British Journal of Medicine & Medical Research
9(4): 1-9, 2015, Article no.BJMMR.18492
ISSN: 2231-0614

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Anti-restenotic Therapies for Peripheral Arterial Disease

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Authors' contributions

This work was carried out in collaboration between both authors. Author VV wrote the first draft of the manuscript and author JCG edited the article and detailed the discussion. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/BJMMR/2015/18492
Editor(s):
(1) Vijayalakshmi i. Balekundri, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru.
Reviewers:
(1) Anonymous, Nagoya City East Medical Center, Japan.
(2) John Abraham, University of St. Thomas, USA.
(3) Anonymous, Dicle University, Turkey.
Complete Peer review History: http://sciencedomain.org/review-history/9925

Mini-review Article

Received 24th April 2015
Accepted 2nd June 2015
Published 27th June 2015

ABSTRACT

Defining the ideal treatment for peripheral arterial disease remains an ongoing endeavor. The initial treatment standard of balloon angioplasty and stenting has produced suboptimal long-term outcomes due to in-stent restenosis and the subsequent need for revascularization. Yet, the field of endovascular medicine has seen an explosion of new technologies, which have yielded promising early and mid-term results. Anti-restenotic drug therapies have the potential to reduce neointimal hyperplasia, in-stent restenosis, and improve vessel patency in femoro-popliteal arteries. We discuss herein current and future drug eluting technologies across various delivery methods and platforms.

Keywords: Peripheral arterial disease; stent; restenosis; anti-restenotic therapy; drug-coated balloon; drug-eluting stent.

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1. INTRODUCTION

Balloon angioplasty (BA) and stenting of the femoro-popliteal (FP) artery induces a localized inflammatory response, which precipitates neointimal proliferation and tissue growth [1,2]. This cellular proliferation can potentially result in significant in-stent restenosis (ISR), thereby causing recurrence or deterioration of clinical symptoms, often necessitating the need for target lesion revascularization (TLR). Several anatomic and clinical risk factors increase the overall occurrence of restenosis, including longer lesion lengths, smaller vessel diameters, and diabetes mellitus [3]. ISR has been reported to occur in up to 40% of FP lesions treated with bare-metal stents within 1 year of treatment [4,5].

Various attempts have been made to attenuate the course of ISR in revascularization of PAD. These primarily include local delivery of anti-restenotic drugs, among which, paclitaxel has been on the forefront. Paclitaxel functions by blocking microtubule formation and inhibiting smooth muscle cell division and migration. It also inhibits inflammatory responses by suppressing the excretion of growth factors, such as platelet-derived growth factor, which mediates vascular smooth muscle cell migration to the intima [6]. Several devices have been investigated utilizing paclitaxel delivery to the vessel wall following balloon angioplasty in an effort to reduce neointimal cell proliferation based on various studies that have demonstrated the penetration and deposition of drug into arterial walls [7,8,9].

2. DRUG-COATED BALLOON

There are several drug-coated balloon (DCB) trials, both completed and ongoing, which have demonstrated the safety and efficacy of DCB technology (Table 1). The THUNDER trial [10] studied 154 patients with occluded or stenotic FP arteries, and randomized patients to 3 treatment arms consisting of BA (control group), DCB, or BA with paclitaxel dissolved in contrast medium. The mean lesion length was 7.4 +/- 6.5 cm, with 27% of lesions being total occlusions. The DCB used was the Paccocath balloon (Bayer Interventional, Minneapolis, MN), which has approximately 3 mcg of paclitaxel per mm^2. At 6-month follow up, the treatment of patients with DCB was found to be associated with significant reductions in late lumen loss compared to patients of the control group (0.4 mm +/- 1.2 mm vs 1.7 mm +/- 1.8 mm, $p<0.001$) or patients treated with paclitaxel dissolved in the contrast medium (2.2 mm +/- 1.6 mm, p=0.11). Moreover, angiographic restenosis was significantly reduced in the DCB arm (17% vs 44%, $p=0.01$) with sustained benefit for DCB seen at 24-month follow-up. The TLR rate at 6 months was only 4% in the DCB arm compared to 37% in the control group and 29% in the group treated with paclitaxel mixed with contrast medium. While there was significant benefit with the use of the Paccocath DCB, there was no benefit noted with the use of paclitaxel-containing contrast medium.

The FemPac trial [11] randomized 87 patients to BA or Paccocath DCB with mean lesion lengths between 5.7 to 6.1 cm.

