Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting for the Treatment of Infrapopliteal Long-Segment Arterial Occlusive Disease

The IDEAS Randomized Controlled Trial

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ABSTRACT

OBJECTIVES This study sought to report the results of a prospective randomized controlled trial comparing paclitaxel-coated balloons (PCB) versus drug-eluting stents (DES) in long infrapopliteal lesions.

BACKGROUND DES have an established role in the treatment of short infrapopliteal lesions, whereas there is increasing evidence for the use of PCB in longer below-the-knee lesions.

METHODS Inclusion criteria were patients with Rutherford classes 3 to 6 and angiographically documented infrapopliteal disease with a minimum lesion length of 70 mm. The primary endpoint was target lesion restenosis (>50%) assessed by digital angiography at 6 months. Secondary endpoints included immediate post-procedure stenosis and target lesion revascularization.

RESULTS Fifty patients were randomized to undergo infrapopliteal PCB angioplasty (25 arteries in 25 limbs; PCB group) or primary DES placement (30 arteries in 27 limbs; DES group). Immediate residual post-procedure stenosis was significantly lower in DES (9.6 ± 2.2% vs. 24.8 ± 3.5% in PCB; p < 0.0001). At 6 months, 5 patients died (2 in PCB vs. 3 in DES; p = 1.00) and 3 suffered a major amputation (1 in PCB vs. 2 in DES; p = 1.00). In total, 44 angiograms were evaluable with quantitative vessel analysis. Binary (>50%) angiographic restenosis rate was significantly lower in DES (7 of 25 [28%] vs. 11 of 19 [57.9%] in PCB; p = 0.0457). There were no significant differences with regard to target lesion revascularization (2 of 26 [7.7%] in DES vs. 3 of 22 [13.6%] in PCB; p = 0.65). Positive vessel wall remodeling was observed in 3 cases in the PCB arm (3 of 19 [15.8%]) vs. 0 of 19 [0%] in DES; p = 0.07).

CONCLUSIONS Compared with PCB in long infrapopliteal lesions, DES are related with significantly lower residual immediate post-procedure stenosis and have shown significantly reduced vessel restenosis at 6 months. PCB may produce positive vessel remodeling. (Infrapopliteal Drug-Eluting Angioplasty Versus Stenting [IDEAS-I]; NCT01517997) (J Am Coll Cardiol Intv 2014;7:1048-56) © 2014 by the American College of Cardiology Foundation.
Endovascular treatment is increasingly being used as the preferred method of revascularization in patients with infrapopliteal arterial disease suffering from critical limb ischemia (CLI). Compared with surgical bypass, which can be technically challenging or not offered at all because of underlying comorbidities of CLI patients, angioplasty of the crural arteries is able to achieve multi-vessel recanalization to the foot in a safer and less invasive way (1-3).

Traditional plain balloon angioplasty has long been the gold standard endovascular therapy in the infrapopliteal field, accompanied by bare-metal stents as a bailout choice (4,5). Nearly a decade ago, certain investigators foresaw the advantages of using drug-eluting stents (DES) in the infrapopliteal region (6-9). Since then, 3 multicenter randomized controlled trials and a meta-analysis have confirmed the superiority of DES in terms of inhibiting restenosis, reducing target lesion revascularization (TLR), and improving event-free survival, thereby providing level IA evidence for their use in short infrapopliteal lesions (10-13).

On the other hand, paclitaxel-coated balloons (PCB) have already been shown to have superior results with less vascular restenosis and fewer TLR events than with plain balloon angioplasty when used in the superficial femoral artery and in failing arteriovenous fistulas (14,15). Recently, a single-arm and 2 randomized controlled trials provided evidence about improved outcomes with PCB in the treatment of infrapopliteal lesions, at 3, 6, and 12 months, compared with percutaneous transluminal angioplasty (16-18).

