Comparison of drug-coating balloon and bare-metal stent for complex femoropopliteal artery lesions: 2-year outcome of a multicenter experience

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Objectives
The aim of this study was to evaluate the 24-month outcome of drug-coating balloon (DCB) versus bare-metal stent (BMS) for the treatment of disabling claudication and critical limb ischemia in patients with complex femoropopliteal lesions regarding technical success, primary patency, secondary patency, target lesion revascularization, and limb salvage rate.

Background
Complex femoropopliteal lesions are difficult to treat, and the effective protocols for intervention remain to be developed.

Patients and methods
This was a multicenter, prospective, randomized controlled two-arm blind interventional study. A total of 80 patients (92 limbs) complaining of disabling claudication or critical limb ischemia owing to complex femoropopliteal occlusive lesions were randomly assigned into two groups according to the intervention approach used from May 2016 to August 2020. Group A included 42 patients (47 limbs) who have been assigned for treatment with paclitaxel DCBs and group B included 38 patients (45 limbs) assigned for treatment with BMSs. The follow-up period was for 24 months, with regular visits at 3, 6, 9, 12, 15, 18, and 24 months or when new concerns emerged. All data were analyzed by using Statistical Package of Social Science for Windows, version 22.0 and MedCalc Windows.

Results
The 1-year primary patency rates in the DCB and BMS groups were 87.2 and 75.6% (P=0.15), respectively, and the corresponding 2-year rates were 76.6 and 57.8, respectively (P=0.05). However, the 1-year secondary patency rates in the DCB and BMS groups were 95.7 and 91.1% (P=0.43), respectively, and the corresponding 2-year rates were 91.4 and 75.5%, respectively (P=0.05). There is a statistically significant difference regarding the primary and secondary patency rates at 24 months between both the groups (P=0.05). The 2-year major limb amputation rate was 6.3% in DCB group versus 11.1% in BMS group (P=0.48), which was statistically insignificant. The postprocedural ankle–brachial index shows highly significant difference between both the groups at 24 months ($P<0.001$).

Conclusion
The 2-year outcomes showed superior efficacy, higher safety, and greater clinical benefits of DCBs than BMSs for the treatment of complex femoropopliteal lesions. A statistically significant lower rate of restenosis and occlusions and statistically significant higher 2-year primary and secondary patency rates were observed in the DCB group than in the BMS group. However, more studies with a larger sample and long-term follow-up are required.

Keywords:
bare-metal stent, complex femoropopliteal lesions, drug-coating balloon, target lesion revascularization

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Introduction

Femoropopliteal territory is among most common sites affected by peripheral arterial disease leading to intermittent claudication and/or critical limb ischemia; this is because of the underlying different biomechanical forces like compression, torsion, flexion, and extension by large muscle groups as well as shearing forces. These factors are contributing toward making endovascular treatment of femoropopliteal lesions particularly challenging [1–3].

Endovascular treatment of superficial femoral artery (SFA) lesions is identified as a safe and effective treatment and recommended by guidelines as a first-line approach, especially in trans-Atlantic intersociety consensus (TASC) A–C lesions and some cases of TASC D. Standard management is plain old balloon angioplasty, whereas stenting is a bailout (flow-limiting dissection, residual stenosis>30% or elastic recoil). However, because of the rise in difficulty, stents are used particularly in the management of some lesions, for example, ulcerated, heavily calcified, and long stenosis/occlusion more than or equal to 150 mm [4–6].

Percutaneous transluminal angioplasty (PTA) for complex lesions is followed by increased incidence of restenosis and recurrence of symptoms in about half of the patients in whom plain old balloon angioplasty is only done. Balloon dilatation can injure arterial wall and may lead to elastic recoil, intimal dissection, and neointimal hyperplasia [7–9].

Stenting prevents elastic recoil and dissection and consequently possibility of early occlusion. However, stenting only is not capable of inhibiting neointimal hyperplasia, which can also be triggered by struts of stent. The biological reaction of arterial wall results in loss of primary patency, loss of late lumen, and occlusion that may necessitate target lesion revascularization (TLR). Usage of self-expandable stents has increased the patency of SFA, but in-stent restenosis (ISR) is a major consequence in up to 40% in first year. However, long stents are liable to fracture owing to physiologic torsion of SFA, which may lead to acute thrombosis or restenosis [10–12].

Recently, antiproliferative drug-coating balloon (DCB) like paclitaxel have been used for reducing ISR in peripheral vessels by inhibiting the neointimal growth and thus reducing restenosis following percutaneous SFA interventions. From a theoretical viewpoint, DCB angioplasty has potential benefit over the standard angioplasty and stent technologies because of the potential homogenous drug transmission to the wall of the vessel, which is not performed with the concentration gradients created by drug-eluting stents (DES). There is an immediate release of drugs without the use of a polymer that can induce persistent irritation and later thrombosis, like seen with some DES [13–15].

The objective of the current study is the comparison of DCB and bare-metal stent (BMS) in the results regarding the efficacy and safety including technical success, primary patency, secondary patency, TLR, and limb salvage rate, for management of complex femoropopliteal lesions.

