PES (Taxus Liberté, Boston Scientific, Boston, Massachusetts) implantation as per standard practice. Eligible patients were age 18 years or older, with a diagnosis of stable or unstable angina or documented silent ischemia and a maximum of 2 angiographically significant de novo target lesions <25 mm in length in native coronary arteries with a visually estimated RVD <2.8 mm. Clinical exclusion criteria included acute myocardial infarction (MI) within the previous 48 h; previous percutaneous coronary intervention within the last 3 months; elective surgery planned within 6 months after the procedure; left ventricular ejection fraction <30%; serum creatinine ≥ 2.0 $\mu\text{mol/l}$; contraindication or suspected intolerance to paclitaxel, aspirin, thienopyridines, or iodinated contrast that cannot be pre-treated; platelet count <50,000 cells/mm; positive pregnancy test; and stroke within the

previous 6 months. Angiographic exclusion criteria were more than 3 epicardial vessels requiring revascularization, aorto-ostial lesions, restenotic lesions, lesions in bypass grafts, chronic total occlusions, thrombus within the target lesion, and bifurcation lesions in which the operator decides that a 2-stent technique as intention to treat is required or bifurcations with side branches ≥ 2.5 mm. Treatment of other lesions not meeting the inclusion criteria (i.e., nontarget lesions located in large vessels) during the index procedure was permitted, but the lesion must have been successfully treated before randomization and not with the study device (DEB).

The study protocol was approved by the ethics committees at each participating center, and all patients provided written informed consent.

Procedure. After successfully treatment of nontarget lesions and crossing of the target lesion with a guidewire, patients were randomized to the treatment arms with the use of sealed opaque envelopes containing a computer-generated randomization sequence. In the case of treatment of more than 1 target lesion, the treatment selected had to remain the same for both lesions. In the DEB arm, pre-dilation with a standard balloon was recommended in all lesions. The diameter and length of the DEB were selected with a balloon:artery ratio of 1:1 and 2.5 to 5 mm (per edge) longer, respectively, than the target lesion. DEB were inflated only once for 30 to 60 s at an inflation pressure approximately or slightly beyond nominal to achieve complete apposition of the balloon on the vessel wall, while trying to avoid edge dissection. Bailout provisional stenting with BMS was permitted in the DEB arm only in cases of a suboptimal result, defined as a persistent residual stenosis refractory to optimal balloon dilation or in cases of flow-limiting dissection. In cases of stenting, the protocol recommended using the shortest stent length to fully cover the residual stenosis or seal the dissection and recommended that the stent be deployed entirely within the area treated with DEB to avoid geographic miss. In the PES arm, stent implantation was performed as per standard practice and post-dilation per operator's discretion.

All patients were pre-treated with aspirin and either ticlopidine or clopidogrel. A 600-mg loading dose of clopidogrel before the index procedure was administered if patients were not pre-treated. Procedural anticoagulation was achieved with either intravenous unfractionated heparin or bivalirudin per standard of care, and the administration of glycoprotein IIb/IIIa inhibitors was per operator's discretion. Following the procedure, an electrocardiogram (ECG) was performed and cardiac enzyme levels were measured. The protocol recommended that patients receive aspirin indefinitely and daily clopidogrel (or ticlopidine, if required) for a minimum of: 1) 30 days in case of treatment with only DEB; 2) 3 months in case of provisional BMS after DEB; and 3) 12 months after DES implantation. Clinical follow-up was performed with visits or telephone contact at

1 and 6 months. Adverse events were monitored throughout the entire study period. Protocol-specified angiographic follow-up was scheduled at 6 months after the procedure for all patients unless necessary at an earlier time for clinical reasons.

