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Review

Drug-coated balloon in peripheral artery disease

Madhan Shanmugasundaram [a,b,*], Sangeetha Murugapandian [a], Huu Tam Truong [a,b], Kapildeo Lotun [a], Subhash Banerjee [c,d]

[a] University of Arizona College of Medicine, Tucson, AZ, United States
[b] Southern Arizona Veterans Affairs Health Care System, Tucson, AZ, United States
[c] University of Texas Southwestern Medical Center, Dallas, Texas, United States
[d] Veterans Affairs North Texas Health Care System, Dallas, Texas, United States

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ABSTRACT

Peripheral artery disease (PAD) is highly prevalent but is often underdiagnosed and undertreated. Lower extremity PAD can often be life style limiting. Revascularization in carefully selected lower extremity PAD patients improves symptoms and functional status. Surgical revascularization used to be the only available strategy, but in the recent years, endovascular strategies have gained popularity due to faster recovery times with low morbidity and mortality rates. Endovascular procedures have increased significantly in the United States in the past few years. That being said, higher restenosis rates and low long-term patency rates have been the limiting factors for this strategy. Drug eluting stents have been introduced to help with lowering restenosis, however lower extremity PAD involves long segment where the outcomes of stents are suboptimal. Also, the disease often crosses joint line that makes it less ideal for the stents. Drug-coated balloons (DCB) have been introduced to improve patency rates following endovascular intervention for lower extremity PAD. They have gained popularity among endovascular specialists due to its ease of use and the concept of "leave nothing behind". This is a review of scientific evidence supporting DCB use in PAD.

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1. Introduction

Peripheral artery disease (PAD) refers to atherosclerotic disease involving any arterial bed except coronary artery. But most commonly the term PAD is used to signify the involvement of lower extremity arteries. It has been estimated that PAD affects approximately 8.5 million Americans aged over 40 years, of which one forth fall into the severe PAD category [1]. Based on Medicare and insurance claims data between 2003 and 2008, the prevalence of PAD was 12% [2]. It is associated with significant morbidity and mortality. In 2014, the age adjusted mortality in patients with PAD was estimated to be 16 per 100,000. The clinical presentation is varied and only 10% of patients present with classic intermittent claudication. About 40% of patients are asymptomatic and 50% present with atypical leg symptoms, hence accurate diagnosis and

* Corresponding author at: 3601 South 6th Avenue, Tucson, Arizona 85723, United States.
E-mail address: msundaram@shc.arizona.edu (M. Shanmugasundaram).

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treatment remains a challenge [3,4]. Regardless of their presentation or symptoms, ankle brachial index (ABI) is a strong predictor of overall mortality and cardiovascular events [5]. Hence, there has been a great interest in both pharmacologic and non-pharmacologic treatment options aimed at improving outcomes in these high-risk patients. Revascularization in carefully selected PAD patients improves symptoms. The 2016 ACC AHA guidelines for management of lower extremity PAD gives a class I recommendation for endovascular therapy in patients with aorto-iliac disease and class IIa recommendation in patients with femoro-popliteal disease [6]. European guidelines on the other hand, recommend an endovascular first strategy in symptomatic femoro-popliteal and below knee PAD [7]. According to a recent study, between the year 1996 and 2005, endovascular interventions have increased by 5% per year and open procedures have decreased by 6.6% per year in the United States (US) [8]. Endovascular intervention is an accepted therapy for patients with symptomatic PAD. Ever since its inception, this field has rapidly expanded and currently is first line therapy or acceptable alternative to surgery. Lower morbidity, mortality rates and faster recovery times associated with endovascular procedures, has made this option very attractive to physicians and patients [9]. One of the major drawbacks of endovascular therapy has been restenosis and sub-optimal long-term patency rates. Percutaneous transluminal angioplasty (PTA) provides good short-term results but is associated with 40–50% restenosis rates at 12 months [10–12]. Then came the bare metal stents to tackle the problem of recoil associated with PTA, but was still associated with 40% restenosis at 12 months due to neointimal hyperplasia causing in-stent restenosis (ISR) [11,13]. This has resulted in a constant search of a technology with better long term patency. Drug eluting stents (DES) and drug-coated balloon (DCB) were introduced to achieve lower restenosis rates. These technologies are a standard practice in the treatment of coronary artery disease, however in PAD even though they are gaining ground, the evidence base is still growing. The objective of this review is to systematically analyze the evidence behind DCB use in PAD interventions.

