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NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

# Is There a Safety Concern for Drug-Coated Balloons in Peripheral Arterial Disease?

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**Abstract**

**Purpose of Review** Drug-coated balloons (DEB) and drug-eluting stents (DES) emerged as a tool to aid in lowering the rates of neointimal hyperplasia and target lesion restenosis following endovascular peripheral arterial disease (PAD) interventions.

**Recent Findings** Although the initial trials comparing these devices with non-drug balloons and stents showed favorable results, more recent data raised concerns regarding the mid to long-term safety of these devices.

**Summary** In this review, we will discuss the evolution of endovascular therapy for PAD, with highlights regarding the recent debates on the long-term safety of the drug-coated devices for treatment of PAD.

**Keywords** Peripheral arterial disease · Endovascular therapy · Paclitaxel · Mortality

## Introduction

Peripheral artery disease (PAD) is an atherosclerotic process predominantly affecting the lower limbs and is associated with significant morbidity and mortality. Ten percent of the worldwide population and approximately eight million US population are affected by PAD [1, 2]. Prevalence of PAD increases dramatically with age and is higher in black ethnicity; however, men and women are equally affected [2, 3]. Diabetes mellitus and cigarette smoking are the most substantial risk factors for PAD, followed by other conventional risk factors. Revascularization is considered in patients with lifestyle-limiting claudication despite guideline-directed medical and exercise therapy and as a mainstay therapy in critical limb ischemia. For patients with claudication, endovascular therapies are considered the first line, reserving surgery for patients with arterial anatomy not favorable to percutaneous approach provided the patient has an acceptable perioperative risk. Femoropopliteal arteries are the most common site of involvement of PAD. However, treatment of femoropopliteal lesions is challenging due to its complex anatomy (multilevel stenosis and complex calcified lesions) and high rate of neointimal hyperplasia leading to high risk for restenosis. This led to the development of newer devices and techniques aimed to lower the risk of restenosis in these patients such as drug-eluting stents and drug-coated balloons.

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## Evolution of Endovascular Therapy for PAD

Endovascular revascularization for PAD has rapidly expanded over the past few decades and is currently performed more often than surgical revascularization. It is associated with lower in-hospital mortality, morbidity, length of stay, and cost compared with surgical intervention; however, restenosis and suboptimal long-term patency have been the limiting

factors. Evolution of device technology and techniques over the past 20 years expanded its use in complex vascular cases with optimal long-term patency [4]. Endovascular techniques include percutaneous transluminal angioplasty (PTA), bare metal stents, drug-eluting devices (drug-eluting stents (DES) and drug-coated balloon (DCB)), and atherectomy [5, 6].

Standard PTA was the first generation of an endovascular intervention invented to treat PDA. It is performed by introducing a balloon-tipped catheter into the target vessel and inflating a balloon at the lesion site and compressing the atheromatous plague towards the vessel wall. It immediately restores the blood flow and can be used in longer lesions and patients with diffuse disease. However, early vessel recoil, residual stenosis, arterial dissection, reduced long-term patency, with a restenosis rate of 50% at 1 year, and the need for repeated target vessel revascularization became a major drawback for PTA.

Self-expanding BMS then evolved to improve vessel patency. This technique involves introducing the nitinol stent over a guidewire and then retracting the sheath to deploy the stent at the target lesion, which then expands and compresses the atherosclerotic lesion towards the vessel wall. In addition to immediately opening the vascular obstruction, the stent acts as a scaffold to keep the lumen open and prevent early vessel recoil and restenosis. Although BMS showed high acute procedural success rate and mid-term patency compared with PTA, randomized controlled trials and meta-analysis failed to show a significant reduction in long-term clinical benefit with first generation BMS compared with PTA [7–13]. Randomized trials on newer generation nitinol stents, however, showed conflicting results on long-term patency [14–17].

Restenosis is the major problem with both PTA and BMS. Immediate vessel recoil after stretch injury and adverse arterial remodeling were the leading causes of restenosis in plain balloon angioplasty, which can be eliminated by placing a stent, yet neointimal hyperplasia is still a major issue with BMS. Acute vascular barotrauma and endothelial injury following angioplasty and constant chronic irritation by BMS trigger the release of pro-inflammatory mediators initiating neointimal hyperplasia. It occurs more frequently in femoropopliteal arteries, long segment lesions, and when multiple stents placed. Drug-eluting devices were then developed to reduce the limiting neointimal hyperplasia [18].

