# Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK)

## A Randomized Trial in Diabetic Patients With Critical Limb Ischemia

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***Background***—The 1-year restenosis rate after balloon angioplasty of long lesions in below-the-knee arteries may be as high as 70%. Our aim was to investigate the efficacy of a paclitaxel drug-eluting balloons versus conventional percutaneous transluminal angioplasty (PTA) for the reduction of restenosis in diabetic patients with critical limb ischemia undergoing endovascular intervention of below-the-knee arteries.

***Methods and Results***—The Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) is a randomized, open-label, single-center study comparing drug-eluting balloons and PTA. Inclusion criteria were diabetes mellitus, critical limb ischemia (Rutherford class 4 or higher), significant stenosis or occlusion >40 mm of at least 1 below-the-knee vessel with distal runoff, and life expectancy >1 year. Binary in-segment restenosis at a 1-year angiographic or ultrasonographic follow-up was the primary end point. Clinically driven target lesion revascularization, major amputation, and target vessel occlusion were the secondary end points. One hundred thirty-two patients with 158 infrapopliteal atherosclerotic lesions were enrolled. Mean length of the treated segments was 129±83 mm in the drug-eluting balloon group compared with 131±79 mm in the PTA group ($P$=0.7). Binary restenosis, assessed by angiography in >90% of patients, occurred in 20 of 74 lesions (27%) in the drug-eluting balloon group compared with 55 of 74 lesions (74%) in the PTA group ($P$<0.001); target lesion revascularization, in 12 (18%) versus 29 (43%; $P$=0.002); and target vessel occlusion, in 12 (17%) versus 41 (55%; $P$<0.001). Only 1 major amputation occurred, in the PTA group ($P$=0.9).

***Conclusions***—Drug-eluting balloons compared with PTA strikingly reduce 1-year restenosis, target lesion revascularization, and target vessel occlusion in the treatment of below-the-knee lesions in diabetic patients with critical limb ischemia.

***Clinical Trial Registration***—URL: http://ClinicalTrials.gov. Unique identifier: NCT01558505.

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**Key Words:** balloon angioplasty ■ critical limb ischemia ■ diabetes mellitus ■ peripheral vascular disease



Critical limb ischemia (CLI), characterized by ischemic rest pain or tissue loss, represents the most advanced state of peripheral artery disease, burdened by high morbidity and mortality.[1,2] CLI generally occurs in diabetics with extensive atherosclerotic disease of below-the-knee (BTK) vessels.[1]

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The optimal strategy for treating CLI patients, however, has not been clearly defined yet. The outcome of medical therapy is unsatisfactory,[3] and early, aggressive percutaneous revascularization with the aim of obtaining direct flow to the foot is increasingly considered a first-line strategy.[4,5] Indeed, although vessel patency alone cannot match patient-centered clinical end points[6] and any endovascular program has to be integrated into a network-based system of care involving different professionals,[7,8] an increased cutaneous oxygen pressure resulting from successful revascularization promotes infection clearance and ulcer granulation at a crucial time point.[9]

The efficacy of percutaneous transluminal angioplasty (PTA) with conventional balloons, however, is limited by the high 12-month restenosis and target lesion revascularization (TLR) rates.[10] Loss of vessel patency affects the healing process, resulting in no healing, decrease-increase behavior of the ulcer, or appearance of new foot lesions.[11] Although drug-eluting stents may offer a therapeutic alternative to PTA in the BTK area,[12,13] 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 (DEBs) has recently shown promising results in the treatment of femoropopliteal disease,[14] and in the BTK area, a reduction in 3-month binary restenosis has been observed

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compared with historical controls treated with PTA.[15] Historical data, however, may not represent an adequate comparator because of changes in technology and clinical practice over time,[16] and the efficacy of DEBs in diabetic patients with CLI has not been validated in a randomized fashion.