Patients and methods

The current study is a multi-center, prospective, randomized controlled two-arm blind interventional study conducted after taking approval of local institutional review board from May 2016 to August 2020 at Vascular Surgery Department, Zagazig University Hospitals, Tanta University Hospitals, Egypt, and Intervention Radiology Department, Alnoor Specialist Hospital, Makkah, Saudi Arabia. A written consent form was given to all patients to sign.

Inclusion criteria

The following were the inclusion criteria:

(1) Patients age more than 40 years.
(2) Patients were fully informed about the study and signed the consent.
(3) Patients understand the duration of the study, agree to follow-up visits.
(4) Rutherford categories 3–6.
(5) Patients have a de novo chronic total occlusion (CTO) TASC C and D lesions with length from 16 to 22 cm or restenosis lesion after previous plain balloon angioplasty with more than70% stenosis (in angiography) but without previous stent.
(6) The lesion is at least 1 cm below the origin of the profunda femoris and had to be located in the native femoropopliteal artery, with at least one patent below-the-knee artery with uninterrupted flow to the pedal arch.

Reference vessel diameter more than or equal to 4 mm and less than or equal to 6.5 mm by visual assessment.

Exclusion criteria

The following were the exclusion criteria:

(1) Life expectancy less than 1 year.
(2) Lesions more than 22 cm length or extending below the proximal popliteal segment.
(3) Previous restenosis/reocclusion of surgical bypass or ISR.
(4) Associated aortoiliac lesions and nonatherosclerotic diseases such as aneurysm, vasculitis, or entrapment.
(5) Coagulopathy or clotting disorders and patients unable to tolerate continuous antiplatelet therapy.
(6) Contraindication to contrast media and hypersensitivity to paclitaxel.
(7) Aneurysm at target lesion.

(8) Patients unable to comply with the follow-up schedule.
(9) Patients in whom guide-wire failed to cross the lesion.

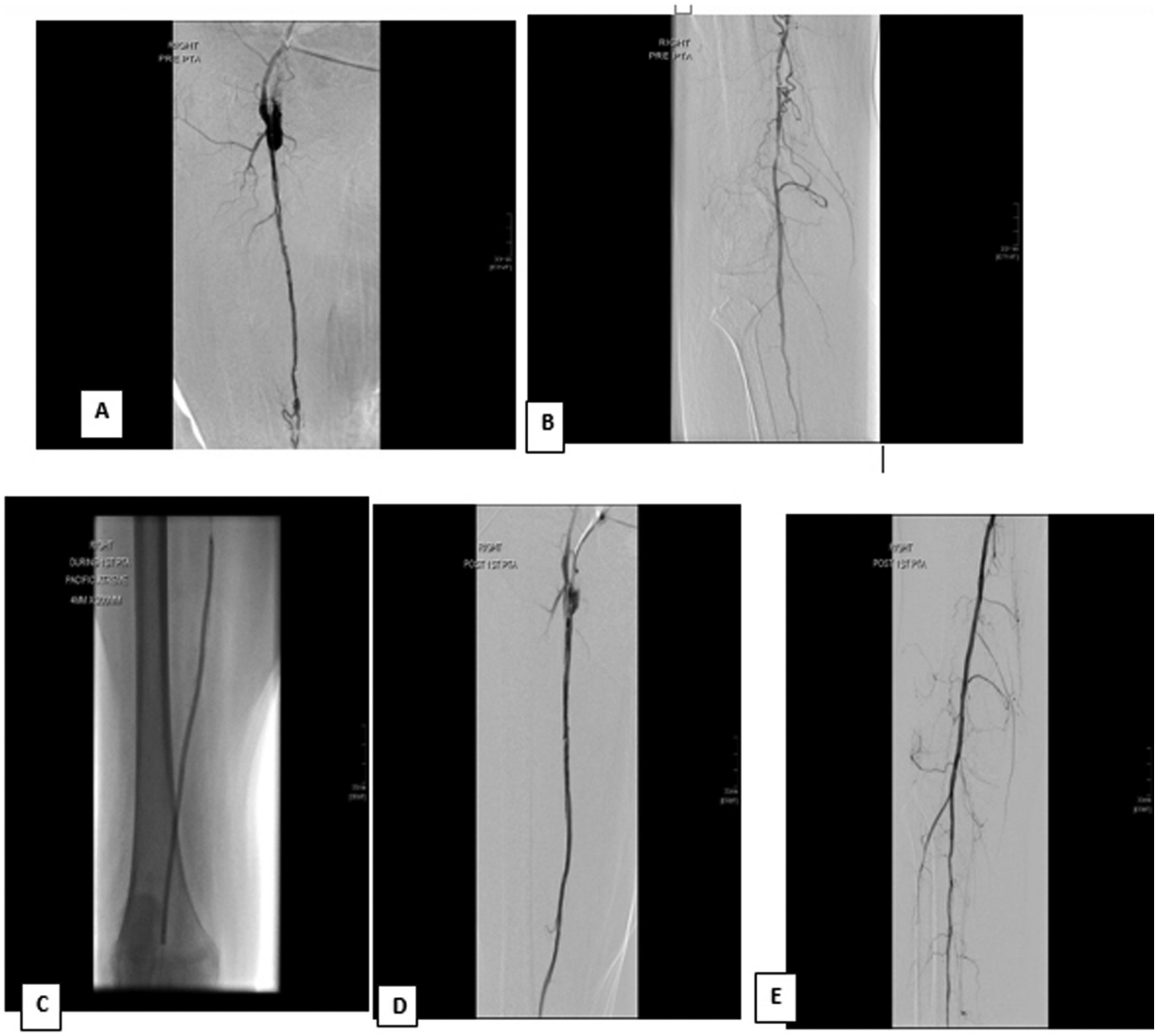
All patients underwent a full history assessment before the operation, clinical examination for blood pressure, and peripheral and carotid pulsations; preprocedural investigations included laboratory examination, ankle–brachial index (ABI) assessment, duplex scanning, and computed tomography angiography. Our study included 80 patients (92 limbs) who were complaining of disabling claudication and/or critical limb ischemia owing to complex femoropopliteal lesions (defined as de novo >15 cm length or restenosis after previous angioplasty, TASC C and D lesions) with age above 40 years. The cases were randomly divided into two groups: group A included 42 cases (47 limbs) who were subjected to the treatment with paclitaxel DCBs and group B included 38 patients (45 limbs) who were subjected to the treatment with primary BMSs. The patients have been premedicated with acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day), and for patients who are not on this regimen, loading dose of 300 mg clopidogrel was given before or directly after intervention. Diameter of the vessel and lesion features (such as length of the lesion and degree of stenosis) have been visually measured.

