Paclitaxel-Coated Balloons: Review of a Promising Interventional Approach to Preventing Restenosis in Femoropopliteal Arteries

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Abstract

Peripheral arterial disease (PAD), a major cause of morbidity and mortality worldwide, is characterized by intermittent claudication and is associated with chronic diseases such as diabetes and hypertension. The goal of treatment is to address the underlying cause and to modify risk factors. Although medical management is the first-line treatment of PAD, some individuals may have severe symptoms and require revascularization with percutaneous transluminal angioplasty with or without stent placement or surgery. Interventional approaches may, however, be associated with high prevalence of restenosis and subsequent complications such as critical limb ischemia and amputation. Drug-eluting balloons (DEBs) are a new interventional technology with the primary goal of preventing restenosis. We review the clinical trials and studies that assessed the efficacy and safety profile of DEB and will focus on the restenosis rate in femoropopliteal arteries including target lesion revascularization (TLR) and late lumen lesion (LLL) using different modalities of intervention such as stents and DEB. Average data collected from the trials reported included restenosis rate of 25%, 0.3 mm LLL, and 14% reduction in TLR with DEB versus uncoated balloons. Below the knee (BTK) only intervention studies were excluded from this review as endovascular approach is usually reserved for critical limb ischemia for BTK disease. Interventional approach to treat PAD with DEB appears to be a promising technology. Additional larger studies are needed to further define safety, efficacy, and longer term outcome with this novel technology.

Keywords

- ▶ peripheral arterial disease
- ▶ angioplasty
- ▶ claudication
- ▶ critical limb ischemia
- ▶ atherosclerosis
- ▶ femoral artery

Atherosclerosis causing peripheral arterial disease (PAD) is a systemic disease from accumulation of lipid and fibrous materials in different layers of medium and large arteries.¹ Although atherosclerosis is the most common cause of PAD, other etiologies include thrombosis and inflammation of the arteries. According to Rutherford classification, symptoms are usually secondary to oxygen and supply imbalance and include claudication, fatigue, nonhealing ulcers, and, in severe cases, gangrene. The prevalence of PAD ranges between 3 and

12% worldwide.² In 2010, it was estimated that 202 million patients worldwide had PAD.³ PAD is more common in association with family history of atherosclerosis, in the elderly, and in those with risk factors for cardiovascular disease, such as chronic kidney disease and diabetes. Due to the direct relationship between impaired glucose tolerance and inflammatory conditions associated with it, atherosclerotic lesions evolve in a micro- and macrovascular fashion in diabetes and prediabetes.⁴ Ciccone et al conducted a study to

evaluate minor events (renal failure, deep venous thrombosis, and restenosis), major events (death, stroke, and cardiac), and recurrent ulcers incidence in diabetic foot ulcer 1-year follow-up after angioplasty. They reported incidence rates of 15 and 34% of major and minor events, respectively.⁵

Because PAD is considered a coronary artery disease equivalent, the same risk factors (hypertension, hyperlipidemia, and tobacco abuse) contribute to its pathogenesis. Limb ischemia is a feared and critical complication, associated with an immediate risk of limb loss. The mortality rate of these patients is up to 25% within 1 year of diagnosis of critical limb ischemia.⁶

The Ankle Brachial Index (ABI) is a powerful diagnostic tool for PAD, with a value < 0.9 being suggestive of arterial stenosis in the presence of other signs and symptoms.⁷ Different modalities are important in detecting the site and severity such as segmental pressure and pulse volume, Doppler ultrasound, exercise testing, and direct vascular imaging.

Treatment of claudication includes initial conservative therapy, with a regimen that includes risk factor modification, exercise, and pharmacological therapy. Vascular or surgical interventions are usually reserved for chronic disabling symptoms refractory to medical therapy or for those with critical limb ischemia. Pharmacological agents, such as cilostazol and naftidrofuryl, are aimed at improving symptoms and quality of life.^{8,9} Among revascularization strategies, one randomized trial showed no significant difference between percutaneous transluminal angioplasty (PTA) and bypass surgery for iliac or femoropopliteal PAD, regardless of claudication or ischemic limb.¹⁰ The interventional approach may be associated with complications such as stent restenosis, thrombosis, infection, and limb-threatening ischemia.