Six-month angiographic follow-up showed less luminal loss in patients who had been treated with the Paccocath DCB in comparison to control subjects (0.5 +/- 1.1 mm vs 1.0 +/- 1.1mm, p=0.031) correlating to lower angiographic restenosis rate in the DCB arm (19% vs 47%) [8]. Additionally the DCB group had less TLR rate, and greater improvement in Rutherford class. This difference was durable at 18 months after intervention.

The PACIFIER trial [12] investigated 91 patients with FP lesion lengths ranging from 3 to 30 cm, with a mean of 6.6 to 7 cm, who were randomized to the IN.PACT paclitaxel DCB

Table 1. Drug-coated balloon trials

Drug coated balloon (DCB) trials	No. patients	Lesion length (cm)	Drug coating formulation	6 month restenosis (DCB vs balloon angioplasty)
THUNDER	154	7.4 +/-6.5	Paclitaxel/Iopromide	17% vs 44%
FEMPAC	87	5.7-6.1	Paclitaxel/Iopromide	19% vs 47%
PACIFIER	91	6.6-7	Paclitaxel/Urea	8.6 %vs 32.4%
LEVANT 1	101	8.1 +/- 3.8	Paclitaxel/ Polysorbate/Sorbital	Late lumen loss 0.46+/-1.13 vs 1.09 +/- 1.07
LEVANT 2	476	6.3 +/- 4.1	Paclitaxel/Polysorbate/Sorbital	7.7% vs 17.3%

(Medtronic Inc, Minneapolis, MN) or standard BA with provisional stenting. The primary endpoint of angiographic late lumen loss at 6 months was significantly better for the DCB cohort (-0.01 mm vs 0.65 mm; P=0.0014). Binary restenosis rates were 8.6% and 32.4% (*p=0.01*), for the DCB and BA respectively.

A meta-analysis of the 6-month results of the THUNDER, FemPac, LEVANT I, and PACIFIER trials demonstrated an absolute risk reduction for restenosis with DCB of 26.7%, and for TLR of 25.5% [13].

The LEVANT 1 trial [14] enrolled 101 patients with FP lesions to the Lutonix paclitaxel-coated DCB (Bard, New Hope, MN) (Fig. 1) versus BA. The DCB used in this study was coated with paclitaxel (2 mcg/mm^2), and utilized a polysorbate/sorbitol carrier. The mean length of treated lesions was 8.1 cm +/- 3.8 cm, with 42% of lesions being total occlusions. At 6 months, late lumen loss was 58% lower in the DCB group in comparison to control (0.46 +/- 1.13 mm vs 1.09 +/- 1.07 mm, *p=0.016*).

The LEVANT 2 clinical trial [15] was a randomized, prospective, multicenter study, which evaluated 476 patients with FP disease by either Lutonix 035 DCB or BA. The study demonstrated primary patency rates to be higher in the DCB group at 12 month follow up (65.2% vs 52.6%; p=0.015). The LEVANT clinical program, which included registry data, enrolled over 1000 subjects and led to FDA approval in October 2014 for the treatment of FP denovo or restenotic disease.

The IN.PACT SFA trial [16] was a prospective, randomized, multicenter trial which enrolled 331 patients randomized in a 2:1 distribution to the IN.PACT Admiral DCB (Medtronic Inc) (Fig. 2) versus BA in FP disease. The mean lesion lengths for the DCB and BA arms were 8.94+/-4.89cm and 8.81+/-5.12 cm, respectively. Twelve-month follow up demonstrated higher primary patency rates in the DCB arm (82.2% vs 52.4%; P<0.001). There was also a lower rate of clinically driven TLR (2.4% versus 20.6%; P<0.001.) in favor of DCB. This data in combination with the IN.PACT SFA Global study, a single arm trial with 1500 subjects, led to FDA approval of the DCB for treatment of FP disease in January 2015.

Several other DCB clinical trials, such as the ILLUMENATE study [17] using the Stellarex paclitaxel-coated balloon (Spectranetics, Colorado Springs, CO) (Fig. 3), are currently underway and actively enrolling patients.