Following explanation of the procedure, as well as benefits and risks to the patient or his/her guardian, informed consent was obtained. Procedure was planned based on computed tomography angiography. All procedures were done under local anesthesia. If required, fentanyl 25–50 μg intravenous or midazolam 3–10 mg intravenous was used as a conscious sedation. After patient preparation, access is created. Access choice depends on the status of iliac arteries, ipsilateral CFA, and proximal segment of diseased SFA as well as the morphology of the lesion and expected difficulty to cross it. So, the access could be ipsilateral CFA, proximal 1–2 cm of SFA, contralateral CFA, retrograde popliteal or tibial, left brachial artery, or combination of the previous accesses in cases of difficulty of re-entry. Access was created with a micropuncture system 4 or 5 F (MAK Mini Access Kit; Merit Medical Systems Inc., South Jordan, Utah, USA). Then a 6-F sheath was introduced; its length depends on the access site, so its tip will be close to the involved segment to provide adequate support (Brite Tip Sheath Introducer, Cordis, Florida, USA). Tibial access was sheathless. Variable diagnostic catheters and wires to reach and negotiate the lesion were used. Diagnostic catheters included hook, pigtail, vertebral, and Berenstein catheters (Impress from Merit Medical-USA, Glide Cath from Terumo and Tempo Aqua from Cordis). Hydrophilic coated 0.035 guide wires like Radio focus (Terumo, Japan) and Aqua track (Cordis, USA) were used, and also 0.018 wires like V-18 (COSTARIC; Boston Scientific, Global Park, Heredia, Costa Rica) and Nitrix (EV3, Covidien, Ireland) were used. Diagnostic angiography was done using 50% (equal volumes of saline mixed with contrast) nonionic water-soluble contrast media (Omnipaque 300 mg/ml). Systemic anticoagulation with intravenous heparin (80–100 IU/kg) was given. Following crossing the lesion, dilatation of the diseased segment with plain balloon with diameter of 1 mm less than that of the reference vessel diameter was done to prepare the artery for DCB. Various types of plain balloon with different lengths and diameters (4–5 mm) were used (Fortex, Medtronic, USA; Pacific-plus-Medtronic-Mexico, Pacific xtreme, Medtronic, USA). Balloon angioplasty was done for 1–3 min to allow good vessel preparation, and when residual stenosis of more than 30% occurred, the balloon catheter was re-inserted and re-inflated at the place of stenosis. In the first group, DCB was available in diameters of 5 and 6 mm, with 150 mm length or less [Lutonix 035 (BARD, Lutonix Inc., USA) or InPact Admiral (Medtronic, Ireland)]. Diameter of the DCB was chosen to be 1 mm greater than the plain balloon to maintain contact with the arterial wall. If more than DCB was used, overlap will be at least 5 mm. Stenting with BMS was permitted if residual stenosis was more than or equal to 50% (by visual estimation) or the incidence of a flow-limiting dissection (Figs 1 and 2).

In group B, self-expandable, BMSs in diameters of 4.5 and 5 mm, with 200 mm length or less like S.M.A.R.T. (Cordis, USA), Ever Flex (EV3, Medtronic, USA), and Supera (Abbott Vascular, Park Lane, Belgium) were used. The stents have been implanted with overlap of 5–10 mm. The overlap zone occurred if more than one stent was used per lesion. Balloon dilation with a noncompliant balloon of either the same diameter or 1 mm less than the diameter of the implanted stent has been achieved. Procedure performance was identified if less than 30% residual stenosis in completion angiography (Fig. 3).

In both groups, additional procedures such as below-the-knee tibial plain balloon angioplasty were performed when necessary. Finally, access was closed with manual compression or a clip-mediated (star close SE) or a suture-mediated (ProGlide) closure device (Abbott Vascular, Santa Clara, California, USA).