Quantitative coronary angiographic measurements. Coronary angiograms were analyzed offline using a validated edge detection system (CMS, version 5.2, Medis Medical Imaging Systems BV, Leiden, the Netherlands) by an expert operator at an independent core laboratory (Mediolanum Cardio Research, Milan, Italy). Minimal lumen diameter (MLD), RVD, and percent diameter stenosis were measured at baseline, post-procedure, and follow-up. All angiographic parameters were calculated both in-stent and in-segment (stent and 5 mm proximal and distal). In the DEB group, in-stent referred to the in-balloon measurement (irrespective of whether bailout BMS implantation was performed), whereas in-segment was defined as the segment treated with the DEB, including 5 mm proximal and distal. For accurate performance of these analyses for the DEB group, the protocol mandated that the operator film the inflated DEB and that the final and follow-up angiogram be performed in the same projection. Late lumen loss was defined as the difference between the MLD immediately after the procedure and at 6-month follow-up. Net lumen gain was defined as the difference between the MLD at follow-up and at baseline. Binary angiographic restenosis was defined as diameter stenosis $\geq 50\%$ by quantitative coronary angiography within a previously stented segment (stent and 5 mm proximal and distal) at the follow-up angiogram. The pattern of restenosis at follow-up was categorized according to the Mehran classification (9).

Study endpoints and definitions. The primary endpoint of the study was angiographic in-stent (in-balloon) late lumen loss at follow-up angiography. Secondary endpoints included the occurrence of major adverse cardiac events (MACE), defined as the composite of death, Q- or non-Q-wave MI, or target vessel revascularization (TVR) at 30 days and 6 months. Additional prespecified secondary endpoints included target lesion revascularization (TLR), binary restenosis, device success, and procedural success. TVR was defined as any repeat revascularization of the target vessel, and TLR was defined as any repeat revascularization within the stented or DEB-treated segment. Periprocedural MI was defined as an elevation of cardiac biomarkers (troponin or creatine kinase-myocardial band) >3 times the upper limit of normal. Nonprocedural acute MI was defined as an elevation of troponin above the upper range limit in combination with at least one of the following: ischemic symptoms, ECG changes indicative of new ischemia, development of new pathological Q waves on ECG, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality (10). Stent thrombosis was classified according to the Academic Research Consortium definition (11). Device success was defined as the ability of the investigational device to be delivered, dilated,

and retrieved from the target lesion. Procedural success was defined as device success without the occurrence of death, MI, or repeat revascularization of the target lesion during the hospital stay. Independent study monitors verified data from case report forms on-site. The clinical study endpoints were adjudicated by an independent clinical events committee, blinded to treatment allocation, after review of original source documentation.

Statistical analysis. The study tested the hypothesis that DEB were noninferior to PES in reducing in-stent (in-balloon) late loss at follow-up angiography. The sample size calculations were based on the assumptions that the standard deviation of late loss was 0.5 mm in both groups, as demonstrated in the ISAR-SMART 3 (Intracoronary Drug-Eluting Stenting to Abrogate Restenosis in Small Arteries) (5) and PEPCAD II (Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease II) (2) trials, and that a noninferiority margin of 0.25 mm between groups was likely to be clinically insignificant. Based on these calculations, a sample size of 77 patients was required in each group to show noninferiority of DEB versus PES with an alpha error of 2.5% and a power of 80%. To account for a 20% rate of withdrawal, lost to follow-up, or patient refusal of follow-up angiography, a total of 182 patients were randomized. Noninferiority for in-stent late loss was declared if the upper limit of the 2-sided 95% confidence interval (CI) difference in late loss (DEB minus PES) did not exceed a delta of 0.25 mm from the observed late loss in the PES group (12). Because noninferiority and superiority can be assessed in the same trial without statistical penalty, superiority testing for the primary endpoint was performed after noninferiority was demonstrated (13,14). Superiority of DEB over PES was declared if the upper limit of the 2-sided 95% CI for the difference in late loss did not exceed zero.