Percutaneous intervention including angioplasty with or without stenting is associated with a significant rate of restenosis, especially for femoropopliteal lesions. Different studies and trials have been conducted to evaluate the most efficacious and safest interventional approach. This review will discuss the trials focusing on drug-eluting balloon (DEB) benefits and risks in percutaneous intervention. We specifically focus on the Lutonix Paclitaxel-Coated Balloon for Prevention of Femoropopliteal Restenosis (LEVANT I) study, which led to the October 2014 Food and Drug Administration approval of Lutonix (Murray Hill, NJ) as the first DEB for clinical use.

Review of Literature

Different Endovascular Approaches to Peripheral Revascularization

A meta-analysis of 40 randomized clinical trials conducted by Simpson et al in 2011 reviewed revascularization in patients with infrainguinal PAD.¹¹ The interventions analyzed included absorbable metal stents, self-expanding stents, balloon-expandable stents and drug-eluting stents, stent grafts, atherectomy, cutting balloon, cryoplasty, radiation by endovascular brachytherapy (EVBT) or external beam radiotherapy, drug-coated balloon, and laser angioplasty. Primary end points were restenosis and reintervention, walking distance, and complications or adverse effects.

Exclusion criteria were any pharmacological treatment, surgical procedures, interventions above the aortoiliac segment, and outdated methods. The analysis evaluated the restenosis risk ratio (RR) of different interventional modalities versus PTA alone. Restenosis rate at 6 months for self-expanding stents was RR 0.50, and 0.67 at 12 months compared with PTA. At 12 months, EVBT, a technology no longer available showed a significant effect (RR 0.63) with no major change in restenosis rates compared with PTA at 6 months. Balloon expandable stents had RR of 0.49 at 6 months with no significant change at 12 months. The use of DEB demonstrated improvement with RR 0.40 at 6 months. The meta-analysis also compared the rate of reintervention between DEB versus PTA. Target lesion revascularization (TLR) was lower with RR of 0.26 at 6 months for DEB and 0.27 at 24 months. Interestingly, walking capacity improved with self-expanding stents at 6 or 12 months but not at 24 months. There was also no significant difference in walking capacity with the other interventional modalities.

The analysis showed variations in the definition of restenosis versus vessel patency that led to comparison difficulties. Nevertheless, the review showed promising results regarding self-expanding stents, DES, and DEB.

Paclitaxel-Coated Balloon Trials

The next section will evaluate these trials with main focus on the restenosis rate, complications, and adverse events as summarized in ►Table 1.

Paclitaxel-Coated Balloons Reduce Restenosis after Femoropopliteal Angioplasty, Results of the PACIFIER Trial Werk et al conducted an investigator-initiated, multicenter, randomized trial in three different German institutions to evaluate DEBs as a means to reduce restenosis after femoropopliteal angioplasty.¹² Patients were randomized to either paclitaxel-coated IN.PACT Pacific ($n = 41$) or uncoated Pacific balloons ($n = 44$). Inclusion criteria consisted of complicated limb vasculopathy, femoropopliteal atherosclerotic disease, lesions between 3 and 30 cm, stenosis > 70%, and the use of dual antiplatelet therapy. Exclusion criteria were aneurysm or thrombus, failure to pass the guide wire, lesions that could not be pretreated, three infrapopliteal diseased vessels, renal failure, allergies, and life expectancy < 2 years. The primary end point was (late lumen lesion [LLL]) at 6 months assessed by blinded angiographic core laboratory quantitative analyses. Secondary end points were binary restenosis and Rutherford classification change at 6 months, and TLR plus major adverse clinical events (major adverse events = death, target limb amputation, or TLR) at 6 and 12 months. Angiographic findings after 6 months showed that the DEB had a lower rate of binary restenosis compared with uncoated balloons (3 [8.6%] vs. 11 [32.4%], $p = 0.01$). DEB was also associated with lower LLL (-0.01 mm [95% confidence interval, -0.29 ; 0.26] vs. 0.65 mm [0.37 ; 0.93] than uncoated balloons, $p = 0.001$).