## Drug-Coated Devices for Femoropopliteal Disease

### Drug-Coated Balloon

DCBs are similar to PTA with the addition of a drug-coat on the device surface. It has three main components: the balloon, the anti-proliferative drug coating, and the excipient, which helps to hold the drug to the vessel wall. The drug released by the balloon inhibits the neointimial hyperplasia and thereby improve its long-term patency and reduced the need for repeat revascularization. Following several RCTs evaluating various agents to inhibit neointimal proliferation, paclitaxel emerged as a potent agent for infra-inguinal PAD due to its high lipophilic properties and resistance to oxidation in addition to its cytotoxic property [19, 20] (Table 1).

Several RCTs investigated the effectiveness and safety of DCBs over PTA. The THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) trial compared a paclitaxel-coated balloon (PCB) with PTA and reported a significant reduction in the binary restenosis at 6 months, late lumen loss at 1 year, and target lesion revascularization (TLR) at 5 years. These results were supported by subsequent studies, i.e., the PACIFIER (Paclitaxel-coated Balloons in Femoral Indication to Defeat Restenosis) [21], DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb Multilevel Treatment) [22], LEVANT II (Moxy Drug Coated Balloon vs. Standard Balloon Angioplasty for the Treatment of Femoropopliteal Arteries) [23], BIOLUX P-1 (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries) [24], AcoArt1 (Acotec Drug-Coated Balloon Catheter: Randomized, Multicenter, Controlled Clinical Study in Femoropopliteal Arteries) [25], IN.PACT SFA (IN.PACT Admiral® Drug Coated Balloon vs Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) [26], and ILLUMENATE (Pivotal Trial of a Novel Paclitaxel-Coated Percutaneous Angioplasty Balloon) trials [27].

However, comparison of patient-centric metrics showed inconsistent results. LEVANT II trial (Lutonix DCB vs. PTA) showed significant improvement in the quality of life (QOL) and maximum walking distance score at 12 months whereas ILLUMENATE trial (Stellarex DCB vs. PTA) and IN.PACT trial (Medtronic Admiral DCB vs. PTA) did not show any significant difference in QOL, maximum walking distance, or 6-min walk test. On the other side, the DEBATE SFA trial (DCB + BMS vs. PTA + BMS) showed a significant reduction in binary restenosis and TLR in the DCB arm at 12 months.

The IN.PACT SFA trial, the largest DCB trial to date, compared the long-term durability of the Medtronic Admiral DCB with PTA and showed significantly higher primary patency and lower TLR at 3 years. Primary safety composite endpoint of freedom from 30-day device- and procedure-related deaths and target limb major amputation and clinically driven-TLR within 24 months was lower in the DCB compared with PTA. Although all-cause mortality was higher in DCB compared with PTA (8.1% vs. 0.9%; $p = 0.008$), there were no device- or procedure-related deaths.

**Table 1** Paclitaxel-coated drug-coated devices available in the USA

| Device name | Manufacturer | Paclitaxel dose (μg/mm$^2$) | Excipient |
|---|---|---|---|
| IN.PACT Admiral | Medtronic, Minneapolis, MN, USA | *3.5* | Urea excipient |
| Lutonix | C.R. Bard, Murray Hill, NJ, USA | 2.0 | Polysorbate/sorbitol excipient |
| Stellarex | Spectranetics, Colorado Springs, CO, USA | 2.0 | Novel excipient and polyethylene glycol |

### Drug-Eluting Stents

Drug-eluting stents consist of a nitinol bare metal stent coated with an anti-proliferative drug that is slowly released locally and prevent neointimal proliferation [28]. The first DES was the Zilver-PTX, which releases paclitaxel from a polymer-free scaffold within 72 h of placement. Once delivered to the vessel wall, paclitaxel remains the arterial wall for up to 56 days. It inhibits cell growth and reduced in-stent restenosis. Approximately 1 month after the stent insertion, endothelialization over the stent occurs and thus reduces the risk of clot formation. Zilver-PTX trial showed improved event-free survival, patency, and clinical benefit of DES over PTA sustained through 5 years (> 40% relative risk reduction of restenosis and TLR at 5 years).

