Drug-Eluting Balloon in peripherAl inTErvention for Below the Knee Angioplasty Evaluation (DEBATE-BTK): A Randomized Trial in Diabetic Patients with Critical Limb Ischemia

Running title: Liistro et al.; Drug-eluting balloon in BTK angioplasty

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Abstract:

**Background**—One-year restenosis rate after balloon angioplasty of long lesions in below-the-knee (BTK) arteries may be as high as 70%. Our aim was to investigate the efficacy of a paclitaxel drug-eluting balloon (DEB) vs. conventional percutaneous transluminal angioplasty (PTA) for the reduction of restenosis in diabetic patients with critical limb ischemia (CLI) undergoing endovascular intervention of BTK arteries.

**Methods and Results**—The Drug Eluting Balloon in peripherAl inTERvention (DEBATE)-BTK is a randomized, open label, single-center study comparing DEB vs. PTA. Inclusion criteria were: diabetes, critical limb ischemia (Rutherford ≥4), significant stenosis or occlusion > 40mm of at least one BTK vessel with distal run-off, and life expectancy > 1 year. Binary in-segment restenosis at 1-year angiographic or ultrasonographic follow-up was the primary endpoint. Clinically-driven target lesion revascularization (TLR), major amputation and target vessel occlusion were the secondary endpoints. One hundred and thirty two patients with 158 infrapopliteal atherosclerotic lesions were enrolled. Mean length of the treated segments was 129±83mm in the DEB vs. 131±79mm in the PTA group (p=0.7). Binary restenosis, assessed by angiography in >90% of patients, occurred in 20/74 (27%) lesions in the DEB group vs. 55/74 (74%) lesions in the PTA group (p<0.001); TLR in 12(18%) vs. 29(43%) (p=0.002); and target vessel occlusion in 12 (17%) vs. 41 (55%) (p<0.001). Only 1 major amputation occurred, in the PTA group (p=0.9).

**Conclusions**—DEB, as compared to PTA, strikingly reduce 1-year restenosis, target lesion revascularization, and target vessel occlusion in the treatment of BTK lesions in diabetic patients with CLI.

**Clinical Trial Registration Information**—http://ClinicalTrials.gov; Identifier: NCT01558505.

**Key words:** percutaneous procedure, peripheral artery disease, restenosis, drug-eluting balloon
Introduction

Critical limb ischemia (CLI), characterized by ischemic rest pain and/or tissue loss, represents the most advanced state of peripheral artery disease, burdened by high morbidity and mortality. CLI generally occurs in diabetics with extensive atherosclerotic disease of below-the-knee (BTK) vessels.

The optimal strategy for treating CLI patients, however, has not been clearly defined yet: the outcome of medical therapy is unsatisfactory, and early, aggressive percutaneous revascularization with the aim to obtain direct flow to the foot is increasingly considered as first-line strategy. Indeed, although vessel patency alone cannot match patient-centered clinical endpoints, and any endovascular program has to be integrated in a network-based system of care involving different professional figures, an increased cutaneous oxygen pressure due to successful revascularization promotes infection clearance and ulcer granulation at a crucial time-point.

The efficacy of conventional percutaneous transluminal angioplasty (PTA) using conventional balloons, however, is limited by the high 12-month restenosis and target lesion revascularization (TLR) rates. Loss of vessel patency affects the healing process resulting in no healing, decrease-increase behavior of the lesion or appearance of new foot lesions. While drug-eluting stents (DES) may offer a therapeutic alternative to PTA in the BTK district, widespread use in CLI patients is limited by the complex pattern of BTK atherosclerosis, characterized by long, calcific stenoses/occlusions.

Local delivery of paclitaxel via drug eluting balloons (DEB) has recently shown promising results in the treatment of femoropopliteal disease, and, in the BTK district, a reduction of 3-month binary restenosis has been observed in comparison with historical controls.
treated with standard PTA\textsuperscript{15}. Historical data, however, may not represent an adequate comparator due to changes in technology and clinical practice over time\textsuperscript{16}, and the efficacy of DEB in diabetic patients with CLI has not been validated in a randomized fashion.