All analyses were conducted according to the intention-to-treat principle. Continuous variables are presented as mean \pm SD and were compared by Student *t* test. Categorical variables were compared with the chi-square or Fisher exact test. A 2-sided *p* value <0.05 was considered statistically significant. All analyses were performed with the statistical program SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 182 patients were enrolled at 15 Italian centers and randomized to treatment with DEB (*n* = 90) in 94 lesions or PES (*n* = 92) in 98 lesions. Baseline clinical characteristics of the patients and treated lesions were well matched between the 2 groups, except for a higher frequency of previous percutaneous revascularization in the DEB group (Table 1). Notably, there was a high incidence of diabetes mellitus in both groups (43.3% in DEB and 38% in PES) and a higher incidence of insulin-treated diabetes in the DEB group (17.8% vs. 9.8%; *p* = 0.12).

| | DEB | PES | p Value |
|--------------------------------|-------------|-------------|---------|
| Patients | 90 | 92 | |
| Age, yrs | 64.8 ± 8.5 | 66.4 ± 9.0 | 0.23 |
| Men | 72 (80) | 71 (77.2) | 0.64 |
| Diabetes mellitus | 39 (43.3) | 35 (38) | 0.47 |
| Insulin-treated diabetes | 16 (17.8) | 9 (9.8) | 0.12 |
| Hypertension | 72 (80) | 75 (81.5) | 0.79 |
| Dyslipidemia | 71 (78.9) | 73 (79.3) | 0.94 |
| Current smokers | 15 (16.7) | 10 (10.9) | 0.17 |
| Previous MI | 46 (51.1) | 33 (35.9) | 0.25 |
| Previous PCI | 52 (57.8) | 39 (42.4) | 0.04 |
| Previous CABG | 9 (10) | 12 (13) | 0.52 |
| Family history of CAD | 24 (26.7) | 23 (25.0) | 0.80 |
| Unstable angina | 22 (24.4) | 20 (21.7) | 0.66 |
| Multivessel disease | 56 (62.2) | 56 (60.9) | 0.88 |
| Lesions | 94 | 97 | |
| Target vessel | | | |
| Left anterior descending | 10 (10.6) | 12 (11.5) | 0.71 |
| Diagonal | 16 (17.0) | 8 (8.2) | 0.07 |
| Left circumflex | 10 (10.6) | 16 (16.5) | 0.24 |
| Obtuse marginal/ramus | 25 (26.6) | 31 (32) | 0.42 |
| Right coronary artery | 8 (8.5) | 9 (9.3) | 0.85 |
| PDA/PL | 25 (26.6) | 21 (21.6) | 0.42 |
| Target lesion | | | |
| Reference vessel diameter, mm* | 2.41 ± 0.34 | 2.41 ± 0.40 | 0.96 |
| Lesion length, mm* | 15.4 ± 6.2 | 14.4 ± 5.6 | 0.23 |
| Diameter stenosis, %* | 81.9 ± 9.6 | 83.3 ± 8.7 | 0.30 |
| AHA type B2/C lesion | 45 (47.9) | 46 (47.4) | 0.89 |

Values are mean ± SD or n (%). *Visually estimated by operator.

AHA = American Heart Association; CABG = coronary artery bypass grafting; CAD = coronary artery disease; DEB = drug-eluting balloons; MI = myocardial infarction; PCI = percutaneous coronary intervention; PDA = posterior descending artery; PES = paclitaxel-eluting stents; PL = posterolateral.

The majority of the treated lesions involved branches of the major epicardial arteries, in keeping with a small-vessel study.

Procedural characteristics are shown in Table 2. Pre-dilation was performed almost routinely in the DEB group, whereas direct stenting was performed in 17.3% of lesions in the PES group. Bailout BMS was required in 20.2% of lesions, and the stent was implanted within the DEB-treated zone in all cases. Device success was not achieved in all lesions treated because of the inability to adequately pre-dilate the lesion (n = 2) or impossibility to deliver the PES (n = 2) or DEB (n = 1) to the lesion.

Angiographic outcomes. Baseline angiographic analyses confirmed that lesion length, MLD, and diameter stenosis were well matched in the 2 groups (Table 3). However, the lesions treated in the DEB group occurred in significantly smaller vessels than those in the PES group (2.15 ± 0.27 mm vs. 2.26 ± 0.24 mm; p = 0.004). Based on the quantitative coronary analyses, all lesions except for 1 in each group had an RVD <2.8 mm as stipulated by the inclusion criteria of the study. When subdivided by vessel size, the proportions of lesions in the DEB and PES group,