The Eluvia stent, which has a polymer-coated paclitaxel scaffold, allows a sustained drug release beyond 1 year. It uses the lowest paclitaxel dose density among all drug-eluting devices (0.167 vs. 3 μg/mm$^2$ in Zilver PTX). Endothelialization for Eluvial stent takes longer and occurs 90 days post-implant.

The recent Imperial trial which compared polymer-coated paclitaxel-eluting Eluvia stent with polymer-free paclitaxel-coated Zilver PTX stent showed non-inferiority of Eluvia for primary patency at 1 year (86.8% with Eluvia and 81.5% with Zilver PTX) and superiority in a prespecified, post hoc analysis leading to recent FDA approval.

## Drug-Coated Balloons Versus Drug-Eluting Stents

DES are relatively contraindicated for treatment of highly mobile distal femoropopliteal segments or anatomically difficult sites (e.g., across the knee joint); however, DCBs are able to be used for these lesions. DCBs release the drug without a stent and thus less continued damage of the endothelium will possibly reduce the restenosis and thrombosis rate. However, due to no scaffold left at the lesion site, DCBs have a concern of vessel recoil and residual vessel dissection. Also, the majority of the drug released by the DCBs does not reach the target lesion due to loss during transit, balloon inflation, as well as some amount, remains in the deflated balloon; thus, delivering only < 30% of the drug to the treated site.

A recent trial published by Bausback et al., comparing primary DES implantation or DCB angioplasty with bail-out stenting, showed a similar rate of primary patency at 12 months (79% DES vs. 80% DCB $p = 0.96$), but slightly better results in 36 months (54% DES vs 38% DCB, $p = 0.17$) [29].

## Safety Concern of Drug-Coated Balloons

Katsanos et al. published a recent meta-analysis in December 2018, which raised safety concerns regarding paclitaxel-coated femoropopliteal devices [30••]. The reported results of an increased risk of long-term mortality created a major debate. Twelve different paclitaxel-coated devices for femoropopliteal arteries were investigated. Twenty-eight trials were included, four trials with paclitaxel DES and 24 trials with different paclitaxel DCB devices comparing either PTA or BMS or PTA + BMS. The study showed no significant difference between the paclitaxel-eluting arm and the control arm in 1-year all-cause mortality. However, 2-year and 5-year all-cause mortality were significantly increased in the paclitaxel arm, relative risks of 1.68 and 1.93, respectively. Although the finding of this study was alarming, several limitations were obvious. For example, less than half the included trials had data for 2 years, and only 3 RCTs had data up to 5-year follow-up. Also, the cause of death was not reported. Intention to treat analysis was not used and did not consider attrition during survival analysis. Those limitations augmented the limitations of individual studies that were not powered to assess mortality.

In response to the safety concerns of drug-coated femoropopliteal devices, the BASIL-3 (BAlloon versus Stenting in severe Ischaemia of the Leg-3) and SWEDEPAD (Swedish Drug-elution Trial in Peripheral Arterial Disease) trials of paclitaxel-coated devices temporarily halted their patient enrollment. In addition, SWEDEPAD trial interim results showed possible adverse signal although these findings have not been published [31, 32].

On January 17, 2019, the United States Food and Drug Administration issued a letter to all providers informing about safety concern of paclitaxel-coated devices and recommended continued survivance and encouraged reporting of adverse events until further evaluation. The Food and Drug Administration stated that the benefits continue to outweigh the risks when used as indicated by guidelines [33]. On March 15, 2019, the Food and Drug Administration issued another letter updating on the preliminary analysis of long-term follow-up data showing a signal towards increase