Figure 1



A 62-year-old male with CLI Rt. LL. (a, b) Femoropopliteal CTO, (c) Rt. femoropopliteal preparation using Pacific xtreme balloon 4 mm×200 mm. (d, e) After PTA with overlapping DCB (Lutonix 035, 4 mm×150 mm) was used. CTO, chronic total occlusion; DCB, drug-coating balloon; PTA, percutaneous transluminal angioplasty.

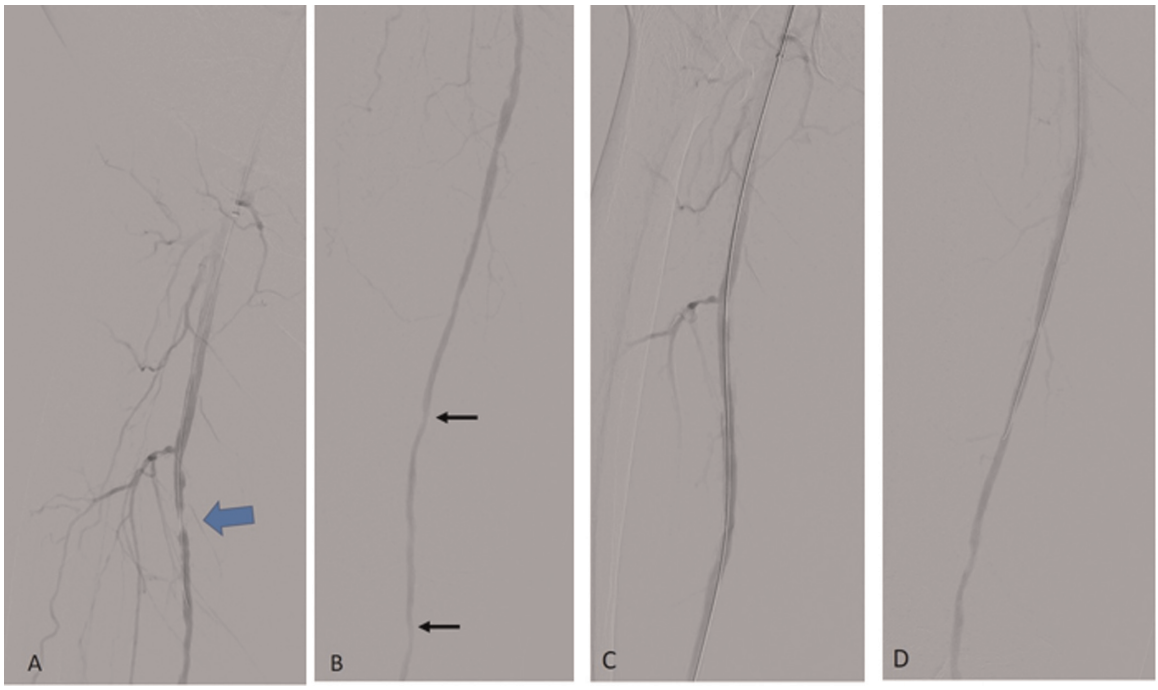
Patients were discharged on aspirin 75–150 mg/day for 1 year, clopidogrel 75 mg/day for 6 months for stented group, and for 3 months for DCB group. Patients were given appropriate foot care consisting of minor debridement, wound dressing, minimal amputations (up to transmetatarsal amputation), and management of infection before discharge.

Before discharge, cases underwent clinical evaluation, ABI estimation, and Doppler. All patients have been followed up for 24 months with regular visits at 3, 6, 9, 12, 15, 18, and 24 months or when new concerns have emerged. Follow-up included clinical evaluation ±imaging study (duplex ultrasound±angiography) if necessary, in cases of absent or reduced pulse or recurrence of symptoms. TLR was done if clinical symptoms or critical stenosis were present. The primary end point was the patency after the procedure defined as freedom from more than 50% restenosis as detected by either ultrasound Doppler (peak systolic velocity ratio <2.4) or digital subtraction angiography. Secondary end points included procedural and clinical success (improvements in ABI, walking disability, and Rutherford category) and clinically driven TLR at 24 months. The safety end points of our study were 30-day procedure-related death and major target limb amputation.

Statistical analysis

Continuous variables expressed as the mean±SD and median (range), and the categorical variables expressed as number (percentage). Continuous variables were checked for normality by using Shapiro–Wilk test. Independent samples Student's *t* test was used to

Figure 2



A 61-year-old male with CLI Rt. L.L due to restenosis 15 months after initial angioplasty with DCB: in addition to diffuse attenuated SFA, there are multiple stenotic segments of variable length and severity (arrows in a and b). Note that restenosis after DCB usually exhibited shorter and more focal lesions, simplifying reintervention. (c, d) Following PTA reintervention. DCB, drug-coating balloon; PTA, percutaneous transluminal angioplasty; SFA, superficial femoral artery.