CLI cases, especially diabetic ones, are typically characterized by long diffuse atherosclerotic lesions in about one-half of the cases (19). To our knowledge, there is only 1 single-arm study testing plain balloon angioplasty in long infrapopliteal lesions, and evidence on the effectiveness of DES in long these lesions is also very scarce (20,21). On the other hand, the 2 randomized controlled trials reported application of PCB in relatively longer lesions. This trial was designed to explore the effectiveness of PCB versus DES specifically for the treatment of long infrapopliteal lesions that are more representative of routine practice in the treatment of CLI.

METHODS

STUDY DESIGN. The IDEAS (Infrapopliteal Drug-Eluting Angioplasty Versus Stenting) trial was designed to be a single-center randomized (1:1) controlled trial comparing PCB versus DES in long infrapopliteal lesions for the treatment of CLI. It was hypothesized that the 2 competing drug technologies would produce similar inhibition of neointimal hyperplasia (NIH); in other words, the null hypothesis was set at equivalence. The expected angiographic restenosis rate >50% at 6 months was estimated at 10% for both groups and the study was powered to exclude a difference between the 2 treatments of >25% (α = 0.05 and statistical power set at 0.80). The number of patients required in each treatment arm was calculated to be 25. No allowance was made for dropouts. One-to-one randomization was computer generated and the method of sealed envelopes was used. The hospital’s ethical and scientific committee approved the protocol. Written informed consent was acquired from all recruited subjects. The study was announced on a public database (NCT01517997) and was performed within standards of care without any financial support from industry or research grants.

PATIENT POPULATIONS. From December 1, 2011 to January 1st 2013, 73 patients were referred to our department for percutaneous revascularization of the infrapopliteal vessels due to intermittent claudication or CLI. After screening for potential enrollment in the trial, 23 patients were excluded in total (13 patients did not fulfill the inclusion criteria; 8 patients suffered from distal below-the-ankle disease; and 2 patients did not consent to be included in the study). Overall, 50 patients met the inclusion criteria, provided a signed informed consent form and were randomized to undergo either PCB angioplasty (PCB group) or DES placement (DES group) for the treatment of long infrapopliteal lesions (>70 mm in length, maximum of 2 arteries per limb) (Figure 1). In order to be included in the trial, patients had to suffer from severe leg ischemia (Rutherford classes 3- to 6) and to have ≥1 angiographically documented infrapopliteal lesion of >70 mm in length. On the other hand, distal arterial occlusive disease compromising below-the-ankle runoff of the target vessel to be treated (e.g., blocked dorsalis pedis in case of anterior tibial artery treatment or occluded planter arteries in case of posterior tibial artery treatment) was the most important exclusion criterion (Table 1). Inflow iliofemoral occlusive disease was treated as necessary.

BALLOON AND STENT DEVICES. The PCB under investigation was the IN.PACT Amphirion (Medtronic, Brescia, Italy), which was available in sizes with 3 to

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**ABBREVIATIONS AND ACRONYMS**

CLI critical limb ischemia  
CTO chronic total occlusion(s)  
DES drug-eluting stent(s)  
IQR interquartile range(s)  
ITT intention-to-treat  
LLL late lumen loss  
NIH neointimal hyperplasia  
PCB paclitaxel-coated balloon  
QVA quantitative vessel analysis  
TLR target lesion revascularization
4 mm diameters and 40 to 120 mm lengths. DES used included zotarolimus-eluting (Resolute stent, Medtronic, Brescia, Italy; diameter: 3 to 4 mm, length: ≥30 mm), sirolimus-eluting (Cypher stent, Cordis, Bridgewater, New Jersey; diameter: 3 to 3.5 mm, length: ≥33 mm), and the everolimus-eluting stents (Promus stent, Boston Scientific, Natick, Massachusetts; diameter: 3 to 4 mm, length: ≥38 mm) according to department’s availability and were applied as a primary treatment (balloon pre-dilation as necessary).