3. ATHERECTOMY WITH DRUG-COATED BALLOON ANGIOPLASTY

The use of atherectomy in combination with DCB is another innovative treatment strategy to reduce FP restenosis. The DEFINITIVE AR study [18] was a prospective, randomized, pilot study, which enrolled 102 patients into either directional atherectomy, using Silverhawk or Turbohawk devices (Medtronic Inc) plus DCB, or DCB alone. It included FP lesions 7 to 15 cm in length. Thirty-day results, which were recently presented, demonstrated better technical

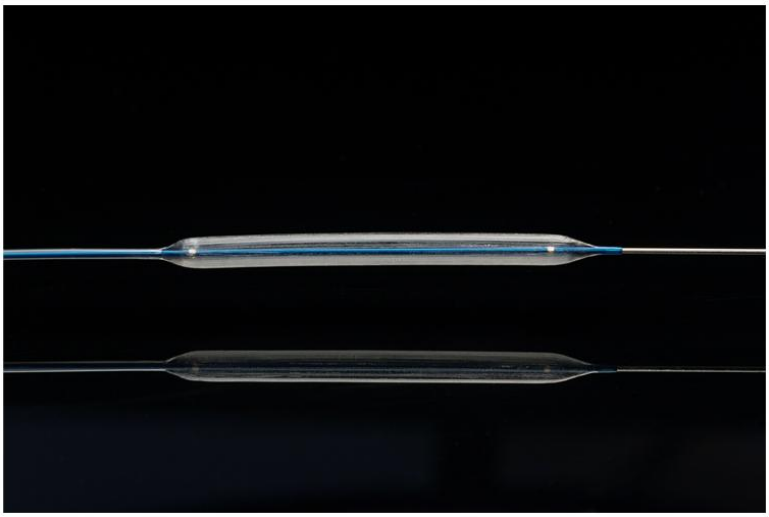

Fig. 1. Lutonix paclitaxel-coated balloon catheter (Bard)

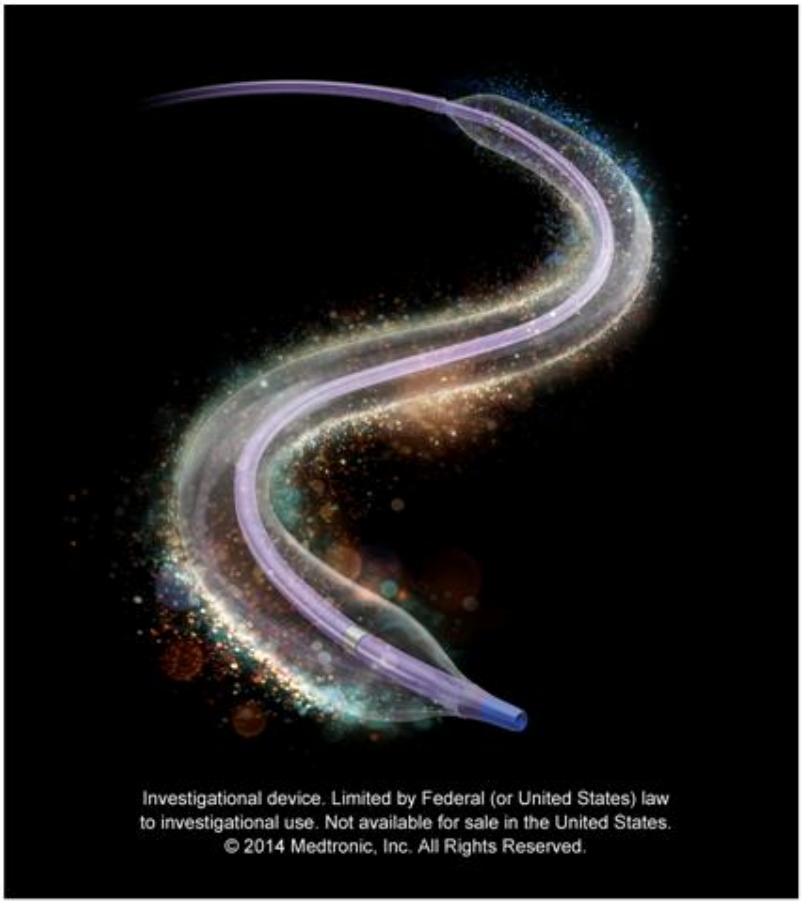

Fig. 2. In pact paclitaxel-coated balloon catheter (Medtronic)

Fig. 3. Stellarex paclitaxel-coated balloon catheter (Spectranetics)

success, defined as ≤ 30% residual stenosis, in the atherectomy with DCB arm compared to the DCB alone arm (90% vs 64%; p=0.004). Adjunctive therapy in the atherectomy with DCB arm consisted of three (6.3%) post-dilations with BA. Adjunctive therapy in the DCB only arm included 18 (33.3%) post-dilations with BA and two (3.7%) stents. Clinical success and improvement in ankle-brachial indices post-procedure were comparable between the two groups. Further long-term follow-up and analysis is underway.