| | DEB (n = 94) | PES (n = 98) | p Value |
|------------------------------------|--------------|--------------|---------|
| Balloon pre-dilation | 91 (96.8) | 81 (82.7) | 0.002 |
| DEB | | | |
| Diameter, mm | 2.49 ± 0.2 | | |
| Length, mm | 25.6 ± 6.3 | | |
| Pressure, atm | 9.6 ± 2.5 | | |
| Duration of inflation, s | 56.6 ± 2.5 | | |
| Bailout BMS stenting | 19 (20.2) | | |
| Stent implanted within DEB segment | 19 (100) | | |
| PES | | | |
| Diameter, mm | | 2.49 ± 0.2 | |
| Length, mm | | 18.5 ± 5.6 | |
| Pressure, atm | | 17.2 ± 3.5 | |
| Post-dilation | | 47 (50.0) | |
| Device success | 92 (97.9) | 95 (96.9) | 0.69 |

Values are mean ± SD or n (%).

BMS = bare-metal stent(s); other abbreviations as in Table 1.

respectively, were as follows: <2.25 mm, 64.9% versus 48.0%; 2.25 to 2.5 mm, 24.5% versus 39.8%; 2.5 to 2.8 mm, 9.6% versus 11.2%; and ≤2.8 mm, 1.1% versus 1.0%. Thus, angiographic analysis confirmed that the majority of lesions (89.4% vs. 87.8%) in the DEB and PES group occurred in vessels with diameters <2.5 mm. The acute post-procedural result was better after stenting as compared with balloon angioplasty with a larger final MLD, less residual stenosis, and greater acute gain in the PES group.

Angiographic follow-up was completed in 86.2% and 83.7% (p = 0.88) of lesions in the DEB and PES groups, respectively (Fig. 1). Angiographic outcomes are displayed in Table 4. The primary endpoint of in-stent (in-balloon) late loss was significantly less in lesions treated with DEB compared

| | DEB (n = 94) | PES (n = 97) | p Value |
|-------------------------------|---------------|---------------|---------|
| Baseline | | | |
| Reference vessel diameter, mm | 2.15 ± 0.27 | 2.26 ± 0.24 | 0.004 |
| Minimal lumen diameter, mm | 0.60 ± 0.24 | 0.62 ± 0.22 | 0.64 |
| Diameter stenosis, % | 72.14 ± 10.05 | 72.78 ± 9.27 | 0.65 |
| Length, mm | 15.32 ± 7.45 | 14.94 ± 7.96 | 0.73 |
| Final | | | |
| Minimal lumen diameter, mm | | | |
| In-stent/in-balloon | 1.56 ± 0.32 | 1.99 ± 0.28 | <0.001 |
| In-segment | 1.47 ± 0.30 | 1.69 ± 0.36 | <0.001 |
| Diameter stenosis, % | | | |
| In-stent/in-balloon | 29.84 ± 10.24 | 15.42 ± 6.92 | <0.001 |
| In-segment | 33.21 ± 10.56 | 26.84 ± 12.54 | <0.001 |
| Acute gain, mm | | | |
| In-stent/in-balloon | 0.96 ± 0.30 | 1.37 ± 0.31 | <0.001 |
| In-segment | 0.87 ± 0.29 | 1.08 ± 0.37 | <0.001 |

Values are mean ± SD.

Abbreviations as in Table 1.