**PROCEDURE.** All procedures were performed with an antegrade access after puncturing the common femoral artery under ultrasound guidance and local anesthetic with lignocaine 1%. A 6-F sheath was inserted and 5,000 IU of heparin were administered. An angiogram was obtained and the target lesion length was measured with the help of a radiopaque ruler. Lesions were crossed with 0.014-inch to 0.018-inch guidewires and the appropriate device was chosen. Pre-dilation was performed in the case of tight stenosis or after an occlusive lesion was crossed in both groups. After the device was deployed (DES) or inflated (PCB), a second angiogram was performed. In the case of residual stenosis, a further prolonged dilation was performed in both groups and a final angiogram was acquired.

In the PCB group, the inflation time was 1 min as recommended in the instructions for use. Devices used were 5 mm longer than the actual measured lesion on each side. In the case where >1 balloon was needed, an overlap subject to visual estimation occurred. In the DES group, inflation time was 20 s and devices were deployed in a length matching that of the actual lesion. The minimum amount of overlapping possible was applied with the help of magnified images. Patients were prescribed on dual antiplatelet therapy for 6 months. Clinical follow-up was scheduled at 1 and 6 months and a digital subtraction angiography was performed at the 6-month time point for quantitative vessel analysis (QVA) purposes.

**STUDY ENDPOINTS.** Primary study endpoint was angiographic restenosis >50% (binary) of the target lesion defined as >50% restenosis of the treated part of the vessel as measured by QVA. Binary restenosis was chosen as a primary endpoint of this trial as both technologies compared are local drug delivery technologies and an antirestenotic effect (NIH inhibition) was anticipated.

Secondary endpoints included technical success defined as the absence of flow-limiting dissection and no significant residual stenosis by visual estimate in both groups. Further secondary outcome measures included the following: immediate post-procedure stenosis; late lumen loss (LLL) as a quantitative endpoint of NIH defined as the difference between the minimal lumen diameter immediately after stenting or PCB angioplasty and the minimal lumen diameter at
6-month follow-up; cases of angiographically proven total vessel occlusion; any clinically driven TLR; major amputations (above-ankle; planned and unplanned); Rutherford class improvement; and wound healing of any baseline tissue loss (classified as complete, partial, or stable wounds). Investigators also included in their QVA analysis the immediate post-procedure residual stenosis as a surrogate endpoint of immediate device efficacy. To further investigate the pattern of restenosis and NIH development, the analysis extended to include the length of the restenosed vascular segment at 6 months (defined as the length of restenosis >50% of the previously treated lesion; in centimeters) as well as any positive vessel remodeling (suggested by a negative LLL).

**STATISTICAL ANALYSIS.** All outcomes were reported and analyzed on an intention-to-treat (ITT) basis. Discrete variables were expressed as counts (percentages), and continuous variables were given as medians (interquartile ranges [IQR]) or as mean ± SD if they passed the Kolmogorov-Smirnov goodness-of-fit normality test. The unpaired Student t test was used to test normally distributed continuous variables; the Mann-Whitney U test was used for qualitative variables and for nonparametric continuous variables. Comparison of proportions was done by testing the null hypothesis that the proportions were equal, and the chi-square test was applied in case of cumulative analysis. Fisher exact test has been applied where appropriate. The threshold of statistical significance was set at p < 0.05. Statistical analysis was performed with the GraphPad Prism statistical software package (version 5, GraphPad Software, La Jolla, California).

**RESULTS**

Within 14 months, 50 patients were randomized (1:1) to PCB or DES treatment of long infrapopliteal lesions. The flow of the study is shown in the chart of Figure 1. Baseline demographical variables were equally distributed between the 2 groups with the sole exception of age (75.3 ± 8.0 years in DES vs. 75.6 ± 11.3 years in PCB, p = 0.03) (Table 2). In total, on an ITT analysis, 52 limbs (PCB group: n = 25, DES group: n = 27) and 55 vessels (PCB group: n = 25, DES group: n = 30) were randomized. Lesion length was slightly higher in the PCB group (148 ± 56.7 mm vs. 127 ± 46.5 mm in the DES group; p = 0.14), whereas chronic total occlusions (CTO) at baseline were numerically more in the DES group (7 of 30 vs. 3 of 25 in the PCB group; p = 0.31). The subintimal approach was used in 6 of 7 occlusions treated in the DES group and in 3 of 3 occlusions in the PCB group (6 of 30 vs. 3 of 25 lesions; p = 0.49). Retrograde pedal access was not applied in any case. Baseline demographics and morphological characteristics of all lesions treated are reported in detail in Table 2. In 1 case, the angioplasty result after PCB treatment was suboptimal (flow-limiting dissection) and the patient crossed over to treatment with DES. Hence, technical success was 24 of 25 (96%) in the PCB