We designed a prospective, randomized trial designed to compare the performance of a novel DEB (Amphirion In.Pact, Medtronic, Santa Rosa, CA) with conventional PTA in diabetics with de-novo, long atherosclerotic lesions of the BTK district, using 1-year binary restenosis rate as primary endpoint.

**Methods**

**Study design**

The Drug Eluting Balloon in peripheral inTervention for Below The Knee angioplasty evaluation (DEBATE-BTK) is a single-center, parallel-group, prospective, randomized, open-label involving the blinded evaluation of end points (PROBE) trial\textsuperscript{17} evaluating the efficacy of a 0.014” guidewire-compatible DEB (Amphirion In.Pact, Medtronic) vs. standard PTA (Amphirion Deep, Medtronic) in reducing 12-month restenosis rate in diabetic patients with CLI undergoing endovascular BTK revascularization. It was approved by the local ethics committee and was carried out in accordance with the Helsinki declaration. All patients provided written informed consent. The study was registered with ClinicalTrials.gov (unique identifier NCT01558505).

The study was performed without any industry financial support.

**Study Patients**

From November 2010 through October 2011, all consecutive diabetic patients with CLI undergoing angioplasty of at least one BTK vessel at our center were screened for enrollment.
Inclusion criteria were: presence of diabetes, CLI (Rutherford class ≥4), stenosis or occlusion ≥40 mm of at least one tibial vessel with distal run off to the foot, and agreement to 12-month angiographic evaluation. Exclusion criteria were: life expectancy < 1 year, allergy to paclitaxel, contraindication to combined antiplatelet treatment and planned major amputation before angiography.

Lesions were randomly assigned to one of the two study arms after successful passage of the guidewire. Randomization was performed in blocks of ten with the use of computer-generated random digits, and the assignments were placed in sealed envelopes.

**Study Procedures**

Interventions were performed mainly by antegrade approach and with the use of 6-French sheaths. In case of failure to recanalize, a retrograde approach was attempted. In DEB group, pre-dilatation of the target lesion with standard balloon(s) was always performed before dilatation with DEB. The DEB used in this study has been previously described\(^{15}\). The DEB/vessel diameter ratio was planned to be 1:1. DEB available during the study period had a diameter of 2.5 to 4.0 mm and a length of 40 to 120 mm. Radiopaque rulers were used to ensure that the zone treated with DEB consistently exceeded at least 10 mm at the proximal and distal edges the area predilated with standard balloons, in order to avoid geographic miss. If more than 1 balloon was used per lesion, the overlap zone was at least 5 mm. Inflation time was at least 2 minutes for both DEB and PTA arms. In case of flow-limiting dissection or residual stenosis of more than 30%, a prolonged dilation of up to 3 min was performed. Drug eluting coronary stents (Xience V, Abbott, CA, USA) were used as a bailout. Technical success was defined as restoration of direct flow in the target vessel with run-off to the foot and a residual stenosis of less than 30%. Clinical success was defined as technical success without clinical events during
hospitalization. Inflow lesions located in the femoropopliteal segment were treated by standard techniques during the same session. In patients with bilateral CLI, an additional procedure for the revascularization of the contralateral limb was planned in a different session to limit the risk of x-rays exposition and contrast-induced nephropathy, maintaining the same randomization arm.

All patients were taking aspirin 100 mg daily. After sheath insertion, 70 IU/Kg heparin was administered. Post-intervention dual antiplatelet therapy with aspirin 100 mg and clopidogrel 75 mg once daily was given at least for 4 weeks and 100 mg aspirin was given daily thereafter.

**Follow-up**

Once discharged, patients were followed in a multidisciplinary, dedicated foot clinic to facilitate healing process and recovery of the ambulatory function. Office visits were scheduled 2 days/week for the first 2 months, once a week for the third month and then every two weeks.