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

## Methods

### Study Design

The Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) is a single-center, parallel-group, PROBE (Prospective Randomized Open Blinded End-Point) trial[17] evaluating the efficacy of a 0.014-in guidewire–compatible DEB (IN.PACT Amphirion, Medtronic) compared with standard PTA (Amphirion Deep, Medtronic) in reducing the 12-month restenosis rate in diabetic patients with CLI undergoing endovascular BTK revascularization. The study 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 www.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 1 BTK vessel at our center were screened for enrollment. Inclusion criteria were the presence of diabetes mellitus, CLI (Rutherford class 4 or greater), stenosis or occlusion ≥40 mm of at least 1 tibial vessel with distal runoff 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 1 of the 2 study arms after successful passage of the guidewire. Randomization was performed in blocks of 10 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 6F sheaths. In case of failure to recanalize, a retrograde approach was attempted. In the DEB group, predilatation of the target lesion with standard balloon(s) was always performed before dilatation with a DEB. The DEB used in this study has previously been described.[15] The ratio of DEB to vessel diameter was planned to be 1:1. DEBs 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(s) consistently exceeded the area predilated with standard balloons by at least 10 mm at the proximal and distal edges to avoid geographic miss. If >1 balloon was used per lesion, the overlap zone was at least 5 mm. Inflation time was at least 2 minutes for both the DEB and PTA arms. In case of flow-limiting dissection or residual stenosis of >30%, a prolonged dilation of up to 3 minutes was performed. Drug-eluting coronary stents (Xience V, Abbott, CA) were used as bailout. Technical success was defined as restoration of direct flow in the target vessel with runoff to the foot and a residual stenosis of <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-ray exposure 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. Postintervention 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 up in a multidisciplinary, dedicated foot clinic to facilitate the healing process and recovery of ambulatory function.[7] Office visits were scheduled twice a week for the first 2 months, once a week for the third month, and then every 2 weeks. Minor amputations planned before the interventions were performed 2 to 4 weeks after revascularization and included finger amputations and metatarsal amputations resulting from necrosis/infection of tissues and bones with preservation of healthy surrounding tissue. All patients were scheduled to be readmitted 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 1 week from diagnosis. In patients undergoing clinically driven repeat angiography of the target limb between 9 and 12 months who did not show evidence of restenosis of the target lesion, scheduled angiography at 12 months was not performed if the DUS evaluation was clearly diagnostic for vessel patency with no restenosis.

### Study End Points and Definitions

Before the intervention, 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 end point of the study was the comparison of the 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 ≥2.5 by DUS.

The prespecified secondary end points of the study were (1) clinically driven TLR, defined as repeat percutaneous intervention or surgical bypass graft resulting from angiographic evidence of restenosis at the level of the treated lesion ±10 mm in the presence of at least 1 of the following criteria: recurrence of pain in the foot at rest that increased in the supine position, recurrence of foot lesion or evidence during follow-up of foot lesion size decrease-increase behavior or appearance of a new foot lesion; (2) major amputation, defined as unplanned amputation of the target limb in which a prosthesis was required for standing or walking; and (3) target vessel occlusion (by either angiography or DUS).

Acquired angiograms and DUS scans were reviewed by 2 blinded investigators who did not actively participate in recruitment (I.P. and G.V.) and had no knowledge of clinical status and randomization group.

Post hoc analyses was performed for the cumulative 12-month prevalence of major adverse events (death, major amputation, TLR, and Rutherford class 4 or greater) in the 2 groups, as well as for other clinical end points 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) and shorter lesions, total occlusions and stenoses, and true lumen and subintimal recanalization techniques.

## Statistical Analysis

Values are reported as numbers with relative percentage or standard deviation. Nominal variables were compared by the Fisher exact test; continuous variables were compared with the *t* test. Twelve-month binary restenosis rate, the primary end point of the study, was compared with the Fisher exact test. Kaplan–Meier estimates and log-rank test survival methods were used to assess freedom from TLR, a secondary end point. Cohen κ statistics was used to compare angiography and DUS for the detection of restenosis. All statistical computations were performed with 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,[10] 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.[18,19] A minimum of 63 evaluable lesions per group were considered necessary to have a 90% power (2-sided 5% significance level) to detect a 50% relative risk reduction in the DEB group. The number of lesions per group was further increased to 70 to maximize study power.

Assuming a rate of eligible lesions per patient of 1.3, a minimum of 110 patients had to be enrolled in the study. The number of patients was increased to 130 considering a dropout rate of 20% resulting from the expected high morbidity and mortality in CLI patients.

# Results

## Patients and Lesions

During the study period, 156 patients were screened for study enrollment; 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 percent of the patients in each study arm were on long-term dialysis, and the majority of patients had 0 to 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. Treated lesions had a high degree of complexity in both study arms; 80% of the lesions were total occlusions and >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 events 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). The percentages of cardiac versus noncardiac death in the 2 groups were not significantly different.