Follow-up at 6 months showed 7.1% TLR in the DEB group versus 21.4% in uncoated balloons. After 12 months, the percentage remained the same in the DEB-treated group versus 15 TLR in 12 cases in the uncoated balloon group.

Table 1 Summary of drug-eluting balloon trials

Trial	N	Trial design	End points	Outcomes	Comments
PACIFIER	85	Multicenter, randomized trial	LLL at 6 mo, binary restenosis, Rutherford classification, TLR, adverse events	8.3% restenosis rate in DEB vs. 32.4% uncoated ones	Adverse events were 7.1% with DEB vs. 26.2% uncoated ones after 6 mo. 7.1 vs. 34.9% after 12 mo
FemPac	87	Randomized trial	Restenosis rate, TLR, and adverse events	47% restenosis rate in control group vs. 19% Paclitaxel group	Adverse events included peripheral embolism, elevated creatinine, and need for hospitalization (48% in Paclitaxel group vs. 52.4% uncoated group)
THUNDER	154	Prospective, randomized, multicenter trial	LLL, restenosis rate, TLR, and adverse events	17% restenosis with Paclitaxel group vs. 44% in control group	45–58% of all patients in the three groups had either progression of atherosclerosis or underlying disease
LEVANT I	101	Prospective, single blind, randomized trial	Patency, LLL, TLR, and adverse events	Primary patency 57% in DCB vs. 40% uncoated ones after 24 mo	Adverse events noted in 39% in DCB vs. 46% uncoated balloons
Debate SFA	104	Prospective, single center, randomized, parallel group, open label trial	Restenosis rate, LLL, TLR	Restenosis rate was 17% in DEB with BMS vs. 47.3% in PTA with BMS	About three patients expired in the study due to cardiac failure and sepsis. Total of three patients had stent fracture

Analysis of adverse events (death, limb amputation, and TLR) showed a lower rate compared with uncoated balloons at 6 months (3 [7.1%] vs. 11 [26.2%], $p = 0.040$) and at 12 months (3 [7.1%] vs. 15 [34.9%], $p < 0.01$).

The study demonstrated a good safety profile in which total paclitaxel dose was 21 mg and found that the average dose to initiate any systemic adverse effect is > 50 mg. Some of the limitations of the study included small sample size, imbalance between patient groups, and that operators were not blinded to the desired treatment because of the different appearance of the balloons.

Paclitaxel-Coated versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial

The Femoral Paclitaxel (FemPac) trial was a randomized study performed in Berlin and Greifswald, Germany from 2004 to 2006 that involved 87 patients (45 received DEB and 42 received uncoated ones) to evaluate the efficacy, safety, and tolerance of DEB compared with uncoated balloons.¹³ Treatment was performed by either conventional uncoated or paclitaxel-coated balloon catheters. The main goal was to assess restenosis rate of femoropopliteal arteries after PTA. Follow-up was conducted by angiography at 6 months after the intervention. Inclusion criteria were stenosis $> 70\%$, age > 18 to 90 years, and guide wire passage through the lesion. Exclusion criteria were conditions that required immediate treatment such as thrombolytics or operation, ischemic