Additional combination studies, such as the PHOTOPAC study [19] using laser atherectomy with paclitaxel-coated balloon are currently underway.

4. PERFUSION BALLOON WITH PACLITAXEL INFUSION

The Clearway balloon (Atrium, Hudson, NH) is a porous polytetrafluoroethylene balloon (Fig. 4), which functions as an infusion catheter, allowing localized delivery of therapeutic medications. It is most often used for delivery of anti-thrombotic agents in the coronary and peripheral vasculature; however, localized delivery of paclitaxel into FP lesions has also been explored. Latif and Hennebry reported their experience in 2 patients, with one lesion being a FP lesion [20]. After atherectomy, a total of 3 mg of paclitaxel was delivered via microporous balloon to the left common and superficial femoral arteries. Three-month follow up

angiography demonstrated no evidence of restenosis.

One of the concerns of using this therapy is possible non-homogenous drug delivery if some of the balloon pores become occluded. Additionally, the possibility of systemic release of paclitaxel may occur if the balloon is not well apposed to the arterial wall.

The IRRITAX trial [21] is a randomized, single center study (which has completed enrollment) investigating FP disease and restenosis using the Clearway balloon and paclitaxel. Trial results are currently pending, but should provide more insight into this innovative treatment strategy.

Recently, the PacTAP study [22] using the Tapas catheter (Thermapeutix, San Diego, CA) (Fig. 5) for localized delivery of paclitaxel has been initiated for enrollment with data pending.

5. DRUG-ELUTING STENT

Drug eluting stents have revolutionized the field of coronary artery disease and percutaneous coronary intervention, effectively lowering the rates of restenosis and lesion revascularization. In 2005, the SIROCCO II trial [23] reported the first results evaluating drug eluting stents in FP lesions. 57 patients were randomized, in a double blind study, to either a sirolimus-eluting stent or bare metal stent. At 6 month follow up, there was no statistically significant difference between the two arms in regards to the primary endpoint which was instent mean lumen diameter (4.94 mm +/- 0.69 for bare metal stent versus 4.76 mm+/- 0.054 Sirolimus stent) as quantified by angiography.

The STRIDES trial [24] evaluated the possible benefit of an everolimus-eluting stent against a bare nitinol stent in 104 patients with FP lesions. At 6-month follow up, the primary vessel patency (freedom from >50% instent restenosis) in the DES arm was impressive at 94 +/- 2.3%; however, at 12-month continued follow up patency decreased to 68 +/- 4.6%. Although the stent was safe to implant, long-term durability was poor.

The Zilver PTX trial [25] was a multicenter, prospective, randomized study evaluating the use of paclitaxel-coated nitinol self-expanding stents in FP lesions (Table 2). Patients were randomly assigned to Zilver PTX (Cook Medical, Bloomington, IN) drug eluting stent (DES) (Fig. 6) implantation (236 patients) or BA (238 patients). The mean lesion length was 6.5 +/- 4 cm. Patients who had acute BA failure underwent secondary randomization to provisional DES (n = 61) or bare metal stent (BMS) implantation (n = 59). In comparison to the BA group, the primary DES group had greater primary patency of 83.1% vs 32.8% ($p<0.001$) at 12-month follow-up. The provisional DES group also exhibited greater primary patency (89.9% vs 73.0%,

Fig. 4. Clear way infusion balloon catheter (Atrium)