Minor amputations which were planned before the interventions were performed 2-4 weeks after revascularization and included: finger amputations, metatarsal amputation due to necrosis/infection of tissues and bones with preservation of healthy surrounding tissue. All patients were scheduled to be re-admitted for control peripheral angiography at 12 months.

Before angiography, duplex ultrasound (DUS) of the target vessel was consistently performed. In case of clinical CLI recurrence, angiography and repeat revascularization were performed within one week from diagnosis. In patients undergoing clinically-driven repeat angiography of the target limb between 9 months and 12 months and who did not show evidence of restenosis of the target lesion, scheduled angiography at 12 months was not performed if DUS evaluation was clearly diagnostic for vessel patency with no restenosis.

**Study Endpoints and Definitions**
Before, immediately after the intervention, and at follow-up, angiography of the target vessel was performed in identical projections (2 orthogonal planes for each treated lesion). The target lesion was identified by an image of the vascular anatomy and specific landmarks (collaterals, bone landmarks), with a second image showing the inflated balloon(s). These images were compared with follow-up angiograms.

The primary endpoint of the study was the comparison of 12-month binary restenosis rates between the DEB and PTA groups. Restenosis was defined by angiography as a reduction in the luminal diameter >50% according to the worst angiographic view within the treated lesion plus the 10-mm segments proximal and distal to it or, in the few patients who did not undergo 12-month angiography, as a peak systolic velocity ratio (PSVR) ≥ 2.5 by DUS.

Pre-specified secondary endpoints of the study were: 1. Clinically-driven target lesion revascularization (TLR), defined as repeat percutaneous intervention or surgical by-pass graft due to the angiographic evidence of restenosis at level of the treated lesion ±10 mm, in presence of at least one of the following criteria: a) recurrence of pain in the foot at rest which increased in the supine position; b) recurrence of foot lesion or evidence during follow-up of foot lesion size decrease-increase behavior; c) appearance of new foot lesion. 2. Major amputation, defined as unplanned amputation of the target limb where prosthesis was required for standing or walking. 3. Target vessel occlusion (either by angiography or DUS).

Acquired angiograms and DUS scans were reviewed by two blinded investigators who did not actively participate in recruitment (I.P. and G.V.) and who had no knowledge of clinical status and randomization group.

Post-hoc analyses was performed for the cumulative 12-month prevalence of major adverse events (MAE: death, major amputation, TLR, and Rutherford class ≥4) in the two groups,
as well as for other clinical endpoints such as rate of complete index ulcer healing, time to complete index ulcer healing and change in ankle-brachial index between baseline and follow-up. Further post-hoc exploratory comparisons were performed between long (>100 mm) vs. shorter lesions, total occlusions vs. stenosis, and true lumen vs. subintimal recanalization technique.

**Statistical Analysis**

Values are reported as numbers with relative percentage or standard deviation. Nominal variables were compared by Fisher’s exact test; continuous variables were compared with t-test. Twelve-month binary restenosis rate, the primary endpoint of the study, was compared with Fisher’s exact test. Kaplan-Meier estimates and log-rank test survival methods were used to assess freedom from TLR, a secondary endpoint. Cohen’s k statistics was used to compare angiography and DUS for detection of restenosis. All statistical computations were performed using SPSS version 17 (SPSS Inc., Chicago, IL).

Assuming a restenosis rate of 60% in the PTA group, as reported for patients with extensive infrapopliteal disease, we hypothesized that DEB would halve the restenosis rate to 30% on the basis of the extremely positive result reported for DEB in the superficial femoral artery. A minimum of 63 evaluable lesions per group were considered necessary to have an 90% power (2-sided 5% significance level) to detect a 50% relative risk reduction (RRR) in the DEB group. The number of lesions per group was further increased to 70 in order to maximize study power.