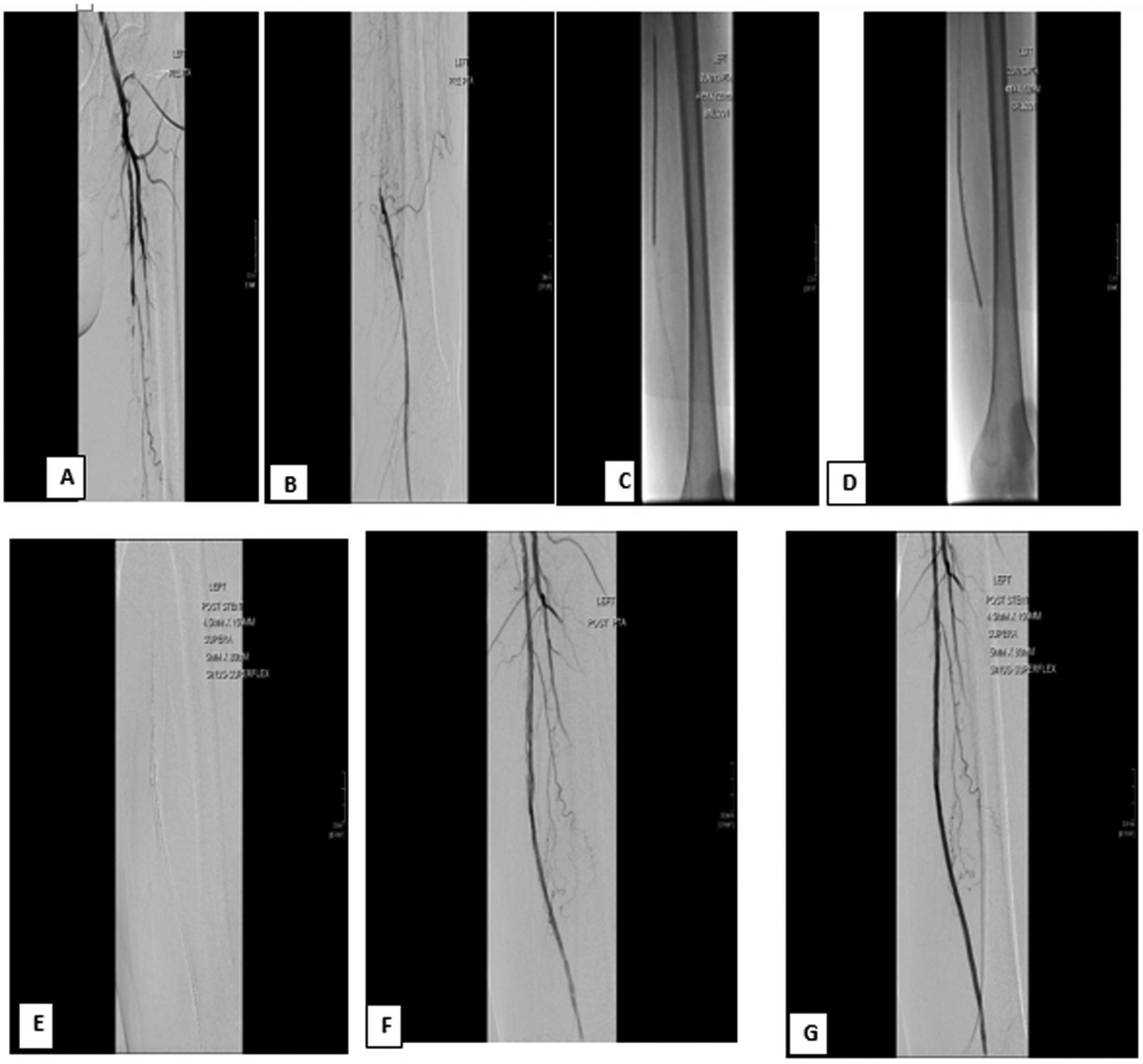
compare between two groups of normally distributed variables. Percentages of categorical variables were compared using Pearson's χ^2 test or Fisher's exact test when was appropriate. Duration of primary patency was defined as duration between intervention until failure, or occlusion or restenosis following first intervention only or censored at time of either last follow-up visit at which balloon/stent was patent or death. Duration of secondary patency was defined as duration between intervention until occlusion or restenosis following both first and second intervention or censored at time of either last follow-up visit at which balloon/stent was patent or death. To estimate patency rates at 3, 6, 9, 12, 15, 18, and 24 months, we used life table method. Time-to-event distributions were estimated using Kaplan–Meier plot method. All tests were two sided. A *P* value less than or equal to 0.05 was considered significant. All data were analyzed by using Statistical Package of Social Science for Windows, version 22.0 (IBM Inc., Chicago, Illinois, USA) and MedCalc Windows (MedCalc Software bvba 18, Ostend, Belgium).

Results

From May 2016 to August 2020, 80 patients (92 limbs) who complained of disabling claudication and/or critical limb ischemia due to complex femoropopliteal atherosclerotic lesions underwent endovascular recanalization either with DCB (*N*=42) or BMS (*N*=38). Demographics are shown in Table 1. The mean age was 60.47±3.82 years in DCB group and 58.76±4.53 in BMS group. Most patients had hypertension and diabetes (88 and 90% in DCB group versus 86.5 and 92% in BMS group, respectively) and almost one-half were hyperlipidemic (52.3% in DCB group vs. 55.2% in BMS group). The mean preinterventional ABI was 0.42±0.04 in DCB group versus 0.43±0.05 in BMS group (*P*=0.32) and the most common Rutherford category was grade 5 (35.5%) in DCB group and 34% in BMS group (*P*=0.64).