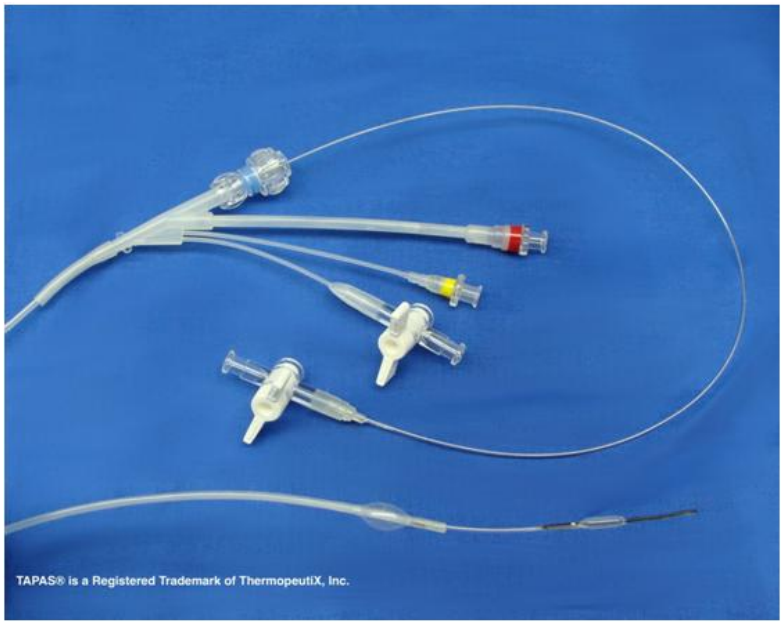

Fig. 5. Tapas isolated infusion catheter (Thermapeutix)

p=0.01) compared to the provisional BMS group. The stent fracture rate was similar for both DES and BMS at 0.9%. Recent 4-year primary patency data from the Zilver PTX trial [26] showed a 75% primary patency rate in DES treated patients, in comparison to the provisional BMS treated patients at 57.9%.

Additionally, a single-arm, prospective, multicenter study [27] was completed, further evaluating Zilver PTX DES for FP disease. 787 patients with symptomatic de novo or restenotic lesions (including ISR) were enrolled. Nine hundred lesions (24.3% restenotic lesions, of which 59.4% were ISR) were treated with 1722 Zilver PTX stents. The mean lesion length was 9.9±8.2 cm. The 12-month primary patency rate was 86.2%, with freedom from TLR at 90.5% [24].

A post-market study of the Zilver PTX stent in long FP lesions [28] was recently presented, which showed a primary patency rate of 86.1% at 12-month follow-up, in lesions with a mean length of 18.9 +/- 9.1 cm.

6. BIO-ABSORBABLE STENT

A bio-absorbable DES has numerous potential advantages including anti-restenotic drug delivery, stent deployment for better immediate procedural success, and stent absorption to prevent stent fracture and delayed ISR. The ESPRIT 1 trial [29] enrolled 35 patients to receive the bio-resorbable vascular scaffold (BVS) system (Abbott Vascular, Santa Clara, CA) (Fig. 7) (Table 3). The BVS dissolves into the blood stream within 18 months to 2 years and is composed of polylactide. The mean lesion length treated was approximately 3.5 cm, with most lesions located in the SFA (88.6%). Nearly 23% of cases treated were complete occlusions, with an average occlusion length of 3.06 cm. The average pre-treatment stenosis was 80%, with a reduction to 13% post treatment. Six-month follow-up data demonstrated 100% patency in all arteries treated (34 patients, 1 patient withdrew from follow up).

7. DISCUSSION

Anti-restenotic drug therapy for FP interventions appears to be the next step in obtaining durable vessel patency and improved clinical outcomes. The mechanism of drug delivery, however, remains a debatable issue. DCB offers the advantage of drug delivery without leaving a stent in place; which has the potential to fracture or develop late ISR. However, DCB alone may fail to address diffusely diseased or heavily calcified FP lesions. Moreover, angioplasty related flow-limiting arterial dissections may require provisional stenting. Debulking plaque with atherectomy prior to DCB should allow for more controlled BA and lower the risk of vessel dissection, as seen in recent studies.

Table 2. Drug-eluting stent trials

Drug eluting stent	No. patients	Mean lesion length (cm)	12 month patency
ZIlver PTX	474	6.5 +/- 4	83.1% vs 32.8% (DES vs BA) p<0.001 89.9% vs 73% (Provisional DES vs BMS) p=0.01