2. Methods

Our aim was to perform an updated clinical review of all studies that examined the use of DCB in PAD. A bibliographic search was completed on MEDLINE database using the search terms “angioplasty”, “peripheral artery disease”, “drug-coated balloon” and “drug eluting balloon”. The search returned 275 articles that were analyzed to select trials that fit our criteria. A total of 25 articles that included observational studies, registry data and randomized clinical trials that examined the use of DCB in PAD were then included in this review. Outcomes of interest include late lumen loss (LLL), binary restenosis, clinically driven target vessel revascularization (TVR), primary patency rates and freedom from major adverse limb events. We also searched the citations of the articles to find other relevant studies.

3. DCB technology

There are many theoretical advantages to DCB over drug coated stent use in PAD including more homogenous transfer of coated drug due to broader area of contact, lack of polymer that is left behind reducing the nidus for delayed inflammation and impaired healing, preserved vessel anatomy and function and ability to treat lesions that are considered to be in the “no-stent” zones. DCB catheter is similar to the conventional angioplasty device but has the drug coated on its surface. DCB has 3 components: the balloon itself, the drug that is coated on the surface and excipient that holds the drug and allows effective transfer of the drug into the arterial wall. The ideal drug would be one that is lipophilic (to enhance tissue uptake), large therapeutic margin (to reduce adverse effects) prolonged tissue retention time (for prolonged efficacy). There have been two classes of drugs that meet the above criteria that include Paclitaxel and Rapamycin (-limus) family. Rapamycin inhibits the mammalian target of rapamycin (mTOR) thereby preventing cells progressing from G1 to S phase that is the underlying cellular mechanism of smooth cell proliferation. Paclitaxel is a cytotoxic drug that arrests the cells in the M phase of mitotic cell cycle. Its lipophilic properties allow high concentration of the drug to be achieved in the vessel wall thereby preventing smooth muscle and fibroblast proliferation that result in restenosis. Due to its lipophilic properties and resistance to oxidation, Paclitaxel became a natural choice for DCB technology. On the other hand, Rapamycin was susceptible to oxidation and hence was unstable on DCB catheters.

There were several technical challenges in the design of DCB including effective transfer of drug from the catheter to the vessel wall, preventing loss of drug before the catheter is advanced to the treatment region and achieving long term anti-proliferative effect on the vessel wall. The excipient on the DCB due to its hydrophilic properties causes effective transfer of the drug on to the vessel wall. Preclinical studies have confirmed that paclitaxel achieved high tissue concentration after brief inflation of the DCB and that 3μg/mm^2 is the effective dose of paclitaxel [14]. There are a number of DCB that are currently in clinical use in Europe (shown in Table 1) but only two of them have FDA approval for use in US.

4. DCB in femoropopliteal disease

Even though the short-term success rates of PTA were good, the long-term patency and TLR rates appear to be poor. This paved the way for development and application of novel technologies such as DCB. The THUNDER (Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries) was the first study that randomized 154 patients with symptomatic FP disease to either PTX coated angioplasty or uncoated balloons with paclitaxel dissolved in the contrast medium or uncoated PTA. There was a significant reduction in late lumen loss and target lesion revascularization at 6 months in the PTX arm compared to uncoated PTA, and no significant benefit was seen in the group treated with paclitaxel in the contrast medium. This was assessed by follow up angiography [15]. A pilot study by Werk et al, demonstrated that in patients with FP disease, PTX coated angioplasty was associated with significant reduction in late lumen loss, target lesion revascularization and improvement in Rutherford class compared to uncoated PTA [16]. PACIFIER trial randomized over 80 patients with symptomatic FP disease to either PTX coated (Medtronic IN.PACT DCB) PTA versus uncoated PTA. At 6 months follow up there was a significant reduction in late lumen loss in the PTX arm with decrease in

Table 1
Drug-coated balloons.