**Table 2** Clinical trials presenting long-term survival outcomes for paclitaxel-coated drug-coated devices

| Trial | Author and year of publication | Number of participants | Inclusion criteria | Study arms | Device used | Primary endpoints | Secondary endpoints | Maximum follow-up period |
|---|---|---|---|---|---|---|---|---|
| THUNDER [52] | Tepe et al. 2015 | 66 (5-year Follow-up) | Chronic occlusions and stenosis (history at least 6 weeks) ≥ 70% diameter<br>Stenosis >2 cm in the arteria femoralis superficialis or arteria poplitea | Paclitaxel-coated balloon (PCB), with angioplasty with paclitaxel in contrast medium, vs. no paclitaxel (control) | Balloon catheters provided by Bavaria Medizintechnologie. The balloons either were uncoated or were coated with paclitaxel at a dose of 3 μg per square millimeter of balloon surface | Late lumen loss of vessel segment following dilatation after 6 months | 1. Thrombotic complications or revascularization of the target vessel, death; adverse reactions known to occur after paclitaxel (high-dose tumor therapy except reactions to the detergent)<br>2. Paclitaxel plasma concentration will be determined immediately after administration | 5 years |
| ZILVER PTX [43] | Dake et al. 2016 | 479 (enrollment) | (1). Rutherford category ≥ 2, (2) ≥ 50% diameter stenosis, (3) reference vessel diameter 4 to 9 mm, (4) lesion length up to 14 cm, and (5) at least 1 patent runoff vessel with < 50% stenosis throughout its course. | Drug-eluting stents (DES) vs. angioplasty | Zilver® PTX™ drug-eluting vascular stent | Event-free survival rate, event-free survival is defined as freedom from the major adverse events of death, target lesion revascularization, target limb ischemia requiring surgical intervention (bypass or amputation of toe, foot or leg), surgical repair of the target vessel (e.g., dissection requiring surgery), and from worsening of the Rutherford classification by 2 classes or to class 5 or 6. | Primary patency, primary patency is defined as a peak systolic velocity (PSV) ratio < 2.0 or angiographic percent diameter stenosis < 50%. | 5 years |
| Schneider et al. [46] | Schneider et al. 2019 | 1980 (pooled), 855 (matched) | (1) Documented diagnosis of PAD in | | IN.PACT Admiral | A composite of freedom from | MAE (major adverse events) which is | 5 years |

**Table 2** (continued)

| Trial | Author and year of publication | Number of participants | Inclusion criteria | Study arms | Device used | Primary endpoints | Secondary endpoints | Maximum follow-up period |
|---|---|---|---|---|---|---|---|---|
| | | | the SFA and/or PPA, (2) Rutherford Clinical Classification (RCC) 2–4, (3) De novo or non-stented restenotic lesions, (4) lesion length between 4 and 18 cm for lesions with a diameter stenosis of ≥ 70% and < 100%, (5) adequate distal run-off to the foot, (6) lesion length of ≤ 10 cm for completely occluded lesions, (7) any iliac lesions had to be treated before the target lesion with approved devices | Drug-eluting stents (DES) vs. angioplasty | | device- and procedure-related mortality through 30 days, freedom from major target limb amputation and TLR within 12-month post-index procedure. | defined as all-cause mortality, clinically driven TVR (target vessel revascularization), major target limb amputation, thrombosis at the target lesion site. | |
| INPACT SFA [53] | Lard et al. 2019 | 243 (5-year follow up) | Target vessel is the superficial femoral artery and/or proximal popliteal artery (above the knee) | Drug-eluting balloons (DEB) vs. angioplasty | IN.PACT Admiral | The composite safety end point was defined as freedom from device- and procedure-related death through 30 days and freedom from target limb major amputation and clinically driven target vessel revascularization (CD-TVR) through 60 months. | Additional end points included the rate of each individual component of the major adverse event composite. | 5 years |

mortality. Three of the five studies (975 subjects) with 5-year follow-up data showed approximately 50% increased risk of mortality in with paclitaxel-coated devices (20.1% versus 13.4% crude risk of death at 5 years) [34]. The Food and Drug Administration recommended alternative treatment options for most patients until additional analysis of the safety signal has been performed [34].