limb, hyperthyroidism, renal failure, distal outflow < 1 vessel, life expectancy < 2 years, allergic reaction or intolerance to the dye, and major gastrointestinal bleeding in the previous 6 months. Follow-up after 6 months demonstrated less LLL in the coated balloon group (0.5 ± 1.1 vs. 1.0 ± 1.1 mm; $p = 0.031$). It was also noted that restenosis developed in 47% of patients in the control group and 19% in the DEB group ($p = 0.035$). Rutherford classification improved in both groups, but more significantly in the DEB group ($p = 0.045$). No major changes were found in the ABL. Adverse events included peripheral embolism and rash in the coated balloon group. Allergic reaction and elevated serum creatinine were also observed in the control group. The need for hospitalization rate was 48.9% in the DEB group versus 52.4% in uncoated balloon intervention. One interesting finding was that the TLR rate was 7% in coated balloons versus 33% in the control group patients who were treated using uncoated balloons ($p = 0.002$). It was also observed that TLR maintained the same rate for both treatment groups up to 18 to 24 months.

Small study size, heterogeneity of the population, and refusal of some patients to undergo follow-up angiography were significant limitations of the study.

Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg, Evaluation of the THUNDER Trial
Tepe et al conducted a prospective, randomized, multicenter trial between 2004 and 2005 in Germany that included a total

of 154 patients in three different centers.¹⁴ Inclusion criteria were age 18 to 95 years, and all patients had vessels with > 70% stenosis or restenosis and 2 cm in length, symptomatic PAD specifically in femoropopliteal vessels. The study excluded patients who were pregnant, those with acute symptoms, with poor inflow, and with life expectancy < 1 year. The selected patients were divided into three groups: the first group received DEB and standard nonionic contrast medium, the second group was treated with uncoated balloons with paclitaxel added to the contrast medium, and the third group was treated with standard uncoated balloon and standard nonionic contrast medium (control). The primary end point was LLL at 6 months.

Angiography at 6 months follow-up showed that the LLL was less in the DEB compared with control group (0.4 ± 1.2 vs. 1.7 ± 1.8 mm; $p < 0.001$). It was noted that LLL in the group treated with paclitaxel in the contrast medium did not differ from the control group ($p = 0.14$). The rate of restenosis was lower in DEBs than in the control group (17 vs. 44%, $p = 0.01$) but with no difference versus the paclitaxel with the contrast medium group ($p = 0.39$). The ABI remained unchanged, as was the case in most of the trials. TLR was performed in 37% of the control group, 29% of the paclitaxel with contrast medium group, and 4% of the DEBs group. The rate of TLR at 12 months was lower in the group treated with DEBs (10%) as compared with 48% in the control group and 35% in the paclitaxel with contrast medium group. Follow-up at 12 to 24 months revealed that the TLR rate remained minimal. Thromboembolic phenomena after 2 weeks of treatment occurred in three patients in the control group, two patients in the DEB group, and seven patients in the paclitaxel with contrast medium group. Serious adverse events rate was 46 to 58% of patients in all groups (progression of atherosclerosis or underlying disease). At 6 months, five patients had died and four underwent major amputation. Limitations of the trial were its relatively small sample size and the limited scope and observation period. A recently published article of 5-year follow-up of the THUNDER trial showed very promising results. The TLR remained significantly lower in the DEB group (21%) than the control group (56%, $p = 0.0005$). Binary restenosis rate was also lower (17 vs. 54%; $p = 0.04$). LLL was also lower 6 months after angioplasty (0.4 ± 1.2 vs. 1.7 ± 1.8 mm; $p < 0.001$). It was also noted that no signs of aneurysm formation or fibrosis were detected.¹⁵

Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment, the DEBELLUM Trial

Fanelli et al conducted the Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment (DEBELLUM) trial, which evaluated 122 lesions in the femoropopliteal vessels (75.4%) or below knee arteries (24.6%).¹⁶ Patients were randomly assigned to the DEB group (25 patients with 57 lesions) or uncoated balloon group (25 patients with 65 lesions). Subgroup analysis of the DEB versus angioplasty balloon showed lower LLL in the superficial femoral artery (SFA) group (0.41 ± 0.5 vs. 1.55 ± 1.3 mm) and 0.62 ± 0.9 versus 1.65 ± 1.5 mm in the below the knee arteries. TLR was

higher in the angioplasty only group (23.6%) versus 6.1% with DEB. The study confirmed the ability of paclitaxel-eluting balloons to reduce restenosis at 6 months. The trial also showed similar results to the previously discussed trials in terms of better clinical outcome and adverse events.