Device	Manufacturer	Paclitaxel dose (μg/mm^2)	FDA approved
Advance 18 PTX	Cook Medical, Bloomington, IN, USA	3	No
Cotavance	MEDRAD, Warrendale, PA, USA	3	No
Stellarax	Spectranetics, Colorado Springs, CO, USA	2	No
Elutax SV	Aachen Resonance, Aachen, Germany	2	No
Biopath	Eurocor, Bonn, Germany	3	No
IN.PACT Pacific	Medtronic, Minneapolis, MN, USA	3	No
IN.PACT Admiral	Medtronic, Minneapolis, MN, USA	3	Yes
IN.PACT Amphirion	Medtronic, Minneapolis, MN, USA	3	No
Legflow	Cardionovum, Bonn, Germany	3	No
Luminor 14/35	iVascular, Barcelona, Spain	3	No
Lutonix 14	C.R. Bard, Murray Hill, NJ, USA	2	No
Lutonix 35	C.R. Bard, Murray Hill, NJ, USA	2	Yes
Passeo-18 Lux	Biotronik, Berlin, Germany	3	No
Ranger	Boston Scientific, Marlborough, MA, USA	2	No

target lesion revascularization that was assessed by a follow up angiogram [17]. The DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb MUltilevel TreatMent) trial randomized 50 patients with FP or below knee disease to PTX coated angioplasty or uncoated PTA. Majority of the lesions (~75%) were FP disease. At 6 months follow up there was a significant reduction of late lumen loss, TLR and binary restenosis rates in PTX coated arm. This was assessed by a follow up angiogram [18]. The LEVANT 1 (Lutonix paclitaxel-coated balloon for the prevention of femoropopliteal restenosis) randomized over 100 patients with symptomatic FP disease to either DCB or conventional PTA. There was a significant reduction in 6-month angiographic late lumen loss in the DCB arm [19]. Long term primary patency and TLR were however no different between DCB and conventional PTA arms, but this was thought to be related to device failure rates in the DCB arm. Following this, LEVANT 2 trial randomized 476 patients with symptomatic FP disease to either DCB or PTA. Primary efficacy end point was 12-month primary patency that was defined as freedom from binary restenosis or clinically driven target lesion revascularization. The primary safety end point was a composite of freedom from perioperative death from any cause and freedom at 12 months from limb-related death (i.e., death from a medical complication related to a limb), amputation, and reintervention. This trial demonstrated a significant reduction in primary patency in the DCB arm driven by reduction in binary restenosis. There was no difference in the safety end point hence establishing the safety profile of DCBs [20].

The DEBATE SFA trial examined the role of DCB before bare metal stent (BMS) implantation by randomized 104 patients with complex FP disease to DCB + BMS versus PTA + BMS. At 12 months follow up there was a significant reduction in binary restenosis and a trend toward decreased TLR in the DCB arm. Most patients underwent follow up angiogram to assess for end point, but patients who withdrew consent or with renal insufficiency, underwent Duplex ultrasound [21]. The largest DCB trial is the IN.PACT SFA trial that randomized 331 patients with symptomatic SFA disease to DCB or PTA. At 12 months, DCB resulted in significantly higher primary patency rates and reduction in clinically driven TLR rates assessed by Duplex ultrasound [10]. These results continued to be significant at 24 months follow up. However, it should be noted that even though the primary safety composite endpoint of freedom from 30-day device- and procedure-related death and target limb major amputation and CD-TVR within 24 months was 87.4% in the DCB group versus 69.8% in the PTA group ($p < 0.001$), the rate of all-cause mortality was higher for patients treated with DCB compared with PTA (8.1% vs. 0.9%; $p = 0.008$). There were no device or procedure related deaths in either group. Majority of the deaths were due to non-cardiovascular etiologies [22]. Most of the previously mentioned trials used a short term angiographic or Duplex Ultrasound end point (late lumen loss), but IN.PACT SFA trial showed significant improvement in clinical end points, thus validating the role of DCB in FP disease. Recently published 3-year outcomes of this trial showed significantly higher primary patency rates and lowed clinically driven target vessel revascularization rates in the DCB arm thus confirming the long-term safety and efficacy of DCB in FP disease [23]. The Biolux P1 trial randomized 60 patients with symptomatic FP disease (de novo atherosclerosis or restenotic lesions) to PTX DCB or PTA and demonstrated significant reduction in late lumen loss, binary restenosis and clinically driven TLR in the DCB arm [24]. The ILLUMENATE trial was a single arm, prospective study that examined the use of novel DCB (Stellarex™) containing low dose PTX in patients with symptomatic FP disease. It demonstrated safety and efficacy of this new DCB [25]. Recently published 12-month outcomes from this study showed a primary patency rate of 81% (assessed by Duplex) and freedom from clinically driven target lesion revascularization was 95% with more than 90% of patients reporting improvement in Rutherford class in the DCB group [26]. A Japanese study randomized 100 patients with FP disease to PTX DCB or PTA and demonstrated superior 12-month primary patency rates and significant reduction in clinically driven TLR [27]. A meta-analysis of 8 randomized trials that examined the use of DCB in FP disease, showed a significant reduction in 12 month TLR with DCB compared to conventional PTA [28]. The IN.PACT Global Study is the largest Real world, prospective, multicenter, single arm independently adjudicated study that included over 1500 patients with symptomatic femoropopliteal disease in whom DCB was used. The primary end point was freedom from clinically driven TLR at 12 months and this was reported to be 92.6%, thus establishing safety and efficacy of DCB in real world patients.