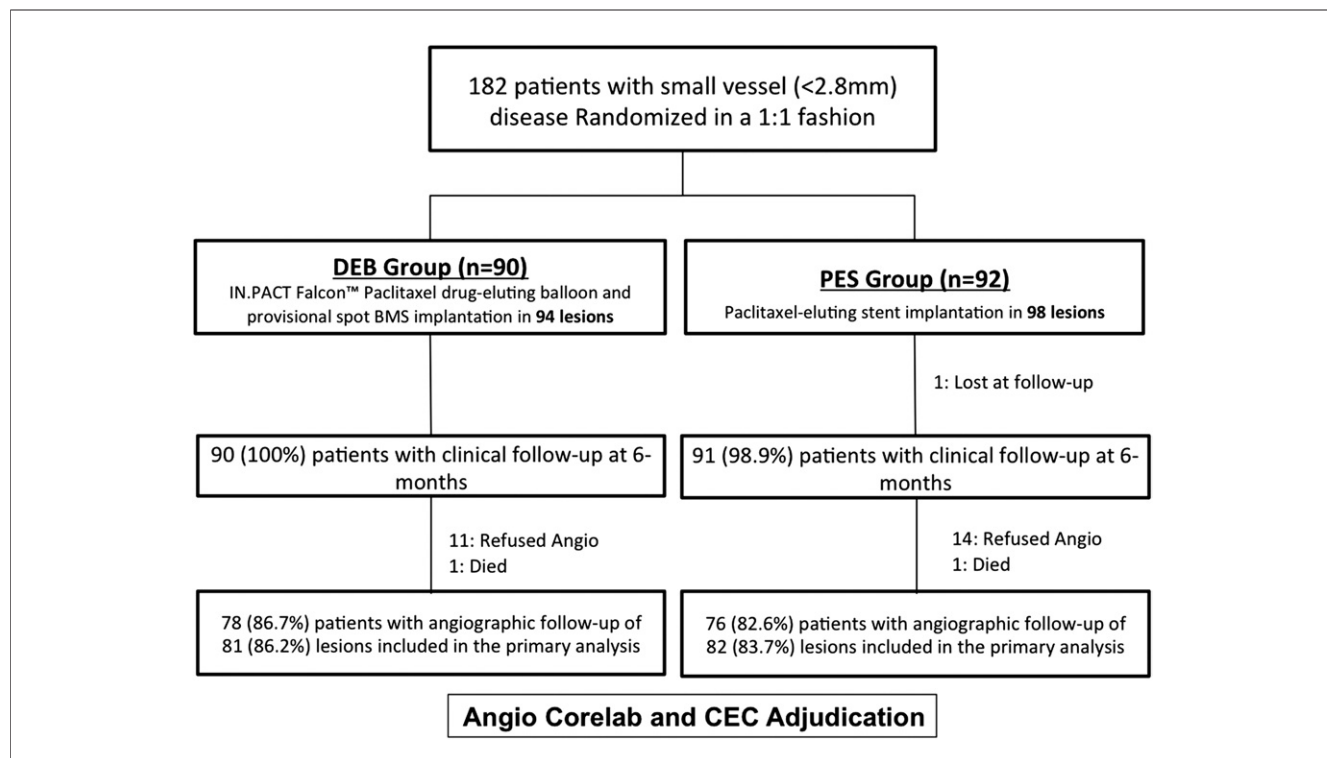


Figure 1 Patient Flow Chart

Flow chart showing patient flow and follow-up during the study. BMS = bare-metal stent(s); DEB = drug-eluting balloon(s); PES = paclitaxel-eluting stent(s).

with PES (0.08 ± 0.38 vs. 0.29 ± 0.44 mm; difference -0.21 ; 95% CI: -0.34 to -0.09 ; $p_{\text{noninferiority}} < 0.0001$; $p_{\text{superiority}} = 0.001$). In-segment late loss was also less in the DEB group (0.05 ± 0.37 vs. 0.17 ± 0.45 mm; difference -0.12 ; 95% CI: -0.25 to 0.01 ; $p_{\text{noninferiority}} < 0.0001$; $p_{\text{superiority}} = 0.06$). Cumulative distribution curves for late loss are shown in Figure 2. Angiographic percentage diameter stenosis at

follow-up angiography was significantly lower in lesions treated with PES, whereas binary in-stent and in-segment restenosis were similar in both groups. Three of the 8 restenoses in the DEB group occurred in lesions treated with bailout BMS. Based on the Mehran classification (9), the patterns of restenosis in the DEB and PES groups were diffuse in 3 lesions (3.7%) versus 6 lesions (7.3%), focal in 3 lesions (3.7%) in both groups, proliferative in 1 lesion (1.2%) in both