Drug-Eluting Balloon in Peripheral Intervention for the Superficial Femoral Artery, the DEBATE Trial

Liistro et al conducted this prospective, single-center, randomized, parallel-group, open-label trial between 2010 and 2011 in Italy.¹⁷ It involved 104 patients with 110 SFA lesions out of 177 patients referred to the catheterization laboratory. The aim of the study was to evaluate the restenosis rate in Paclitaxel DEB with predilation PTA followed by systematic placement of self-expanding nitinol bare metal stents (BMS). Inclusion criteria were age > 18 years, angiographic findings of stenosis > 50% with 40-mm length in the SFA or popliteal artery, clear area of stenosis between SFA and common femoral artery and between popliteal and tibioperoneal arteries, and at least one patent tibial vessel. Exclusion criteria were < 1 year life expectancy, any contraindication to the use of dual antiplatelet therapy, presence of allergies to either nickel or paclitaxel, need for amputation, and failure to perform canalization. The randomization occurred in 1:1 fashion, in which one group had DEB with BMS and the other had PTA with BMS. All patients were followed up before, immediately after, and 12 months after the intervention. The evaluation done by either angiography or Doppler ultra sound (DUS) if there was a severe renal impairment. The primary end point was identified as evaluation of binary restenosis rate (at least > 50% of diameter or peak systolic velocity > 2.5 by DUS). The secondary end point focused on TLR incidence rate and > 50% stenosis of target lesion diameter. Other variables used in the trial were comparison between long lesions (> 100 mm) and short ones. It also evaluated LLL and true lumen versus subintimal recanalization. The binary restenosis rate was 17% in the DEB with BMS group versus 47.3% in the PTA with BMS group ($p = 0.008$). The secondary end point was evaluated by the Kaplan-Meier curves (log-rank [Mantel-Cox] test), which is defined as estimation of the survival function from lifetime data, showing 12-month free TLR in the DEB group. Long lesions had lower restenosis rate (21% in DEB and BMS vs. 62% in PTA with BMS; $p = 0.01$). Other variables such as LLL and recanalization approach showed similar lower rates in the DEB with BMS group. Three patients died in the study (two patients in the DEB with BMS group due to cardiac failure and sepsis, respectively, and one patient in the PTA with BMS group). Stent fractures evaluated by angiography were noted in a total of three patients (two in the DEB with BMS group). There were no major amputation events observed during the 12-month follow-up. Another interesting finding was the improvement in Rutherford classification in the DEB group (81.8%). The study concluded that DEB with BMS was superior to PTA with BMS. It reduced the restenosis rate and subsequent TLR irrespective of the technique. It also had the same promising results on long lesions and LLL rate. The study had some limitations, which included, but were not limited to, small sample size and being a single-

center study. There was a potential bias because restenosis rate was measured by DUS in a small number of lesions (27%) due to renal impairment. Longer term follow-up (> 24 months) could have provided more information regarding safety profile and adverse events. Another interesting finding is the high complexity of systematic stenting placement procedures reflects the high-risk patient population in that particular practice.