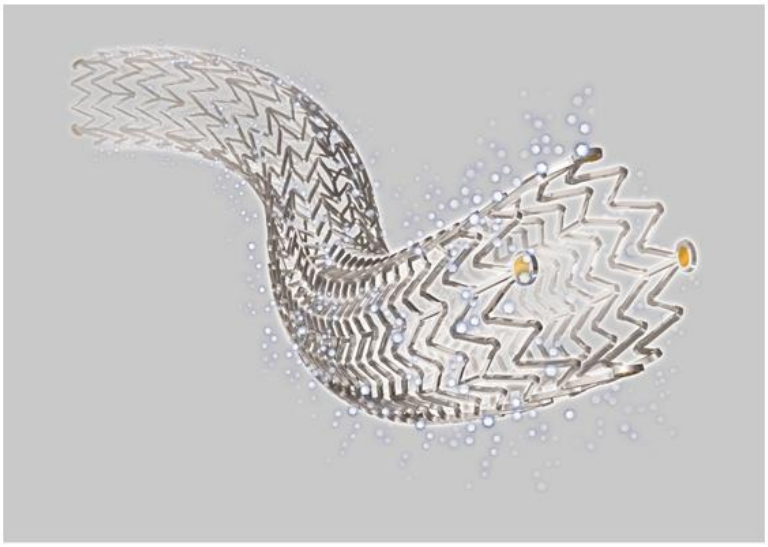

Fig. 6. Zilver PTX drug eluting stent (Cook)

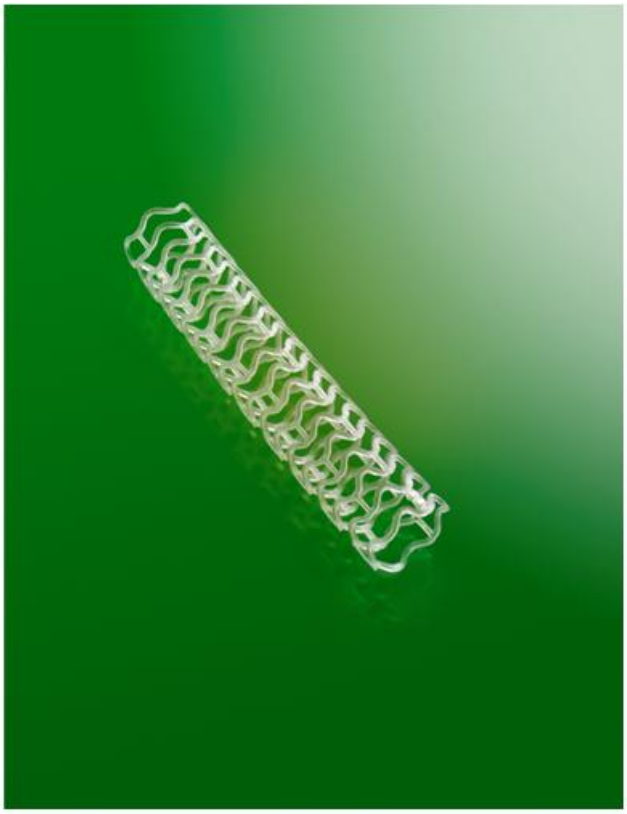

Fig. 7. Bio-resorbable vascular scaffold (BVS) stent (Abbott)

Table 3. Bio-absorbable stent trials

Bioabsorbable vascular scaffold	No. patients	Mean lesion length (cm)	6 month patency
ESPRIT 1	35	3.5	100%

DES offers the advantage of both drug delivery, and a vascular scaffold for improved radial force. This may address diffusely diseased and heavily calcified vessels as well as, post-angioplasty dissection. However, DES can have potential disadvantages as well: prior to complete drug elution, DES can trigger stent thrombosis in the absence of adequate anti-platelet therapy; and once complete drug elution has occurred, the remaining stent can potentially fracture or develop ISR.

Bio-absorbable DES may offer the benefit of both DCB and DES, and has promising early data. Nonetheless, it will require long-term follow-up with drug elution in longer lesion lengths before determining the value of the product in FP disease.

8. CONCLUSION

Based off numerous trials and registries data, our center has implemented the adoption of drug eluting therapies in the form of both DCB and DES. Furthermore, atherectomy is frequently utilized as an initial debulking modality, followed by drug eluting therapy in order to mitigate the incidence of restenosis.

With multiple clinical trials on anti-restenotic therapy demonstrating improved FP vessel patency, and numerous others underway, the future of endovascular FP disease treatment will undoubtedly involve drug-eluting therapies.

CONSENT

Consent from the patient is not applicable for publication of this report as it is a mini-review article without patient information. Furthermore, written consent has been obtained for publication of all the included images.

ETHICAL APPROVAL

No human or animal subjects were involved in the writing of this manuscript.

ACKNOWLEDGEMENTS

Vincent Varghese DO has no conflicts pertaining to this manuscript. Jon C. George MD is a consultant for Abbott, Atrium, Cook, and Covidien.

COMPETING INTERESTS

There were no human and/or animal research studies performed directly for the publication of this manuscript.

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Peer-review history:
The peer review history for this paper can be accessed here:
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