Table 4 Angiographic Outcomes at Follow-up

| | DEB | PES | p Value |
|---------------------------------|-------------------|-------------------|---------|
| No. with angiographic follow-up | 81 | 82 | |
| Minimal lumen diameter, mm | | | |
| In-stent/in-balloon | 1.48 ± 0.41 | 1.68 ± 0.51 | 0.006 |
| In-segment | 1.42 ± 0.40 | 1.52 ± 0.50 | 0.16 |
| Diameter stenosis, % | | | |
| In-stent/in-balloon | 32.31 ± 16.66 | 26.69 ± 20.38 | 0.06 |
| In-segment | 34.99 ± 15.97 | 33.33 ± 19.99 | 0.56 |
| Late lumen loss, mm | | | |
| In-stent/in-balloon | 0.08 ± 0.38 | 0.29 ± 0.44 | 0.001 |
| In-segment | 0.05 ± 0.37 | 0.17 ± 0.45 | 0.06 |
| Net gain, mm | | | |
| In-stent/in-balloon | 0.87 ± 0.41 | 1.06 ± 0.52 | 0.009 |
| In-segment | 0.81 ± 0.39 | 0.90 ± 0.49 | 0.20 |
| Binary restenosis, % | | | |
| In-stent/in-balloon | 8 (10) | 10 (12.4) | 0.64 |
| In-segment | 8 (10) | 12 (14.6) | 0.35 |

Values are mean \pm SD or n (%).
Abbreviations as in Table 1.

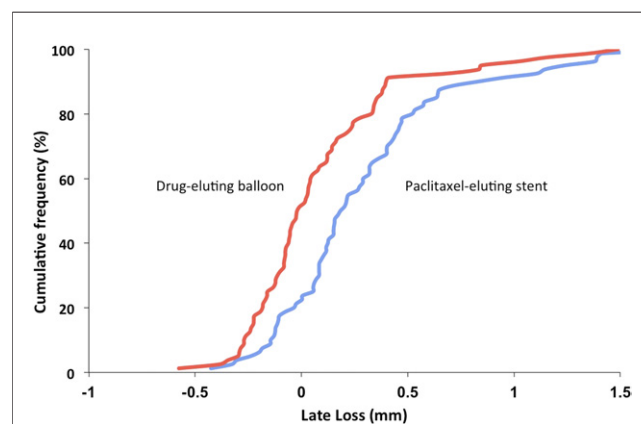


Figure 2 Late Loss Distribution

Cumulative frequency distribution curves of in-stent (in-balloon) late loss at follow-up angiography.

Table 5 Clinical Outcomes

| | DEB (n = 90) | PES (n = 92) | p Value |
|-------------------------------------|--------------|--------------|---------|
| In-hospital MACE | | | |
| Periprocedural MI | 1 (1.1) | 3 (3.3) | 0.33 |
| Recurrent PCI | 0 | 0 | |
| Death | 0 | 0 | |
| 30-day MACE (days 0-30) | | | |
| MACE | 2 (2.2) | 4 (4.3) | 0.42 |
| MI | 1 (1.1) | 4 (4.4) | 0.18 |
| TLR | 1 (1.1) | 0 | 0.31 |
| TVR (including TLR) | 2 (2.2) | 0 | 0.15 |
| Death | 0 | 0 | |
| Cumulative MACE (days 0-180) | | | |
| MACE | 9 (10) | 15 (16.3) | 0.21 |
| MI | 1 (1.1) | 5 (5.5) | 0.10 |
| TLR | 4 (4.4) | 7 (7.6) | 0.37 |
| TVR (including TLR) | 7 (7.8) | 10 (11.0) | 0.46 |
| Death | 1 (1.1) | 1 (1.1) | 0.99 |

Values are n (%).

MACE = major adverse cardiac events; TLR = target lesion revascularization; TVR = target vessel revascularization; other abbreviations as in Table 1.

groups, and occlusive in 1 lesion (1.2%) versus 2 lesions (2.4%). No aneurysms were present at follow-up angiography in either group.