Of the 124 patients alive at 12 months (60 patients with 74 lesions in the DEB group versus 64 patients with 74 lesions in the PTA group), angiographic follow-up could not be obtained in 13 patients (5 patients for worsening of preexisting renal failure, 2 patients for major stroke, 2 patients for congestive heart failure, and 4 patients who refused the examination); they 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 κ 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.

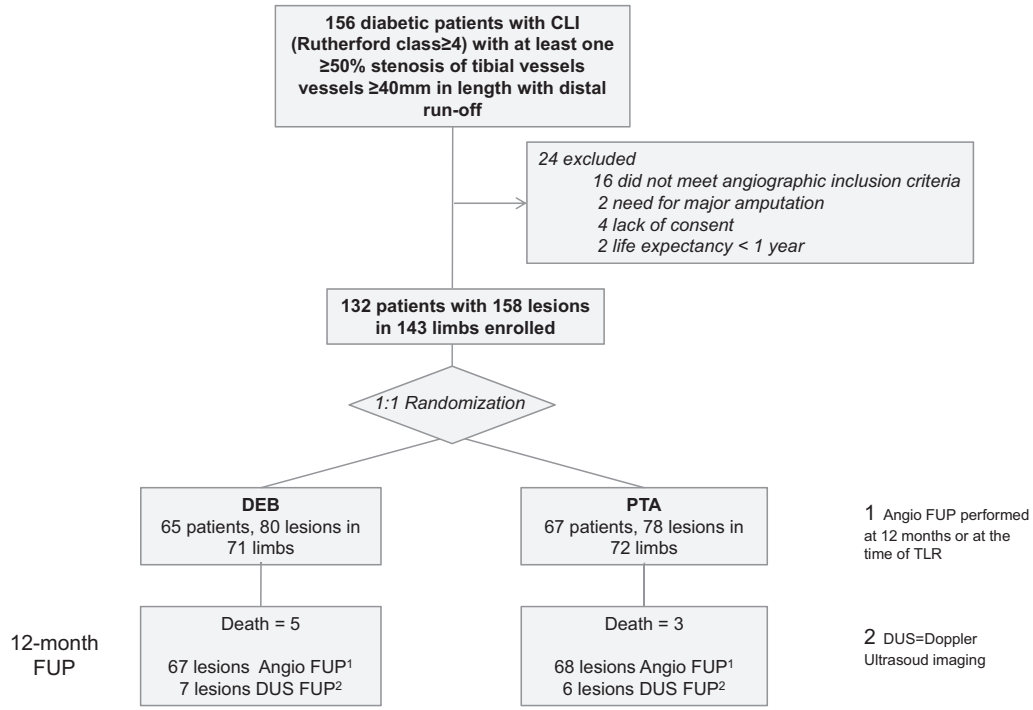


**Figure 1.** Study flow. Angio indicates angiography; CLI, critical limb ischemia; DEB, drug-eluting balloon; DUS, duplex ultrasound; FUP, follow-up; PTA, percutaneous transluminal angioplasty; and TLR, target lesion revascularization.

**Table 1. Patients' Baseline Characteristics**

| | DEB | PTA | *P* Value |
|---|---|---|---|
| Patients, n | 65 | 67 | |
| Age, y | 74±9.4 | 75±9.6 | 0.7 |
| Male, n (%) | 54 (83.1) | 52 (77.6) | 0.5 |
| Diabetes mellitus, n (%) | 65 (100) | 67 (100) | 1 |
| Hypertension, n (%) | 46 (70.8) | 52 (77.6) | 0.4 |
| Smoking, n (%) | 13 (20.0) | 7 (10.4) | 0.1 |
| Hypercholesterolemia, n (%) | 23 (35.4) | 16 (23.9) | 0.1 |
| Dialysis, n (%) | 7 (10.8) | 7 (10.4) | 1 |
| Serum creatinine, mg/dL | 1.2±0.4 | 1.2±0.5 | 0.9 |
| eGFR, mL·min$^{-1}$·1.73 m$^{-2}$ | 51±27 | 54±23 | 0.8 |
| Coronary artery disease, n (%) | 12 (18.5) | 10 (14.9) | 0.6 |
| Cerebrovascular disease, n (%) | 5 (7.7) | 7 (10.4) | 0.7 |
| Limbs, n | 71 | 72 | |
| Patent tibial vessels, n (%) | | | |
| 0 | 23 (35.4) | 19 (28.4) | |
| 1 | 30 (46.2) | 37 (55.2) | 0.5 |
| 2 | 12 (18.5) | 11 (16.4) | |
| ABI | 0.31±0.2 | 0.29±0.3 | 0.6 |
| Inflow lesion treatment, n (%) | 32 (49.2) | 35 (52.2) | 0.8 |
| Mean Rutherford class, n (%) | 5.15±0.4 | 5.09±0.4 | 0.4 |
| 4 | 2 (2.8) | 3 (4.2) | |
| 5 | 56 (78.9) | 59 (81.9) | 0.7 |
| 6 | 13 (18.3) | 10 (13.9) | |