New Paclitaxel Safety data were presented at the Leipzig Interventional Course (LINC) in January 2019 and updated data presented at the Vascular Leaders Forum in March 2019 that mostly contradicted with the recent concerns and highlighted disparities based on patient follow-up, which lead to more need for further patient-level rather than summary-level evidence [35–38]. The Society for Vascular Surgery established a Task Force on Paclitaxel Safety to evaluate all available data related to paclitaxel use in patients with PAD [39]. Following this, two major trials, IMPACT global and Zilver PTX, released corrections to their previously published data [40, 41]. In February 2019, Medtronic issued a press release stating that a data programming error was made in the IN.PACT Global post-market study as an unspecified number of patient deaths was inadvertently omitted from the analysis [40]. After correcting the error, 5-year mortality rates in the study remained comparable. All-cause mortality between DCB and PTA was 13.2% versus 11%, $p$ value = 0.19 [42•]. The original paper of the 5-year Zilver PTX trial comparing DES with PTA was published in 2016 and reported 5-year mortality rates of 10.2% with DES and 16.9% with PTA, $p$ value = 0.03 [43]. A correction to this publication was issued in February 2019, stating that the numbers for the two groups were inadvertently reversed and the final results should read as "The 5-year all-cause mortality rate was 13.6% (16.9% for the primary DES group and 10.2% for the PTA group, P=0.03), and no deaths were adjudicated as procedure or device related." [41]. The 5-year post-market study on Zilver PTX, $n$ = 904, showed positive long-term safety and effectiveness in challenging real-world patients with complex lesions. A separate analysis comparing the Japanese Post-Market Studies on Zilver PTX and BMS showed no significant difference in mortality, same mortality rate of 5.1% per year for PTX and BMS, $p$ value = 0.92 [44].

Another study, a large nationwide analysis on 16,560 Medicare and Medicaid Services beneficiaries, comparing drug-coated devices with non-drug-coated devices, showed no significant difference in all-cause mortality at 600 days after multivariable adjustment [45].

In May 2019, Schneider et al. reported results of an independent, individual patient-level meta-analysis of 4 studies evaluating the correlation between paclitaxel exposure and mortality comparing 1837 DCB cases, IN.PACT Admiral paclitaxel DCB, with 143 uncoated PTA controls. There was no statistically significant difference in all-cause mortality between DCB and PTA through 5 years (9.3% vs. 11.2%; $p$ = 0.399) was seen. All deaths were adjudicated, and none was related to the device. No significant differences were observed between groups based on the dose of paclitaxel exposure with survival rates of 85.8%, 84.2%, and 88.2% in low, middle, and high exposure groups ($p$ value = 0.731) [46] (Table 2).

Many underlying reasons may potentially suggest a correlation of high mortality with paclitaxel-eluting devices for peripheral vascular disease, yet, it seems unlikely as paclitaxel has been used for numerous other indications with extensively documented survival data without much evidence to support a causal relationship. When paclitaxel-eluting devices were first used for cardiovascular interventions, the early generation DES for coronary revascularization had a very high paclitaxel dose and were associated with a higher rate of stent thrombosis and myocardial infarction [47]. However, newer generations, with lower doses of paclitaxel, outperformed bare metal stents and older generations of DES with no increase in myocardial infarction, or long-term mortality yet a small increase in the risk of late stent stenosis was documented [48, 49]. Given the evidence suggesting that lower dose paclitaxel DES were safe for coronary revascularization and given the wide range of extensive oncological evidence without clear causal relationship, it seems unlikely that paclitaxel-coated devices directly increase long-term mortality [50, 51]. Whether late stent stenosis or systemic absorption plays any role in the suspected long mortality is still debatable and further research is warranted to better understand the long-term mortality.

## Conclusions

Data regarding safety of drug-eluting devices for treatment of PAD appears to be rather unclear. The exact reasons for the possible increased mortality with paclitaxel-eluting devices are not fully understood. The corrections that occurred to the major trials evaluating these devices raise concerns regarding the validity and integrity of their results. Thus, larger post-marketing studies evaluating the safety of paclitaxel-eluting PAD devices are mandatory to exclude or confirm their safety.

### Compliance with Ethical Standards

**Conflict of Interest** Mohamed M. Gad, Antonette K. Karrthik, Ahmad A Mahmoud, and Ahmed N. Mahmoud declare no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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