Assuming a rate of eligible lesions/patient=1.3, a minimum of 110 patients had to be enrolled in the study. The number of patients was increased to 130 considering a drop-out rate of 20% due to the expected high morbidity and mortality in CLI patients.
Results

Patients and Lesions

During the study period, 156 patients were screened for study enrolment and 132 met the inclusion criteria and were randomized, 65 patients (80 lesions in 71 limbs) to DEB and 67 (78 lesions in 72 limbs) to PTA (Figure 1). Baseline clinical characteristics were similar between study groups (Table 1). Ten per cent of the patients in each study arm were on chronic dialysis and the majority of patients had 0-1 patent tibial arteries at baseline.

Procedural and angiographic characteristics are reported in Table 2. The most frequently treated vessel was the anterior tibial artery (ATA). Treated lesions had a high degree of complexity in both study arms, as 80% of the lesions were total occlusions and more than 20% were heavily calcified. Subintimal recanalization was performed in one fifth of the lesions.

About 50% of patients in both study arms underwent inflow lesion treatment. Technical and clinical success was obtained in all patients.

Follow-up and clinical outcome

No major adverse event occurred in-hospital. Eight patients died during follow-up: causes of death included sudden death (n=3), respiratory failure (n=1), stroke (n=1), heart failure (n=1), and sepsis (n=1). Percentages of cardiac vs. noncardiac death in the two groups were not significantly different.

Of the 124 patients alive at 12 months (60 patients with 74 lesions in DEB group vs. 64 patients with 74 lesions in PTA group), angiographic follow-up could not be obtained in 13 patients (5 patients for worsening of pre-existing renal failure, 2 for major stroke, 2 for congestive heart failure and 4 patients refused the examination), who underwent DUS. In the 135 lesions with both angiographic and DUS follow-up assessment, agreement for restenosis
detection (see Methods for definitions) was good, with a k value of 0.88. Among the 73 lesions with angiographic restenosis, DUS revealed Doppler restenosis in 67 (91.7%). All cases of DUS-defined restenosis were confirmed by angiography. Among those patients who could not undergo 12-month angiography, only 2 lesions in 2 patients (1 in each group) were found to have restenosis, which was of the occlusive pattern in both.

Angiograms were thus available for 67 of 74 (91%) and 68 of 74 (92%) eligible lesions in the DEB and PTA arms, respectively. No patient was lost to follow-up.

Clinical and angiographic data of 12-month follow-up are presented in Table 3. The primary endpoint, 12-month binary restenosis, occurred in 20(27%) and 55(75%) lesions in the DEB and PTA groups (p<0.001), respectively. Freedom from TLR was significantly higher in the DEB group (Figure 2). Thirty six (mainly planned) minor amputations were performed, 19 in the PTA and 17 in the DEB arm, respectively (p=0.8). Only 1 major amputation occurred, in the PTA group (p=0.9). Target vessel occlusion occurred in 13(17%) DEB-treated vs. 41(55%) PTA-treated vessels (p<0.001). Twelve-month MAE occurred less frequently in the DEB (31%) than in PTA (51%) group (p=0.02), mainly driven by a reduction in TLR and better ulcer healing. Rate of complete healing of the index ulcer was higher and time to index ulcer healing was shorter in the DEB group (Table 3).

Subanalyses for lesion length, baseline vessel status (stenosis or occlusion) and revascularization technique (intraluminal vs. subintimal) yielded similar comparative results (Figure 3). Three vessels treated with DEB showed an increase ≥30% in reference vessel diameter at follow-up: interestingly, no angiographically evident flaps were visible during the initial procedure in these 3 cases.

Examples of DEB-treated lesions are shown in Figures 4 and 5.
Discussion

The DEBATE-BTK is the first randomized study evaluating the efficacy, in terms of 12-month restenosis and TLR, of DEB vs. standard PTA in diabetic patients with CLI undergoing revascularization of BTK arteries. DEB significantly reduce 12-month restenosis, with a relative risk reduction (RRR) of 64%. This advantage was irrespective of lesion length, revascularization technique and baseline vessel conditions. When DEB failed to match 12-month vessel patency, the length of reocclusion was significantly shorter compared to that observed after standard PTA, facilitating re-intervention. Our findings confirm, in a randomized fashion, those previously reported in a single center registry\textsuperscript{15}, which evaluated 3-month binary restenosis in unselected CLI patients treated with the same DEB platform as in our study. Our data show the persistence of the results at 12 months and add important clinical endpoints. Moreover, the high frequency of angiographic follow-up and the very low rate of bail-out treatment with drug-eluting stents ensure the reliability of our results.