Values are mean±SD when appropriate. ABI indicates ankle-brachial index; DEB, drug-eluting balloon; eGFR, estimated glomerular filtration rate; and PTA, percutaneous transluminal angioplasty.

Clinical and angiographic data of 12-month follow-up are presented in Table 3. The primary end point, 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 ($P=0.8$). Only 1 major amputation occurred, in the PTA group ($P=0.9$). Target vessel occlusion occurred in 13 (17%) DEB-treated versus 41 (55%) PTA-treated vessels ($P<0.001$). Twelve-month major adverse events occurred less frequently in the DEB (31%) than in the PTA (51%) group ($P=0.02$), driven mainly by a reduction in TLR and better ulcer healing. The 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 versus subintimal) yielded similar comparative results (Figure 3). Three vessels treated with DEB showed an increase of ≥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

DEBATE-BTK is the first randomized study evaluating the efficacy, in terms of 12-month restenosis and TLR, of DEB versus standard PTA in diabetic patients with CLI undergoing revascularization of BTK arteries. DEB significantly reduced 12-month restenosis, with a relative risk reduction of 64%. This advantage was independent of lesion length, revascularization technique, and baseline vessel conditions. When DEBs failed to match the 12-month vessel patency, the length of reocclusion was significantly shorter compared with that observed after standard PTA, facilitating reintervention. Our findings confirm, in a randomized fashion, those previously reported in a single-center registry[15] that 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 end points. Moreover, the high frequency of angiographic follow-up and the very low rate of bailout 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 end point of the study. TLR has an important prognostic value in CLI patients because early failure of endovascular recanalization was found to predict limb loss and poor prognosis,[20] and repeat interventions with multiple contrast exposures are harmful in these sick patients with frequent life-threatening comorbidities. Besides major amputation, our study did not have preplanned

**Table 2. Procedural and Angiographic Characteristics**

| | DEB | PTA | *P* Value |
|---|---|---|---|
| Lesions, n | 80 | 78 | |
| Vessel location, n (%) | | | |
| ATA | 37 (46.3) | 32 (41.0) | |
| PT | 13 (16.3) | 18 (23.1) | |
| PA | 14 (17.5) | 21 (26.9) | 0.5 |
| TPT | 16 (20.0) | 7 (9.0) | |
| Complete vessel occlusion, n (%) | 62 (77.5) | 64 (82.1) | 0.5 |
| Lesion length, mm | 129±83 | 131±79 | 0.9 |
| Severe calcification, n (%) | 20 (25.0) | 22 (28.2) | 0.5 |
| RVD, mm | 2.91±0.27 | 2.87±0.29 | 0.7 |
| MLD, mm | 0.06±0.14 | 0.05±0.14 | 0.6 |
| DS, % | 97.2±7.7 | 97.1±8.0 | 0.9 |
| Predilatation, n (%) | 80 (100.0) | … | |
| Subintimal recanalization, n (%) | 17 (21.3) | 17 (21.8) | 0.8 |
| Antegrade recanalization, n (%) | 78 (97.5) | 75 (96.2) | 0.7 |
| Retrograde recanalization, n (%) | 2 (2.5) | 3 (3.8) | 0.7 |
| Balloon inflation time, s | 142±38 | 140±50 | 0.5 |
| Balloon diameter, mm | 2.90±0.39 | 2.85±0.36 | 0.4 |
| Balloon length, mm | 148±83 | 140±79 | 0.5 |
| Bailout stenting, n (%) | 1 (1.3) | 1 (1.3) | 0.9 |
| Technical success, n (%) | 80 (100) | 78 (100) | 1 |
| Procedural success, n (%) | 65 (100) | 67 (100) | 1 |