Lesion characteristics are shown in Table 2. Of the 92 lesions, 70% in DCB group and 66.7% in BMS group (*P*=0.71) were found within SFA only, and 30% in DCB group and 33.7% in BMS involved both SFA and proximal popliteal artery. More than half of interventions were done in de novo lesions (66% in DCB group and 60% in BMS group, *P*=0.55), and the remaining lesions (34% in DCB group and 40% in BMS group) were treated for restenosis of previous angioplasty. The mean length of the lesion was 18.5 ±3.25 cm in DCB group and 17.8±2.69 cm in BMS group (*P*=0.58). In DCB, 59.6% of lesions were stenotic and 40.4% were CTO, whereas in BMS group, 55.6% of lesions were stenotic and 44.4% were CTO (*P*=0.70).

Figure 3



A 59-year-old female with CLI Lt. LL. (a, b) Superficial femoral artery CTO. (c, d) Lt. SFA preparation using pacific xtreme balloon 4 mm×120 mm. (e) revascularization with overlapping 4.5 mm×100 mm Supera stents was used. (f, g) Good opacification of SFA after stenting. CTO, chronic total occlusion; SFA, superficial femoral artery.

In CTOs, recanalization was subintimal in 87.5% of CTO lesions in DCB group and in 82.4% in BMS group, whereas a retrograde popliteal and trans-tibial approaches was necessary in 12.5% of CTO lesions in DCB and in 17.6% in BMS group as a combination with other access when re-entry could not be achieved. Two DCBs were used in all lesions in diameters of 5 and 6 mm, with 150 mm length or less, whereas two BMSs were used in 21 (46.6%) lesions and one BMS was used in 24 (53.4%) lesions in diameters of 4.5 and 5 mm, with 200 mm length or less (Table 3).

The postprocedural results are shown in Table 4. In six DCB patients (seven limbs=14.8%), bailout stent deployment was required owing to flow-limiting dissection (2/7), residual stenosis greater than 50% due to highly calcific lesion (3/7), and vessel perforation (2/7). In two patients of BMS group, improper stent deployment with crumbled stent occurred, resulting in acute thrombosis, which was treated by great saphenous bypass.

Procedural success (defined as residual stenosis <30%) was achieved in 93.6% (44/47) in the DCB group and 95.5% (43/45) in the BMS group (P=1.00). Acute thrombosis occurred in two DCB patients (4.2%) (3, 9 days postprocedure) and was treated with catheter-directed thrombolysis. However, acute thrombosis occurred in five (10.5%) BMS patients: two patients owing to improper deployment of stent causing stent crumbling and vessel thrombosis and were treated with great saphenous bypass, and in three patients at 2, 3, and 7 days after procedure, and all were treated with catheter-directed thrombolysis using alteplase (16±6.52 mg in DCB group and 18±4.73 in BMS group) (P=0.26). Vessel perforation and

Table 1 Patients' characteristics

Patients' characteristics	DCB (*N*=42)	BMS (*N*=38)	Test	*P* value
Sex				
Male	25 (59.5)	23 (60.5)	0.008[b]	0.93
Female	17 (40.5)	15 (39.5)		
Age (years)				
Mean±SD	60.47±3.82	58.76±4.53	1.720[a]	0.09
Comorbidity				
Diabetes mellitus	38 (90)	35 (92)	0.066[b]	1.00
Hypertension	37 (88)	33 (86.5)	0.028[c]	1.00
Ischemic heart disease	25 (59.5)	17 (44.7)	1.749[b]	0.19
Current smoker	30 (71)	31 (81)	1.135[b]	0.29
Hyperlipidemia	22 (52.3)	21 (55.2)	0.066[c]	0.80
Carotid artery disease	21 (50)	18 (47.3)	0.055[b]	0.81
Obesity	19 (28.5)	21 (55)	0.802[b]	0.37
Cerebrovascular disease	23 (54.5)	25 (65.5)	1.010[b]	0.31
Limb affection				
Unilateral	37 (88)	31 (81.5)	0.664[b]	0.42
Bilateral	5 (12)	7 (18.5)		
Rutherford clinical category				
3	10 (24)	6 (16)	1.682[b]	0.64
4	12 (28.5)	11 (29)		
5	15 (35.5)	13 (34)		
6	5 (12)	8 (21)		
Preoperative ABI				
Mean±SD	0.42±0.04	0.43±0.05	0.992[a]	0.32

Categorical variables expressed as *n* (%). Continuous quantitative variables expressed as mean±SD. ABI, ankle–brachial index; BMS, bare-metal stent; DCB, drug-coating balloon. [a]Independent Student *t* test. [b]χ^2 test. [c]Fisher's exact test. *P* value less than or equal to 0.05 is significant.