<table>
<thead>
<tr>
<th>Table 2 Baseline Demographics and Lesion Characteristics</th>
<th>DES Group</th>
<th>PCB Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18/25 (72)</td>
<td>20/25 (80)</td>
<td>0.51</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>75.3 ± 8.0</td>
<td>67.6 ± 11.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16/25 (64)</td>
<td>19/25 (76)</td>
<td>0.35</td>
</tr>
<tr>
<td>Smoking</td>
<td>6/25 (24)</td>
<td>9/25 (36)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hypertension</td>
<td>11/25 (44)</td>
<td>14/25 (56)</td>
<td>0.40</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13/25 (52)</td>
<td>10/25 (40)</td>
<td>0.39</td>
</tr>
<tr>
<td>Chronic total occlusions</td>
<td>7/30 (23)</td>
<td>3/25 (12)</td>
<td>0.31</td>
</tr>
<tr>
<td>Baseline stenosis, %</td>
<td>86.8 ± 10.1</td>
<td>85.3 ± 8.9</td>
<td>0.58</td>
</tr>
<tr>
<td>Baseline wounds</td>
<td>12/25 (48)</td>
<td>12/25 (48)</td>
<td>1.00</td>
</tr>
<tr>
<td>Target vessels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior tibial artery</td>
<td>15/30 (50)</td>
<td>13/25 (52)</td>
<td>0.88</td>
</tr>
<tr>
<td>Posterior tibial artery</td>
<td>8/30 (27)</td>
<td>6/25 (24)</td>
<td>0.82</td>
</tr>
<tr>
<td>Peroneal artery</td>
<td>7/30 (23)</td>
<td>6/25 (24)</td>
<td>0.94</td>
</tr>
<tr>
<td>Severe calcifications</td>
<td>15/30 (50)</td>
<td>11/25 (44)</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Values are n, n/N (%), mean ± SD, or median (interquartile range).

<table>
<thead>
<tr>
<th>Table 3 Angiographic and Clinical Outcomes: QVA and Outcome Measures at 6 Months (ITT Analysis)</th>
<th>DES Group</th>
<th>PCB Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>QVA analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-procedure stenosis, %</td>
<td>9.6 ± 2.2</td>
<td>24.8 ± 3.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6-month vessel stenosis, %</td>
<td>50.6 ± 6.6</td>
<td>54.3 ± 8.1</td>
<td>0.73</td>
</tr>
<tr>
<td>Late lumen loss, mm</td>
<td>1.35 ± 0.2</td>
<td>1.15 ± 0.3</td>
<td>0.62</td>
</tr>
<tr>
<td>Length of &gt;50% restenosis, cm</td>
<td>3.6 ± 1.5</td>
<td>4.3 ± 1.6</td>
<td>0.16</td>
</tr>
<tr>
<td>Outcome measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binary restenosis &gt;50%</td>
<td>7/25 (28)</td>
<td>11/19 (57.9)</td>
<td>0.0457</td>
</tr>
<tr>
<td>Positive remodelling, late lumen loss &lt;0 mm</td>
<td>0/25 (0)</td>
<td>3/19 (15.8)</td>
<td>0.07</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>2/26 (7.7)</td>
<td>3/22 (13.6)</td>
<td>0.65</td>
</tr>
<tr>
<td>Rutherford class at 6 months</td>
<td>1 (1, 2.75)</td>
<td>1 (1, 3.5)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Values are mean ± SD, n/N (%), or median (interquartile range).
Immediate residual post-procedure stenosis was significantly lower in DES (9.6 ± 2.2% vs. 24.8 ± 3.5% in PCB; p < 0.0001). Three (3 of 25) and 1 (1 of 25) patients were lost to follow-up from the PCB and the DES group, respectively (p = 0.61). There were 2 deaths (2 of 25) after PCB and 3 after DES treatment (3 of 25; p = 1.00). All deaths were attributed to cardiovascular events because of underlying comorbidities. One limb was amputated in the PCB group (1 of 25) and 2 in the DES group (2 of 27; p = 1.00) (Table 3).