Values are mean±SD when appropriate. ATA indicates anterior tibial artery; DEB, drug-eluting balloon; DS, diameter stenosis; MLD, minimal lumen diameter; PA, peroneal artery; PT, posterior tibial artery; PTA, percutaneous transluminal angioplasty; RVD, reference vessel diameter; and TPT, tibioperoneal trunk.

**Table 3. Clinical and Angiographic Outcome at 12 Months**

| | DEB | PTA | *P* Value |
|---|---|---|---|
| Death, n (%) | 5 (7.7) | 3 (4.5) | 0.4 |
| Major amputation, n (%) | 0 (0.0) | 1 (1.5) | 0.9 |
| CVA, n (%) | 2 (3.1) | 3 (4.5) | 0.9 |
| AMI, n (%) | 3 (4.6) | 3 (4.5) | 0.9 |
| MAEs, n (%) | 20 (31) | 34 (51) | 0.05 |
| Limbs available for 12-mo follow-up, n | 66 | 67 | |
| ABI | 0.78±0.22 | 0.47±0.28 | <0.001 |
| Mean Rutherford class category, n (%) | 0.90±1.8 | 2.0±2.3 | 0.004 |
| 0–3 | 57 (86.3) | 44 (65.7) | 0.06 |
| 4 | 0 (0) | 2 (3) | |
| 5 | 8 (12.2) | 19 (28.3) | |
| 6 | 1 (1.5) | 2 (3) | |
| Complete index ulcer healing, n (%)* | 56/65 (86) | 43/64 (67) | 0.01 |
| Time to index ulcer healing, mo* | 4.4±1.5 | 5.2±1.6 | 0.01 |
| Lesions available for 12-mo follow-up | 74 | 74 | |
| Binary restenosis (>50%), n (%)† | 20 (27.0) | 55 (74.3) | <0.001 |
| Vessel occlusion, n (%)† | 13 (17.6) | 41 (55.4) | <0.001 |
| Occlusion length, mm† | 87±88 | 128±75 | <0.001 |

Values are mean±SD when appropriate. ABI indicates ankle-brachial index; AMI, acute myocardial infarction, CVA, cerebrovascular accident; DEB, drug-eluting balloon; MAE, major adverse event; and PTA, percutaneous transluminal angioplasty.

*Refers to limbs available for 12-month follow-up with Rutherford class 5 to 6 at baseline.

†Per-lesion analysis.

end points of minor amputation and healing because vessel patency alone is considered necessary but not sufficient to guarantee amputation-free survival.[2,8,21] However, post hoc analysis revealed that DEBs 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.

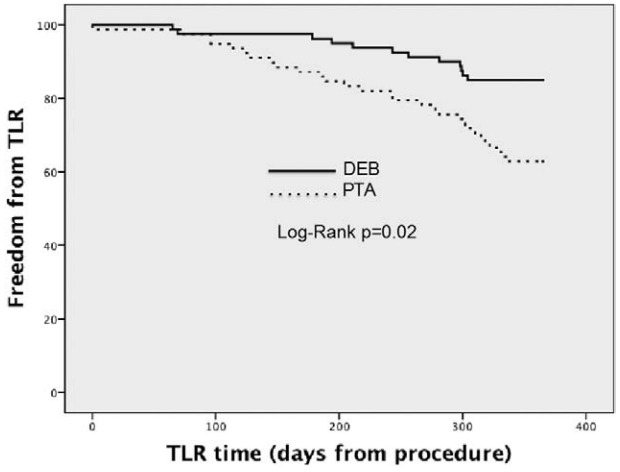


**Figure 2.** Kaplan–Meier analysis for survival free from target lesion revascularization (TLR) in both study groups. DEB indicates drug-eluting balloon; and PTA, percutaneous transluminal angioplasty.