Important FP trials are summarized in Table 2. It should be noted that most of these trials either used angiographic or Duplex ultrasound end-points.

5. DCB in infrapopliteal PAD

Below knee or Infrapopliteal PAD if often diffuse with limited treatment options. Most patients present with critical limb ischemia (gangrene, ulceration of extremity or rest pain). The diffuse nature of the disease and small caliber vessels pose unique treatment challenge. Balloon angioplasty is associated with high restenosis rates and stents have limited long term patency due to small vessel size and long segment stenosis. This has resulted in the use of DCB in Infrapopliteal PAD. Initial reports of DCB use in Infrapopliteal PAD were from Schmidt et al. who studied the use of IN.PACT Amphirion PTX coated DCB in over 100 patients with critical limb ischemia (CLI). They demonstrated significantly lower rates of angiographic restenosis at 3 months compared to historical controls (uncoated PTA) [29,30]. The DEBELLUM (Drug-Eluting Balloon Evaluation for Lower Limb MUltilevel TreatMent) trial randomized 50 patients with 122 lesions of which 25% were Infrapopliteal in location to DCB or PTA. This trial showed a significant reduction in late lumen loss, TLR and improvement in binary restenosis in the DCB arm [18]. The DEBATE BTK (Drug-Eluting Balloon in Peripheral Intervention for Below the Knee Angioplasty Evaluation) was a single center study that randomized over 100 patients with Infrapopliteal disease and critical limb ischemia to either DCB or uncoated PTA. There was a significant improvement in binary restenosis as seen by angiography or Duplex in the DCB arm compared to the PTA arm. Secondary end points such as clinically driven TLR and target vessel occlusion were also significantly lowed in the DCB arm thus proving the superiority of DCB in this challenging vascular bed [31]. Following the encouraging results of these trials, a much larger randomized trial was designed to examine the role of DCB in infrapopliteal disease. This was the INPACT DEEP (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia) trial that randomized over 300 patients with CLI and Infrapopliteal disease to either DCB or standard PTA therapy. Co-primary efficacy outcomes were clinically driven TLR and angiographic late lumen loss (LLL) at 12 months. The primary safety endpoint was a 6-month composite of all-cause mortality, clinically driven TLR or major amputation. In this trial, DCB failed to show a benefit in terms of LLL or TLR at 12 months over standard PTA. In addition, there was a trend toward more major amputation in the DCB arm which raised concerns over the use of DCB in infrapopliteal PAD. The negative results in this study were attributed in part to some differences in baseline characteristics between the groups and the increase in amputation was explained by possible distal embolization of drug, excipient, coating, improper drug dosing, and patient selection bias [32]. Lastly the BIOLUX P-II trial was a small trial that randomized 72 patients with infrapopliteal disease and CLI to DCB (Passeo-18 Lux) or standard PTA. There was no significant difference in the 30-day primary safety end point (major adverse event rate, composite of all-cause mortality, major amputation or TLR) between the treatment and control groups. The primary efficacy end point defined as loss of angiographic patency at 6 months was also not significantly different between the groups [33]. Thus, this is a negative trial but the safety concerns that were seen in the INPACT DEEP study was not reproduced in this study. However, given the safety concerns in a prior large randomized trial resulted in withdrawal of DCB from market for this indication. Hence pending

Table 2
DCB trials in FP disease.