In total, 44 angiograms were evaluable with QVA at 6 months (Figure 2). Total vessel reocclusion occurred in 3 of 19 (15.8%) of the treated lesions in the PCB group versus 5 of 25 (20.0%) in the DES group (p = 0.72). Although stent thrombosis could not be verified in any of the cases, it was strongly suspected in the 2 cases of limb amputation occurring in the DES group 2 months after the procedure. Events of target lesion >50% angiographic restenosis were significantly fewer in the DES group (7 of 25 [28%]) vs. 11 of 19 [57.9%] in PCB; p = 0.0457) (Table 3). LLL at 6 months was similar in both groups (1.35 ± 0.2 mm in DES vs. 1.15 ± 0.3 mm in PCB; p = 0.62) (Figure 3). Positive vessel wall remodeling was observed in 3 cases in the PCB arm (3 of 19 [15.8%] vs. 0 of 19 [0%] in DES; p = 0.07). The length of the restenosed vessel segment was slightly lower in DES, but not significantly so (3.6 ± 1.5 cm vs. 4.3 ± 1.6 cm; p = 0.16) (Figure 3). There were no significant differences with regard to TLR (2 of 26 [7.7%] in DES vs. 3 of 22 [13.6%] in PCB; p = 0.65) and Rutherford class at 6 months (median: stage 1 [IQR: 1 to 2.75] in DES vs. 1 [IQR: 1 to 3.5] in PCB; p = 0.87) (Figure 4). Similar counts of complete, partial, and unchanged wound healing were observed in both groups after 6 months (Figure 5). Examples of follow-up angiograms in both the DES and PCB study arms are shown in Figures 6 and 7, respectively. During angiographic follow-up, no stent fractures were detected in the DES group. Finally, no procedure-related minor or major complication was noted.

**DISCUSSION**

Endovascular treatment of below-the-knee arterial occlusive disease is increasingly proposed as the method of choice for revascularization of the crural arteries, especially in patients suffering from CLI (1-3). Although DES have established their superiority over plain balloon angioplasty and bare-metal stents for the treatment of short infrapopliteal lesions (13), there is no strong evidence to support their use in longer lesions (21). Below-the-knee application of DES has been also hampered by cost issues because with current devices (the longest
available is 38 mm) multiple overlapping stents would be necessary for full coverage of any lesion >10 cm, raising procedural costs (22). In addition, the expected increased difficulty to cross an occluded stent compared with a reoccluded native lesion previously treated with balloon angioplasty could be another factor to take into consideration during decision making for long infrapopliteal lesions. On the other hand, application of PCB devices has been received enthusiastically in the femoropopliteal arteries, and recently, promising results have also been shown in the below-the-knee arena (15-18).

The IDEAS trial is the first study to directly compare head-to-head the use of DES versus PCB for the treatment of long infrapopliteal lesions that typically characterize most cases of tibial revascularization. The study was designed to compare the 2 most commonly used local drug delivery technologies for endovascular treatment. The purpose of both technologies is the inhibition of restenosis and thereby reduction of repeat angioplasty and improvement of clinical outcomes. Hence, the trial was powered on the basis of an equivalence hypothesis, and angiographic restenosis >50% was set as the primary endpoint in order to compare NIH inhibition.