Lutonix Paclitaxel-Coated Balloon for Prevention of Femoropopliteal Restenosis

This prospective, single-blind, randomized trial evaluated and compared LLL in femoropopliteal lesions treated with Lutonix DEB versus uncoated balloons.¹⁸ Lutonix is a DEB coated with 2 µg/mm² of paclitaxel and a polysorbate/sorbitol carrier. Inclusion criteria for the study were patients with single de novo restenotic lesions (89%) in which > 70% stenosis, lesions > 4 cm and < 15 cm (mean 80.5 mm), age > 18 years, and Rutherford clinical categories 2 to 5. Exclusion criteria were life expectancy < 2 years, creatinine > 2.5 mg/dL, hemorrhagic stroke < 3 months, previous lesion requiring surgery or intervention less than 30 days, use of pharmacological therapy, severe vessel calcification, sudden symptoms or events such as thrombosis, and severe inflow disease. The study was conducted in nine centers in Germany from June 2009 to December 2009 and the included subjects were divided into a Lutonix DEB group (*n* = 49) and an uncoated balloons group (*n* = 52). The primary end point was angiographic LLL at 6 months. Secondary outcomes included adjudicated major adverse events (death, amputation, target lesion thrombosis, reintervention), functional outcomes, and pharmacokinetics. The analysis was conducted by a blinded core laboratory and was not powered by clinical outcomes. At 6 months, the LLL was 58% lower in the Lutonix DEB group (0.46 ± 1.13 mm) compared with the control group (1.09 ± 1.07 mm; *p* = 0.016). TLR was 36% for DEB versus 49% in uncoated balloons at 24-month follow-up. DEB subjects showed 57% primary patency at the same time frame versus 40% with uncoated balloons. The adverse events were 39% for the DEB group and included the need for revascularization, amputation, thrombosis, and death as compared with 46% for the uncoated balloons group (*p* = 0.45). The antirestenotic benefit of DEB was observed whether DEB was used alone or in combination with stents.

Study limitations included single-blind design, limited balloon sizes, short follow-up period, and small sample size. A further significant limitation was that eight DEBs maldeployed, affecting the intention-to-treat analysis and possibly explaining the difference between TLRs in the DEB group.

Future Studies and Trials

At present, several trials are being conducted to evaluate the efficacy of DEB technology in prevention of restenosis. The efficacy study of stenting, paclitaxel-eluting balloon, or atherectomy to treat peripheral artery disease (ISAR-STATH) is being conducted in Germany to evaluate restenosis rate as a

primary end point using angiography and adverse effects including mortality as a secondary endpoint.¹⁹ The Lutonix Moxy (Murray Hill, NJ) drug-coated balloon versus standard balloon angioplasty for the treatment of femoropopliteal arteries (LEVANT 2) is an ongoing single-blind study to evaluate Moxy DEB in comparison to PTA in the treatment of femoropopliteal arteries stenosis. The primary outcome of the study is to measure freedom from all-cause perioperative death and index limb amputation, reintervention, and limb-related death. Another main focus will be estimating the primary patency at 12 months.²⁰ IN.PACT admiral DEB versus standard balloon angioplasty for the treatment of SFA and proximal popliteal artery (PPA) (IN.PACT SFA II) is ongoing single-blind study to evaluate the efficacy and safety of IN.PACT DEB compared with standard balloon therapy in the treatment of PAD in SFA and PPA. The primary end point is to evaluate the efficacy, including primary patency at 12 months, and to focus on the safety profile of the device itself such as procedure-related death, amputation, and target vessel revascularization. The secondary end points are evaluation of TLR, Rutherford classification, walking distance, and binary restenosis.²¹

Conclusion

Percutaneous interventional approaches are effective in the treatment of PAD, but the rates of restenosis may be quite high, despite advanced technology. DEB is a new interventional technique to help minimize restenosis rate and prevent future complications. Available data report that the LLL was very almost similar between the Pilot, THUNDER, DEBELLUM, and LEVANT trials (0.5, 0.4, 0.41, and 0.46 mm, respectively) at 6 months but the TLR in these trials showed significant differences (7, 10, 23.6, and 36%, respectively). The restenosis rates were very similar in the Pilot and THUNDER trials (19 and 17%, respectively) after 6 months. One can conclude that most of these trials had similar results in terms of the LLL and restenosis rate with some variations noted in the TLR which highlights the need for further evaluation in that aspect. It is important to conduct additional larger prospective studies with clinically driven end points and longer terms follow-up. At this time, drug-coated balloons appear safe and significantly more effective than uncoated balloons for the treatment of femoropopliteal arterial disease and an effective clinical strategy for these patients.

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