Trial	Sample size	Treatment arm	Control arm	Primary outcome(s)	Secondary outcome(s)
THUNDER [15]	154	PTX coated balloon catheters and PTX dissolved in contrast medium	PTA	6-month LLL 0.4 ± 1.2 vs 1.7 ± 1.8 mm ($p < 0.001$)	• 6-month TLR rates 4% vs 37% ($p < 0.001$)
PACIFIER [17]	85	PTX DCB	PTA	6-month LLL 0.01 vs 0.65 mm ($p = 0.001$)	• 6-month binary restenosis rates 8.6% vs 32.4% ($p = 0.01$) • 6-month major adverse events 7.1% vs 34.9% ($p < 0.01$) • 6-month TLR rates 7.1% vs 27.9% ($p = 0.02$)
DEBELLUM [18]	50	PTX DCB	PTA	6-month LLL 0.5 ± 1.4 vs 1.6 ± 1.7 mm ($p < 0.01$)	• 6-month TLR rates 6.1% vs 23.6 % ($p = 0.02$) • 6-month binary restenosis rates 9.1% vs 28.9 % ($p = 0.03$) • Amputation and thrombosis rates not significant
LEVANT 1 [19]	101	PTX DCB	PTA	6-month LLL 0.45 ± 1.18 mm vs 1.19 ± 1.15 mm ($p = 0.024$)	• 24-month major adverse event rate 39% vs 46%
LEVANT 2 [20]	476	PTX DCB	PTA	24-month primary efficacy end point – primary patency rate 65.2% vs. 52.6% ($p = 0.02$) 24-month primary safety end point – freedom from primary safety events 83.9% vs 79% ($p = 0.005$ for noninferiority)	• 24-month major amputation rates, death, TLR rates and thrombosis rates not significant
DEBATE SFA [21]	104	PTX DCB + BMS	PTA + BMS	12-month binary restenosis rates 17% vs 47.3% (pp = 0.008)	• 12-month freedom from TLR and major amputation rates not significant
IN.PACT SFA [10]	331	PTX DCB	PTA	24-month primary patency rates 7 8.9% vs. 50.1% ($p < 0.001$)	• 24-month TLR rates 9.1% vs 28.3% ($p < 0.001$) • Mortality rate higher in DCB group 8.1% vs 0.9% ($p = 0.008$) • Thrombosis and amputation rates not significant
BIOLUX P-1 [23]	60	PTX DCB	PTA	6-month LLL 0.51 ±0.72 vs. 1.04 ± 1.00 mm ($p = 0.033$)	• 6-month binary restenosis 11.5% vs. 34.6% ($p = 0.048$) • 6-month TLR rates 15.4% vs. 41.7% ($p = 0.064$)

newer evidence DCB cannot be routinely used in infrapopliteal PAD. A more recent Lutonix® 014 DCB global below knee registry study demonstrated over 90% freedom from major adverse limb event rate and perioperative death rate and 88% freedom from clinically driven TLR at 6-months [34]. Recently published meta-analysis of 5 randomized trials that examined the use of DCB in infrapopliteal PAD concluded that there was no significant difference in TLR, amputation rates or mortality between DCB or conventional PTA but there was a significant reduction in late lumen loss with DCB therapy [35]. Table 3 summarizes all key studies.

6. DCB for instent restenosis

In stent restenosis continues to be a major problem that plagues endovascular therapy for PAD. DCB have been tested to improve outcomes in these patients. The DEBATE ISR study (Drug-Eluting Balloon in Peripheral Intervention for In-Stent Restenosis) is a prospective, all comer registry trial that included diabetic patients with symptomatic FP ISR undergoing DCB therapy and compared them to historical controls. This study demonstrated a significant reduction in recurrent restenosis (assessed by angiography or Duplex ultrasound) and symptomatic

Table 3
DCB trials in infrapopliteal disease.

Trial	Sample size	Treatment arm	Control arm	Primary outcome(s)	Secondary outcome(s)
In.PACT Amphirion [27]	104	PTX DCB	Historical controls	3-Month binary restenosis rate was 27.4%	NA
DEBATE BTK [29]	132	PTX DCB	PTA	12-Month binary restenosis rate 27% vs 74% ($p < 0.001$)	• 12-month TLR rates 18% vs 20% ($p = 0.002$) • 12-month target vessel occlusion rates 17% vs 55% ($p < 0.001$) • No difference in amputation rates
IN.PACT DEEP [30]	358	PTX DCB	PTA	12-Month co-primary end point of LLL 0.61 ± 0.78 mm versus 0.62 ± 0.78 mm ($p = 0.950$) and TLR 9.2% versus 13.1% ($p = 0.291$) 6-month primary safety endpoint composite of all-cause mortality, major amputation, and CD-TLR was 17.7% versus 15.8% ($p = 0.021$) driven by major amputations	NA
BIOLUX PII [31]	72	PTX DCB	PTA	Primary safety endpoint: 30-day composite of all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularization – 0% vs 8.3% ($p = 0.239$) Primary performance endpoint (patency loss at 6 months) was 17.1% vs 26.1% ($p = 0.298$)	Binary restenosis rates, late lumen loss, TLR – no difference