The IDEAS study has shown that infrapopliteal use of PCB, compared with DES, was associated with statistically significantly higher binary vascular restenosis at the 6-month time point. Of note, technical success was very high in both groups with only 1 crossover from the PCB to the DES group, albeit a small number of CTO were treated. CTO are theoretically more prone to require bailout stenting because of a suboptimal angioplasty result. Not surprisingly, immediate post-procedure residual stenosis was significantly higher after PCB use (more than double than with DES), which is not an unexpected finding as there is no permanent vascular scaffolding like there is in the case of metal stenting. It could be argued therefore that this “handicap” at the beginning of the study after completion of the index procedure may have partly contributed to the higher vessel restenosis noted in the cases of the PCB treated lesions.

We further investigated the morphology and pattern of NIH by analyzing the LLL and length of restenosed vascular segment as quantitative surrogate markers of the extent of vascular restenosis. Length was slightly higher but not significantly so in the PCB group. On the other hand, QVA showed the paradox that binary restenosis was significantly lower in DES, but LLL was numerically lower in cases of PCB. However, this may be explained by the positive vessel wall remodeling (negative LLL) that was identified in 3 PCB cases (3 of 19; 15.8%) and may have counteracted in part the increased post-procedure stenosis of PCB at baseline. Of note, positive remodeling has been described also after DES implantation in the coronary arteries, where it...
was associated with aneurysmal degeneration and stent malapposition (23). It has also been reported after PCB use in the superficial femoral artery with the hypothesis of plaque regression at 6 months (24).

Furthermore, the reported difference of binary restenosis did not translate into any significant differences in the secondary clinical outcome measures. Similar improvement in the Rutherford classes and wound healing progression was noted in both study arms, and as those patients were mainly CLI cases, mortality and amputation rates were within the expected range (1). It is evident though that the trial was not adequately powered to detect any such differences.

The significantly lower rate of restenosis found in the case of DES in the IDEAS study is in line with previously published cohort and randomized trials that included a variety of lesion lengths and follow-up periods (13,21). On the other hand, there was some discrepancy in the results of PCB compared with those of previously published studies. In a cohort of 109 CLI limbs (mean lesion length: 17 cm), Schmidt et al. (16) reported a restenosis rate of nearly 30% at 3 months (84 lesions analyzed) with >90% clinical improvement and around 75% complete wound healing at 1 year. Liistro et al. (18) performed a randomized comparison (the DEBATE-BTK [Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation] trial) of PCB versus plain balloon angioplasty in 132 patients with 158 infrapopliteal lesions (>4 cm). The investigators recently reported a striking reduction of angiographic restenosis in the PCB
group with a rate of 27% versus 74% in the control group after 1 year (p < 0.001). Only 1 major amputation was reported out of 132 CLI patients corresponding to a limb salvage rate of nearly 100% in both groups (18).

**STUDY LIMITATIONS.** The scientific evidence amassed and reported by the IDEAS randomized trial suffers from certain limitations. First, this was a single-center study and a relatively small number of patients with a low rate of CTO were recruited. Second, overall follow-up was limited to 6 months when a digital angiogram was performed for QVA purposes. In addition, there was an absence of an independent core lab for the QVA analysis, but there was no commercial sponsor or other source of funding. The study was designed as an exploratory study for equivalence between DES and PCB and was appropriately powered only for the outcome of restenosis in order to compare NIH between the 2 treatments. Hence, robust conclusions on long-term efficacy and clinical outcomes cannot be derived.

**CONCLUSIONS**

DES are related with significantly better immediate residual post-procedure stenosis and lower vessel restenosis than PCB when used in long infrapopliteal lesions. PCB may produce positive vessel remodeling. Larger scale multicenter trials are needed to verify these results and to investigate further whether this finding may translate to improved clinical outcomes.

**REFERENCES**


KEY WORDS drug-eluting stents, infrapopliteal lesions, neointimal hyperplasia, paclitaxel-coated balloons, restenosis