The advantage conferred by DEB on restenosis resulted in a significant decrease in clinically-driven TLR, a secondary endpoint of the study. TLR has an important prognostic value in CLI patients, as early failure of endovascular recanalization was found to predict limb loss and poor prognosis\textsuperscript{20}, and repeat interventions with multiple contrast exposures are harmful in these very sick patients with frequent life-threatening comorbidities. Besides major amputation, our study did not have pre-planned endpoints of minor amputation and healing due to the fact that vessel patency alone is considered necessary but not sufficient to guarantee amputation-free survival.\textsuperscript{2,8,21} However, post hoc analysis revealed that DEB are likely to provide significant improvement in the rate of complete index ulcer healing at 12 months. The possibility that treatment with DEB might result in significant clinical benefit is further compounded by the
more favorable distribution of Rutherford classes at follow-up and faster index ulcer healing in
the DEB group.

Treatment with DEB, however, did not translate to a significantly higher rate of limb
salvage due to the very low rate of major amputations (1 limb out of 143). This low rate of limb
loss may depend on several factors: 1) patients were enrolled in the study only after successful
wiring of the target vessel and, therefore, the rate of major amputation observed cannot be
compared to that derived from studies designed on an intention-to-treat basis; 2) we established a
dedicated multidisciplinary team providing wound care and continuous surveillance regimen of
the foot lesion and vessel patency, including fast-track angiography and re-intervention when
clinically needed\textsuperscript{8,21}. We previously showed the long-term benefit of this integrated
multidisciplinary framework in this high-risk subset of patients\textsuperscript{7}.

The safety of DEB, moreover, was similar to conventional balloons, as no acute
thrombosis occurred on 1 month dual antiplatelet therapy in both arms. In few cases, DEB were
associated with a limited increase in reference vessel diameter at follow-up. Longer follow-up
will clarify if this phenomenon is of clinical relevance.

\textbf{Study Limitations}

Like many device trials in interventional cardiology, this is not a blinded study. In addition,
patients were enrolled only in a single, high-volume center that might have a unique patient
referral pattern and interventional technique. In addition, this study had no financial support and
no external angiography or DUS core laboratory was available for adjudication of the endpoints.
However, the size of the observed effect and the additional evidence in favor of DEB in the
femoropopliteal district\textsuperscript{14} leaves few chances for these results to be controverted in a multicenter
randomized study. We used everolimus drug-eluting stents as a bailout, which could have
potentially affected the study results and interacted with DEB leading to excessive neointimal inhibition. However, only two DES were implanted (one in each study group) and we did not observe any sign of positive remodelling in the single patient that was eventually treated with DEB+DES. Finally, clinical results achieved by an integrated multidisciplinary approach to CLI may not reproduced with DEB in other centers with different organization.

Conclusions

DEB angioplasty of tibial vessel in diabetic patients with CLI is associated with a significant reduction in binary restenosis, TLR and vessel occlusion at 12 months. The higher vessel patency provided by DEB translated into some clinical advantage, although our single-center trial does not have the power to evaluate more patient-centered outcomes. Large multicenter randomized trials will be needed to assess whether the increased patency of limb arteries afforded by DEB promotes clear improvement in limb salvage and survival.

Conflict of Interest Disclosures: None.