Clinical outcomes. All patients, except for 1 in the PES group, completed the 6-month follow-up. In the DEB group, there were no cases of clinically apparent acute vessel closure and only 1 periprocedural MI. As shown in Table 5, the cumulative MACE rate at 6 months was 10% with DEB and 16.3% with PES treatment in small vessels (p = 0.21). There were no statistically significant differences between DEB and PES in the rates of death, MI, TLR, or TVR. There were also no cases of definite or probable stent thrombosis in the study.

Subgroup analysis. Table 6 shows the results of the subgroup analysis with formal interaction testing, which was performed to explore whether the reduction in the primary endpoint of in-stent (in-balloon) late loss was consistent

among important subgroups (of which diabetes and DEB alone or DEB plus bailout BMS were pre-specified). The reduction in late loss was consistent across the subgroups tested, with no significant interactions between the randomized treatment and angiographic outcomes.

Discussion

The principal findings of the BELLO randomized trial were that among patients treated for small coronary vessels, the IN.PACT Falcon paclitaxel-coated DEB was noninferior to PES in suppressing neointimal proliferation, as measured by angiographic late loss at 6 months. Furthermore, DEB and PES are associated with similar rates of angiographic restenosis, MACE, and repeat revascularization in small vessels. These results were obtained with the need to implant BMS in 20% of patients randomized to DEB and in a patient population including more than 40% of patients with treated diabetes mellitus.

The reduction of angiographic in-stent (in-balloon) late loss with DEB as compared with PES met the pre-specified criteria not only for noninferiority but also for superiority. Similarly, the reduction in in-segment late loss with DEB was noninferior to that with PES. These findings confirmed those of studies that demonstrated the efficacy of DEB in reducing angiographic late loss after the treatment of coronary in-stent restenosis (1,2,4) or peripheral vascular disease (15-17). However, the validity of late loss as a primary endpoint in a study comparing a balloon with a stent in de novo disease may be questioned. In the seminal trials comparing balloon angioplasty with BMS in de novo coronary disease, balloon angioplasty was associated with a smaller final MLD, less acute gain, and lower late loss at follow-up (18,19). Similarly, in this study, balloon angioplasty was associated with a suboptimal acute angiographic result as measured by final MLD and acute gain. Despite these immediate results, DEB were associated with similar angiographic restenosis and repeat revascularization rates as compared with PES. This is probably explained by the fact

Table 6 Subgroup Analysis of In-Stent (In-Balloon) Late Loss

| | No. of Lesions | | Late Loss, mm | | p Value | p Value for Interaction |
|----------------------------------|----------------|-----|---------------|-------------|---------|-------------------------|
| | DEB | PES | DEB | PES | | |
| Diabetes | | | | | | |
| Yes | 32 | 31 | 0.05 ± 0.41 | 0.32 ± 0.52 | 0.001 | 0.52 |
| No | 49 | 51 | 0.10 ± 0.36 | 0.28 ± 0.39 | 0.06 | |
| Reference vessel diameter | | | | | | |
| <2.25 mm | 54 | 41 | 0.07 ± 0.35 | 0.29 ± 0.41 | 0.006 | 0.12 |
| 2.25-2.5 mm | 19 | 31 | 0.06 ± 0.41 | 0.37 ± 0.49 | 0.02 | |
| Lesion length | | | | | | |
| ≤13.9 mm (median) | 40 | 41 | 0.05 ± 0.33 | 0.29 ± 0.45 | 0.008 | 0.71 |
| >13.9 mm (median) | 41 | 41 | 0.11 ± 0.42 | 0.30 ± 0.43 | 0.03 | |
| DEB only | 67 | 82 | 0.02 ± 0.32 | 0.29 ± 0.44 | <0.001 | — |
| DEB + BMS | 14 | 82 | 0.37 ± 0.51 | 0.29 ± 0.44 | 0.59 | |

Values are mean ± SD.

Abbreviations as in Tables 1 and 2.

that the lower acute gain with DEB was counterbalanced by the very low late loss resulting in a net lumen gain, which was comparable in both groups, particularly for the treated segment (20,21). Furthermore, as compared with that previously reported with an uncoated balloon in de novo disease (18–21), the mean late loss (0.08) with DEB in this study was very low, with more than half of the lesions treated having a negative late loss. Finally, it should be noted that in 2 recent randomized studies comparing DEB versus stenting, late loss was used as a primary endpoint to demonstrate efficacy (2) or the lack of it (22).