TLR [36]. The only randomized trial that examined the use of DCB in ISR was the FAIR (Femoral Artery Instent Restenosis) study which randomized over 100 patients with CLI and SFA ISR to either DCB or PTA. At 6-month Duplex ultrasound follow up there was a significant reduction of recurrent ISR and freedom from TLR in the DCB arm. At 12 months, there was a significant improvement in Rutherford category ≥1 and freedom from TLR in the DCB group with no increase in major amputation. It should however note that 30% of patients were lost to follow up in both arms of this study [37].

7. DCB technique

It is critical to avoid geographic miss when using DCB, hence it is recommended that appropriate length of DCB need to be chosen such that there is healthy vessel on either ends of the treatment zone. This also ensures good long-term patency rates. The drug starts to elute as soon as it comes in contact with liquid medium, hence it is recommended that the DCB is kept in his protective packaging until it is time to advance into the body. Also given the profile of the DCB and the need for uniform drug delivery, predilation of the stenosis is very critical at this time. As soon as the DCB is advanced into the introducer sheath, it needs to be quickly advanced across the lesion. Prolonged inflation (3-minutes) at nominal pressure is recommended for best results.

Cost effectiveness of DCB has been reported in few trials [38–40]. The upfront cost of DCB is certainly higher compared to conventional PTA or bare metal stent use and hence the revenue to the hospitals are lower with DCB. However, in the long term, if the costs of repeat revascularization procedures with bare metal stents or PTA are taken into account, DCB offers the greatest economic value. A recently published international statement on drug-coated balloon treatment for lower extremity PAD summarizes all key trials that studied the use of DCB in these patients. The authors recommend the use of DCB in TASC IIA and B de novo and restenotic femoropopliteal PAD, however they note the lack of long term outcomes data with DCB use. In the infrapopliteal disease segment, the authors concluded that no specific recommendations could be made at this time due to lack of efficacy data and that rigorous studies were needed to answer this question [41].

8. Future directions

There are several new DCBs that are currently being studied for use in PAD. For FP disease, trials such as Advance 18PTX balloon catheter study, BASIL 3 study [42], CVI drug-coated balloon clinical trial, Illumenate study and PREVEIL are ongoing. For infrapopliteal disease, ongoing trials include ACOART-BTK and LUTONIX BTK study among several others. European BTK registry is currently evaluating patients with infrapopliteal disease undergoing treatment with Lutonix DCB. Another ongoing trial (OPTIMIZE BTK) is examining the role of combining orbital atherectomy with DCB use in infrapopliteal PAD. Non PTX compounds such as "limus" drugs are also being tested in DCB arena. These have larger therapeutic window and may have an advantage over PTX in safety outcomes. The SELUTION DCB is the first human study of Sirolimus coated DCB in FP disease. Apart from these novel DCBs, there is some interest in combining DCB with adjunctive devices such as atherectomy or stenting, in the hopes of improving long term patency rates. Early registry data showed high primary patency rates and low TLR rates with atherectomy combined with DCB [43]. Directional atherectomy combined with DCB was shown to have significantly lower TLR rates at 12 months in a single center study [44]. The REALITY study is currently investigating the combination of directional atherectomy with DCB in treatment for long, calcific FP stenosis.

9. Conclusions

The DCBs have certainly established their role in FP disease with excellent short-term patency rates and low TLR rates compared to PTA alone. They have also shown to be safe. The data in infrapopliteal disease is more controversial at this time. Nevertheless, given the reduction in TLR and its ease of use, DCBs present an attractive alternative to conventional PTA. More randomized trials are needed to optimize the dose of drug needed for better long-term outcomes, evaluation of limus based DCB and establishing their safety in infrapopliteal disease.

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