References:


Table 1. Patients baseline characteristics

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<th></th>
<th>DEB</th>
<th>PTA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>65</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Age — yr</td>
<td>74±9.4</td>
<td>75±9.6</td>
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<tr>
<td>Male gender — no. (%)</td>
<td>54 (83.1)</td>
<td>52 (77.6)</td>
<td>0.5</td>
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<td>Diabetes — no. (%)</td>
<td>65 (100)</td>
<td>67 (100)</td>
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<td>Hypertension — no. (%)</td>
<td>46 (70.8)</td>
<td>52 (77.6)</td>
<td>0.4</td>
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<td>Smoking — no. (%)</td>
<td>13 (20.0)</td>
<td>7 (10.4)</td>
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<tr>
<td>Hypercholesterolemia — no. (%)</td>
<td>23 (35.4)</td>
<td>16 (23.9)</td>
<td>0.1</td>
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<td>Serum creatinine — mg/dl</td>
<td>1.2±0.4</td>
<td>1.2±0.5</td>
<td>0.9</td>
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<td>eGFR— ml/min/1.73m2</td>
<td>51±27</td>
<td>54±23</td>
<td>0.8</td>
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<td>Coronary artery disease — no. (%)</td>
<td>12 (18.5)</td>
<td>10 (14.9)</td>
<td>0.6</td>
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<tr>
<td>Cerebrovascular disease — no. (%)</td>
<td>5 (7.7)</td>
<td>7 (10.4)</td>
<td>0.7</td>
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<tr>
<td>Number of limbs</td>
<td>71</td>
<td>72</td>
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<td>Patent tibial vessels — no. (%)</td>
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<td>0</td>
<td>23 (35.4)</td>
<td>19 (28.4)</td>
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<td>1</td>
<td>30 (46.2)</td>
<td>37 (55.2)</td>
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<td>2</td>
<td>12 (18.5)</td>
<td>11 (16.4)</td>
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<tr>
<td>ABI</td>
<td>0.31±0.2</td>
<td>0.29±0.3</td>
<td>0.6</td>
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<td>Inflow lesion treatment — no. (%)</td>
<td>32 (49.2)</td>
<td>35 (52.2)</td>
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<tr>
<td>Mean Rutherford Class</td>
<td>5.15±0.4</td>
<td>5.09±0.4</td>
<td>0.4</td>
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<tr>
<td>Rutherford Class 4 — no. (%)</td>
<td>2 (2.8)</td>
<td>3 (4.2)</td>
<td>0.7</td>
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<tr>
<td>Rutherford Class 5 — no. (%)</td>
<td>56 (78.9)</td>
<td>59 (81.9)</td>
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<tr>
<td>Rutherford Class 6 — no. (%)</td>
<td>13 (18.3)</td>
<td>10 (13.9)</td>
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Plus–minus values are means ±SD.

ABI: Ankle-brachial-index
Table 2. Procedural and angiographic characteristics

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<th></th>
<th>DEB</th>
<th>PTA</th>
<th>P value</th>
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<tbody>
<tr>
<td>Number of lesions</td>
<td>80</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Vessel location — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATA</td>
<td>37 (46.3)</td>
<td>32 (41.0)</td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>13 (16.3)</td>
<td>18 (23.1)</td>
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<td>PA</td>
<td>14 (17.5)</td>
<td>21 (26.9)</td>
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<td>TPT</td>
<td>16 (20.0)</td>
<td>7 (9.0)</td>
<td></td>
</tr>
<tr>
<td>Complete vessel occlusion — no. (%)</td>
<td>62 (77.5)</td>
<td>64 (82.1)</td>
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<td>Lesion length — mm</td>
<td>129±83</td>
<td>131±79</td>
<td>0.9</td>
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<td>Severe calcification — no. (%)</td>
<td>20 (25.0)</td>
<td>22 (28.2)</td>
<td>0.5</td>
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<td>RVD — mm</td>
<td>2.91±0.27</td>
<td>2.87±0.29</td>
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<tr>
<td>MLD — mm</td>
<td>0.06±0.14</td>
<td>0.05±0.14</td>
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<tr>
<td>DS — %</td>
<td>97.2±7.7</td>
<td>97.1±8.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Predilatation — no. (%)</td>
<td>80 (100.0)</td>
<td>-</td>
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<tr>
<td>Subintimal recanalization — no. (%)</td>
<td>17 (21.3)</td>
<td>17 (21.8)</td>
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<td>Antegrade recanalization — no. (%)</td>
<td>78 (97.5)</td>
<td>75 (96.2)</td>
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<td>Retrograde recanalization — no. (%)</td>
<td>2 (2.5)</td>
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<td>Balloon inflation time — sec</td>
<td>142±38</td>
<td>140±50</td>
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<tr>
<td>Balloon diameter — mm</td>
<td>2.90±0.39</td>
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<td>Balloon length — mm</td>
<td>148±83</td>
<td>140±79</td>
<td>0.5</td>
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<td>Bailout stenting — no. (%)</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
<td>0.9</td>
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<td>Technical success — no. (%)</td>
<td>80 (100)</td>
<td>78 (100)</td>
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<td>Procedural success — no. (%)</td>
<td>65(100)</td>
<td>67(100)</td>
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Plus–minus values are means ±SD.