Table 2 Lesion characteristics

Lesion characteristics	DCB (*N*=47 limbs)	BMS (*N*=45 limbs)	Test	*P* value
Lesion type				
De novo atherosclerosis	31 (66)	27 (60)	0.350[b]	0.55
RPA	16 (34)	18 (40)		
Lesion site				
SFA	33 (70)	30 (66.7)	0.133[b]	0.71
SFA extending to PPA	14 (30)	15 (33.3)		
Nature of lesion				
CTO lesions	19 (40.4)	20 (44.4)	0.152[b]	0.70
Stenotic lesions	28 (59.6)	25 (55.6)		
Lesion length (cm)				
Mean±SD	18.5±3.25	17.8±2.69	–0.555[a]	0.58
TASC lesion type				
TASC C	39 (82.9)	38 (84.4)	0.350[b]	0.55
TASC D	8 (17.1)	7 (40)		
Patent run off vessel				
1	10 (21)	8 (18)	0.408[b]	0.82
2	22 (47)	24 (53)		
3	15 (32)	13 (29)		

Categorical variables are expressed as *n* (%). Continuous quantitative variables are expressed as mean±SD. BMS, bare-metal stent; CTO, chronic total occlusion; DCB, drug-coating balloon; PPA, proximal popliteal artery; RPA, restenosis of previous angioplasty; SFA, superficial femoral artery; TASC, trans-Atlantic intersociety consensus. [a]Independent Student *t* test. [b]χ^2 test. *P* value less than or equal to 0.05 is significant.

extravasation due to highly calcified lesions occurred in four patients, two of whom were in DCB group and were treated with balloon inflation followed by stenting, and the other two belonged to the BMS group.

Clinical success was defined as procedural success without complications (death, major amputation, thrombosis or target vessel revascularization) before discharge, which was achieved in 87.2% (41/47) in the DCB group and 84.4% (38/45) in the BMS group (*P*=0.83).

Table 3 Procedural characteristics

Procedural characteristics	DCB (*N*=47 limbs)	BMS (*N*=45 limbs)	Test	*P* value
Access				
Antegrade femoral	13 (27.6)	12 (26.7)	1.583[b]	0.81
Crossover	25 (53.2)	21 (46.6)		
Trans-brachial	9 (19.2)	12 (26.7)		
Retrograde popliteal	4 (8.5)	5 (11)		
Trans-tibial	2 (4)	3 (6.6)		
Predilatation performed	47 (100)	45 (100)	0.000[b]	1.00
Postdilatation performed	16 (34)	45 (100)	44.278[c]	<0.001
Dissection				
Flow limiting dissection	2 (4.2)	4 (18.5)	0.809[c]	0.43
Non flow limiting dissection	6 (12.7)	7 (15.5)	0.147[b]	0.70
Stenting	7 (14.8)	45 (100)	67.021[c]	<0.001

Categorical variables expressed as *n* (%). BMS, bare-metal stent; DCB, drug-coating balloon. [b]χ^2 test. [c]Fisher's exact test. *P* value less than or equal to 0.05 is significant.

Table 4 Procedural results

Procedural results	DCB (*N*=47 limbs)	BMS (*N*=45 limbs)	Test	*P* value
Improper stent deployment treated with bypass surgery	0	2 (4.3)	2.112[c]	0.24
Residual stenosis	3 (6.3)	0	2.937[c]	0.24
Procedural success	44 (93.6)	43 (95.5)	0.168[c]	1.00
Postprocedural acute thrombosis	2 (4.3)	3 (6.7)	1.537[c]	0.26
Death	1 (2.1)	2 (4.4)	0.301[c]	1.00
PRLA	0	0	0.000[b]	1.00
Clinical success	41 (87.2)	38 (84.4)	0.046[b]	0.83
Postprocedural ABI	Mean±SD	Mean±SD		
1 month	0.84±0.06	0.88±0.07	2.947[a]	0.06
6 months	0.80±0.04	0.82±0.05	2.123[a]	0.07
12 months	0.79±0.06	0.70±0.04	–8.427[a]	<0.001
24 months	0.78±0.05	0.61±0.03	–19.666[a]	<0.001

Categorical variables expressed as *n* (%). Continuous quantitative expressed as mean±SD. ABI, ankle–brachial index; BMS, bare-metal stent; DCB, drug-coating balloon; PRLA, procedure-related limb amputation. [a]Independent Student *t* test. [b]χ^2 test. [c]Fisher's exact test. *P* value less than or equal to 0.05 is significant.

Primary patency rate at 1 year was 41 (87.2%) in the DCB group owing to occlusion of six (12.8%) lesions. This occlusion was due to acute thrombosis in two lesions and restenosis owing to intimal hyperplasia in four lesions. However, primary patency rate at 1 year was 34 (75.6%) in BMS group owing to occlusion of 11 (24.4%) lesions. This occlusion was due to acute thrombosis in five lesions and ISR due to intimal hyperplasia in six lesions, which was statistically insignificant for patency (*P*=0.15). These occlusions were reported by clinical follow-up, duplex ultrasound, and repeated angiography following the diagnosis. All postprocedural acute thrombotic occlusions in both groups were treated with catheter-directed thrombolysis. Repeated plain balloon angioplasty was performed in three DCB lesions [two succeeded and one failed for which above knee amputation (AKA) was done], and the remaining restenotic lesion was treated conservatively as the stenosis is less than 50% and did not threaten the limb. However, in BMS group, two in-stent restenotic lesions were treated conservatively as the stenosis is less than 50%; repeated angioplasty was done in two lesions (one lesion succeeded but the other lesion failed for which bypass surgery was done), and AKA was done for the remaining two patients. So, the secondary patency rate at 12 months was 45 (95.7%) in DCB group and 41 (91.1%) in BMS group, which was not statistically significant for patency (*P*=0.43) (Table 5).