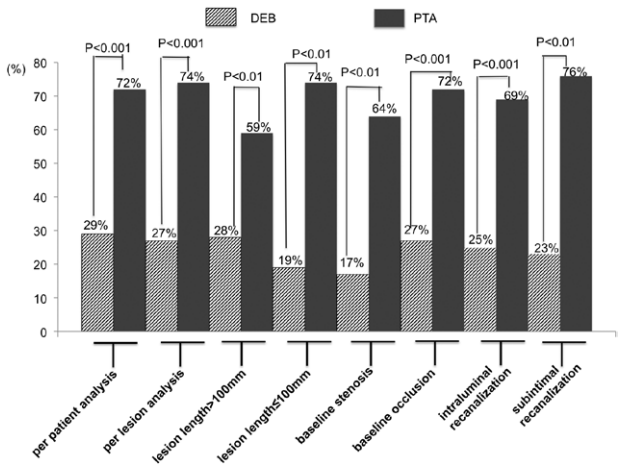


**Figure 3.** Post hoc analysis of restenosis (%) in different subgroups of the 2 study groups. DEB indicates drug-eluting balloon; and PTA, percutaneous transluminal angioplasty.

Treatment with DEB, however, did not translate to a significantly higher rate of limb salvage owing to the very low rate of major amputations (1 of 143 limbs). This low rate of limb loss

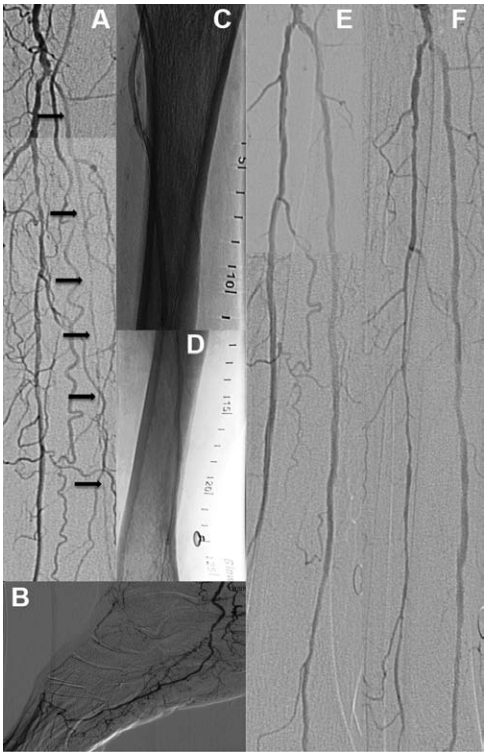


**Figure 4.** Right limb below-the-knee vessels in a 76-year-old man with critical limb ischemia. **A**, Stenosis in the proximal segment of the peroneal artery, and long-diseased segment of the posterior tibial artery (black arrows). **B**, Patent plantar arteries. **C**, Dilatation of the proximal segment of the tibioperoneal trunk and posterior tibial artery with a 3.0×120-mm drug-eluting balloon (DEB; Amphirion In.Pact, Medtronic, Santa Rosa, CA). **D**, Dilatation of the mid-distal segment of the posterior tibial artery with a 3.0×120-mm DEB (IN. PACT Amphirion) overlapping the segment previously treated with the other DEB for 10 mm. **E**, Immediate angiographic result with good patency of the posterior tibial artery without residual stenosis. The peroneal artery lesion could not be enrolled in the study (length <40 mm) and was dilated with conventional, noneluting balloon (not shown). **F**, Twelve-month follow-up angiography showing optimal patency of the posterior tibial artery without restenosis.