ATA: anterior tibial artery, PTA: posterior tibial artery, PA: peroneal artery, TPT: tibioperoneal trunk, RVD: reference vessel diameter, MLD: minimal lumen diameter, %DS: percentage diameter stenosis
Table 3. Clinical and angiographic outcome at 12 months

<table>
<thead>
<tr>
<th></th>
<th>DEB</th>
<th>PTA</th>
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<tbody>
<tr>
<td>Death — no. (%)</td>
<td>5(7.7)</td>
<td>3(4.5)</td>
<td>0.4</td>
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<td>Major Amputation — no. (%)</td>
<td>0(0.0)</td>
<td>1 (1.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>CVA — no. (%)</td>
<td>2 (3.1)</td>
<td>3 (4.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>AMI — no. (%)</td>
<td>3 (4.6)</td>
<td>3 (4.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>MAE — no. (%)</td>
<td>20 (31)</td>
<td>34 (51)</td>
<td>0.05</td>
</tr>
<tr>
<td>Limbs available for 12-month follow-up</td>
<td>66</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>ABI</td>
<td>0.78±0.22</td>
<td>0.47±0.28</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean Rutherford class category</td>
<td>0.90±1.8</td>
<td>2.0±2.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Rutherford Class 0-3 — no. (%)</td>
<td>57 (86.3)</td>
<td>44 (65.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>Rutherford Class 4 — no. (%)</td>
<td>0 (0)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Rutherford Class 5 — no. (%)</td>
<td>8 (12.2)</td>
<td>19 (28.3)</td>
<td></td>
</tr>
<tr>
<td>Rutherford Class 6 — no. (%)</td>
<td>1 (1.5)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Complete index ulcer healing* — no. (%)</td>
<td>56/65 (86)</td>
<td>43/64 (67)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time to index ulcer healing* — months</td>
<td>4.4±1.5</td>
<td>5.2±1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Lesions available for 12-month follow-up</td>
<td>74</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Binary Restenosis (&gt;50%) — no. (%)†</td>
<td>20(27.0)</td>
<td>55(74.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Vessel Occlusion — no. (%)†</td>
<td>13(17.6)</td>
<td>41(55.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Occlusion length — mm†</td>
<td>87±88</td>
<td>128±75</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Plus–minus values are means ±SD.
CVA: cerebrovascular accident, AMI: acute myocardial infarction, MAE: major adverse events.
*Refers to limbs available for 12-month follow-up with Rutherford class 5-6 at baseline
†Per lesion analysis

Figure Legends:

Figure 1. Study Flow.

Figure 2. Kaplan-Meyer analysis for survival free from target lesion revascularization (TLR) in both study groups.