DEB may be particularly advantageous over DES in the treatment of small vessels by providing an immediate and homogenous drug uptake, avoiding inflammatory reaction to stent struts or polymers, and respecting the normal vessel anatomy (23,24). DEB also provide a therapeutic option in very small vessels (<2.25 mm), which comprised more than half of the lesions treated in this study, for which DES sizes are not available. These lesions continue to be associated with high rates of restenosis (6,25).

There are limited data available regarding DEB in de novo small-vessel disease, and angiographic analysis of the treated lesions confirmed that BELLO was a true small-vessel study with the majority of lesions having a vessel diameter <2.5 mm, confirming its applicability to this complex lesion subset. The only other published study, PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small Coronary Artery Diseases), was a small single-center trial that randomized 60 patients with small-vessel disease (≤ 2.75 mm) to the Dior paclitaxel-coated balloon (Eurocor, Bonn, Germany) or PES. The study was prematurely stopped before complete enrollment because of the clear superiority of PES, which was associated with a lower rate of angiographic restenosis (10.3% vs. 32.1%; $p = 0.04$) and MACE (13.8% vs. 35.7%; $p = 0.054$). Although the Dior and IN.PACT Falcon DEB are both coated with paclitaxel at $3 \mu\text{g}/\text{mm}^2$, these technologies are not comparable and differ significantly in regards to the balloon technology, drug-coating process, and excipient used as drug carrier and transport facilitator to the vessel wall. As has been demonstrated with DES platforms, clinical outcomes may be very different, despite elution of the same drug. The only other DEB data available on small-vessel disease is the PEPCAD I SVD (PEPCAD to Treat Small Vessel Coronary Artery Disease) study (8). In this prospective, nonrandomized multicenter study, 122 patients with coronary disease in small vessels (RVD 2.25 to 2.8 mm) were treated with the SeQuent Please paclitaxel-coated balloon catheter (B. Braun, Melsungen, Germany). This study demonstrated a significantly higher late loss and restenosis rate in lesions treated with a combination of DEB and BMS, especially if geographic mismatch occurred (i.e., stent implanted in an area that was not treated with DEB). The investigators in the BELLO study were particularly careful to ensure that any needed stent was implanted within the DEB-treated zone. As expected, we

found a lower late loss when only a DEB was used (Table 6). This finding may have 2 possible explanations: the absence of additional late loss associated with stent implantation or a natural selection of less complex lesions not requiring additional stenting. It is important to acknowledge that patients treated with DEB and without stenting did not experience any thrombotic event, acute vessel closure, or a higher rate of periprocedural MI.

In our opinion, the findings of the BELLO study should not be interpreted in the context of DEB as a generic substitute to DES but rather as an adjunctive tool. These data give support to the use of DEB in circumstances in which the operator may not be fully confident to deploy a DES (e.g., small vessel size, long lesions, excessive number of DES required) because the results of DES are not as optimal and in an attempt to limit the amount of metal implanted. Additional data are necessary to support the usage of this strategy in patients who have trouble adhering to prolonged dual antiplatelet therapy.

Study limitations. Because the study was powered for an angiographic endpoint, the sample size may be too small to detect small differences in clinical outcomes between the 2 groups. The choice of first-generation PES rather than second-generation DES may also be interpreted as a limitation. However, the objective in this study was to evaluate 2 different modalities of delivery of the same drug without introducing the confounder of differing efficacy of antirestenotic drugs.

Conclusions

In this randomized trial, treatment of small-vessel disease with paclitaxel-coated DEB was associated with less angiographic late loss and similar rates of restenosis and revascularization as DES coated with the same drug. DEB appear to be an acceptable alternative to DES in small-vessel disease.


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- Key Words:** drug-eluting balloon ■ drug-eluting stent ■ late loss ■ paclitaxel ■ restenosis ■ revascularization.
-  **APPENDIX**
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- For a list of the principal investigators, co-investigators, and participating centers in the BELLO study, please see the online version of this article.**