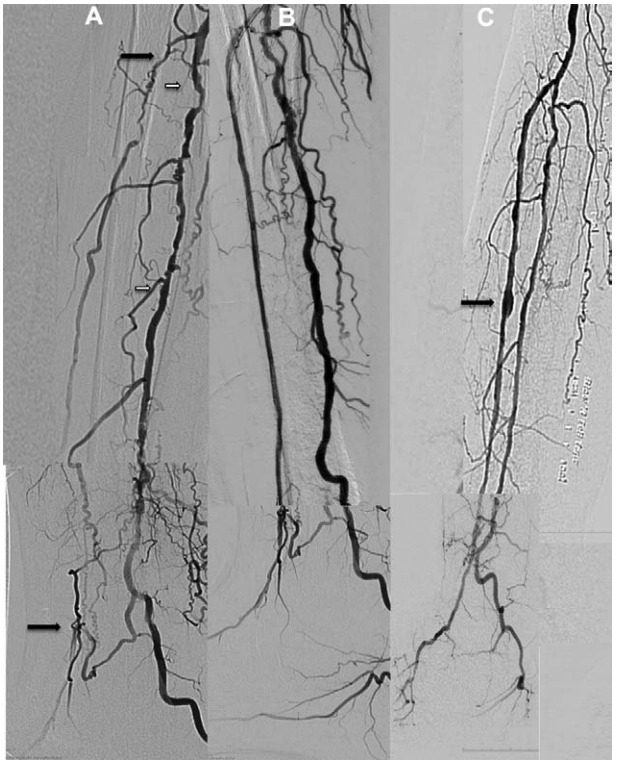


**Figure 5.** Right limb below-the-knee vessels in a 78-year-old man with critical limb ischemia. **A**, Proximal occlusion of the anterior tibial artery (top black arrow) with filling of the dorsalis pedis artery (bottom black arrow) by the peroneal artery, which shows significant stenosis in the proximal segment (white arrows), and occlusion of the posterior tibial artery with collateral filling of the plantar arteries by the peroneal artery. **B**, Immediate results after drug-eluting balloon (DEB; IN.PACT Amphirion, Medtronic, Santa Rosa, CA) dilation of both the anterior tibial artery (3.5×120 mm+3×120 mm+3×80 mm) and peroneal artery (3.5×120 mm). **B**, Immediate angiographic result with no residual stenosis of both the anterior tibial and peroneal arteries. **C**, Twelve-month follow-up angiography showing good patency of both the anterior tibial and peroneal arteries. Black arrow indicates the focal ectasia of the anterior tibial artery in the segment previously treated with a DEB.

may depend on 2 factors: 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 with that derived from studies designed on an intention-to-treat basis; and 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 reintervention when clinically needed.[8,21] We previously showed the long-term benefit of this integrated multidisciplinary framework in this high-risk subset of patients.[7]

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

### Study Limitations

Like many device trials in interventional cardiology, this was 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. This study had no financial support, and no external angiography or DUS core laboratory was available for adjudication of the end points. However, the size of the observed effect and the additional evidence in favor of DEBs in the femoropopliteal district[14] leave few chances for these results to be controverted in a multicenter, randomized study. We used everolimus drug-eluting stents as bailout, which could have potentially affected the study results and interacted with DEBs, leading to excessive neointimal inhibition. However, only 2 drug-eluting stents were implanted (1 in each study group), and we did not observe any sign of positive remodeling in the single patient who was eventually treated with a DEB plus a drug-eluting stent. Finally, clinical results achieved by an integrated multidisciplinary approach to CLI may not be reproduced with DEBs in other centers with different organization.

### Conclusions

DEB angioplasty of tibial vessels 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 DEBs translated into clinical advantage, although our single-center trial does not have the power to evaluate more patient-centered outcomes. Large multicenter, randomized trials are needed to assess whether the increased patency of limb arteries afforded by DEBs promotes clear improvement in limb salvage and survival.

## Disclosures

None.

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## CLINICAL PERSPECTIVE

Critical limb ischemia, characterized by ischemic rest pain or tissue loss, represents the most advanced state of peripheral artery disease, burdened by extremely high morbidity and mortality. Critical limb ischemia generally occurs in diabetics with extensive atherosclerotic disease of the below-the-knee vessels. The optimal strategy for treating critical limb ischemia patients, however, has not been clearly defined, and the 1-year restenosis rate after balloon angioplasty (percutaneous transluminal angioplasty) of long lesions in below-the-knee arteries may be as high as 70%. The Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation (DEBATE-BTK) is the first randomized study evaluating the efficacy, in terms of 12-month restenosis and target lesion revascularization, of drug-eluting balloons compared with standard percutaneous transluminal angioplasty in diabetic patients with de novo long atherosclerotic lesions and critical limb ischemia undergoing revascularization of below-the-knee arteries. Our study demonstrates that the drug-eluting balloons significantly reduced 12-month restenosis, regardless of lesion length, revascularization technique, and baseline vessel conditions. The advantage conferred by drug-eluting balloons on restenosis resulted in a significant decrease in clinically driven target lesion revascularization, and this benefit is further compounded by the more favorable distribution of Rutherford classes at follow-up and faster index ulcer healing in the drug-eluting balloon group.