Figure 3. Post-hoc analysis of restenosis (%) in different subgroups of the 2 study groups.
**Figure 4.** Right limb below the knee (BTK) vessels in a 76-year old male with critical limb ischemia. Panel A: stenosis in the proximal segment of the peroneal artery (PA); long diseased segment of the posterior tibial artery (PTA, black arrows). Panel B: patent plantar arteries. Panel C: Dilatation of the proximal segment of the tibioperoneal trunk and PTA with a 3.0x120mm drug-eluting balloon (DEB, Amphirion In.Pact, Medtronic, Santa Rosa, CA). Panel D: Dilatation of the mid-distal segment of the PTA with a 3.0x120mm DEB (Amphirion In.Pact, Medtronic, Santa Rosa, CA) overlapping for 10mm with the segment previously treated with the other DEB. Panel E: immediate angiographic result with good patency of the PTA without residual stenosis. The PA lesion could not be enrolled in the study (length <40 mm) and was dilated with conventional, non-eluting balloon (not shown). Panel D: Twelve-month follow-up angiography showing optimal patency of the PTA without restenosis.

**Figure 5.** Right limb below the knee (BTK) vessels in a 78-year old male with critical limb ischemia: Panel A: proximal occlusion of the anterior tibial artery (ATA) (upper black arrow) with filling of the dorsalis pedis artery (lower black arrow) by the peroneal artery (PA), which shows significant stenosis in the proximal segment (white arrows); occlusion of the posterior tibial artery (PTA) with collateral filling of the plantar arteries by the PA. Panel B: Immediate results after drug-eluting balloon (DEB, Amphirion In.Pact, Medtronic, Santa Rosa, CA) dilation of both ATA (3.5x120mm+3x120mm+3x80mm) and PA (3.5x120mm). Panel B: immediate angiographic result with no residual stenosis of both ATA and PA. Panel C: Twelve-month follow-up angiography showing good patency of both ATA and PA arteries. Black arrow indicates focal ectasia of the ATA in the segment previously treated with DEB.
156 diabetic patients with CLI (Rutherford class ≥ 4) with at least one ≥ 50% stenosis of tibial vessels vessels ≥ 40 mm in length with distal run-off

24 excluded
- 16 did not meet angiographic inclusion criteria
- 2 need for major amputation
- 4 lack of consent
- 2 life expectancy < 1 year

132 patients with 158 lesions in 143 limbs enrolled

1:1 Randomization

DEB
65 patients, 80 lesions in 71 limbs
- Death = 5
  - 67 lesions Angio FUP¹
  - 7 lesions DUS FUP²

PTA
67 patients, 78 lesions in 72 limbs
- Death = 3
  - 68 lesions Angio FUP¹
  - 6 lesions DUS FUP²

12-month FUP

1 Angio FUP performed at 12 months or at the time of TLR
2 DUS = Doppler Ultrasound imaging

Figure 1
Figure 2

- **DEB**
- **PTA**

Log-Rank p = 0.02
Figure 3

The figure illustrates the comparison between DEB and PTA treatments across different criteria. It shows that DEB consistently outperforms PTA in terms of success rates, with statistical significance indicated by P-values:

- Per patient analysis: 72% (DEB) vs. 74% (PTA), P<0.001
- Per lesion analysis: 74% (DEB) vs. 59% (PTA), P<0.01
- Lesion length > 100mm: 64% (DEB) vs. 69% (PTA), P<0.001
- Lesion length ≤ 100mm: 72% (DEB) vs. 69% (PTA), P<0.001
- Baseline stenosis: 29% (DEB) vs. 27% (PTA), 0.2
- Baseline occlusion: 27% (DEB) vs. 25% (PTA), 0.2
- Intraluminal recanalization: 23% (DEB) vs. 25% (PTA), 0.2
- Subintimal recanalization: 23% (DEB) vs. 25% (PTA), 0.2

The success rates for DEB are consistently higher than those for PTA across all categories, with statistical significance for most comparisons.
Figure 5
Drug-Eluting Balloon in peripherAl inTERvention for Below the Knee Angioplasty Evaluation (DEBATE-BTK): A Randomized Trial in Diabetic Patients with Critical Limb Ischemia
Francesco Liistro, Italo Porto, Paolo Angioli, Simone Grotti, Lucia Ricci, Kenneth Ducci, Giovanni Falsini, Giorgio Ventoruzzo, Filippo Turini, Guido Bellandi and Leonardo Bolognese