Primary patency rate at 2 years was 36 (76.6%) in DCB group owing to occlusion of five lesions. This occlusion was owing to intimal hyperplasia. However, primary patency rate at 2 years was 26 (57.8%) in BMS group owing to occlusion of eight lesions. This occlusion was due to intimal hyperplasia in six lesions and stent fracture in two lesions, which was statistically significant for patency (*P*=0.05). For DCB group, AKA was done in two patients, whereas revascularization with repeated angioplasty was performed in three lesions which succeeded. However, for BMS group, AKA was done in three

Table 5 Outcome characteristics

Outcome characteristics	DCB (*N*=47 limbs)	BMS (*N*=45 limbs)	Test	*P* value
Primary patency				
12 months	41 (87.2)	34 (75.6)	2.081[a]	0.15
24 months	36 (76.6)	26 (57.8)	3.704[a]	0.05
Restenosis and vessel occlusion				
12 months	6 (12.7)	11 (24.4)	2.081[a]	0.15
24 months	11 (23.4)	19 (42.2)	3.704[a]	0.05
Target lesion revascularization				
12 months	5 (10.6)	7 (15.5)	0.490[a]	0.48
24 months	7 (14.9)	8 (17.7)	0.371[a]	0.67
Secondary patency				
12 months	45 (95.7)	41 (91.1)	0.809[b]	0.43
24 months	43 (91.4)	34 (75.5)	3.704[a]	0.05
Clinical improvement				
Intact target limb				
12 months	46 (97.8)	43 (95.5)	0.391[b]	0.61
24 months	44 (93.6)	40 (88.8)	0.647[b]	0.48
Increase at Rutherford classification				
12 months	45 (95.7)	41 (91.1)	0.809[b]	0.43
24 months	42 (89.3)	37 (82.2)	0.965[a]	0.33
Safety outcomes				
30 days procedure related death	1 (2.1)	2 (4.4)	0.301[b]	1.00
Target limb amputation				
12 months	1 (2.1)	2 (4.3)	0.391[b]	0.61
24 months	3 (6.3)	5 (11.1)	0.647[b]	0.48

Categorical variables expressed as *n* (%). BMS, bare-metal stent; DCB, drug-coating balloon. [a]χ^2 test. [b]Fisher's exact test. *P* value less than or equal to 0.05 is significant.

Table 6 Life table analysis of primary patency rate

Interval	At risk	Failed during interval	Withdrawn during interval	Interval Failure rate	Cumulative patency rate	SE
DCB						
0–3	47	2	1	0.043	95.7%	2.9%
3–6	44	1	0	0.023	93.5%	3.6%
6–9	43	2	0	0.047	89.1%	4.5%
9–12	41	1	1	0.025	87.2%	5.1%
12–15	39	3	1	0.077	80.8%	5.8%
15–18	35	2	1	0.058	76.6%	6.4%
18–24	32	0	0	0.000	76.6%	6.6%
BMS						
0–3	45	5	2	0.113	88.8%	4.4%
3–6	38	1	0	0.026	86.5%	5.1%
6–9	37	3	0	0.081	79.6%	5.8%
9–12	34	2	2	0.060	75.6%	6.4%
12–15	30	4	1	0.136	66.7%	6.9%
15–18	25	4	2	0.166	57.8%	7.5%
18–24	19	0	0	0.000	57.8%	8.6%

BMS, bare-metal stent; DCB, drug-coating balloon.

patients and two patients continued conservative treatment while revascularization with repeated angioplasty was performed in three lesions; two of them failed and prepared for bypass surgery which failed, and the third lesion succeeded. So, the secondary patency rate at 24 months was 43 (91.4%) in DCB group and 34 (75.5%) in BMS group (*P*=0.05), which was statistically significant for patency (Tables 5–7).

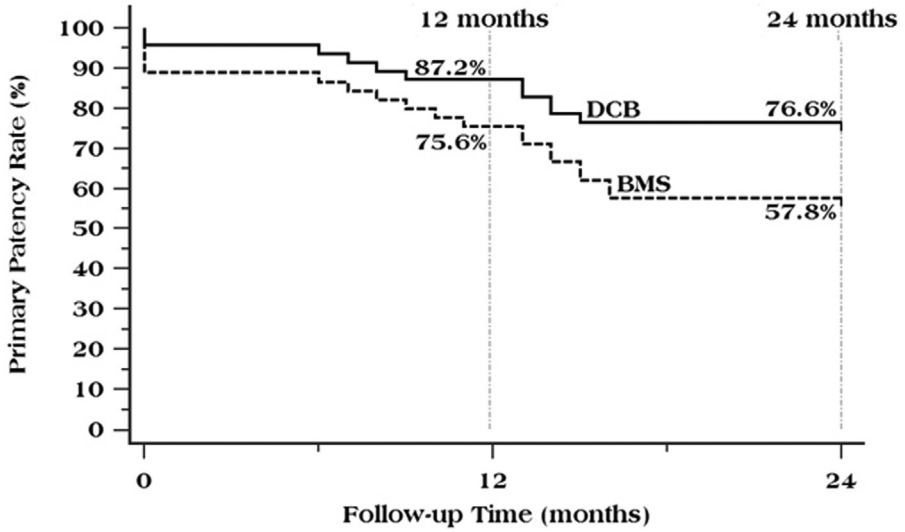
There is a statistically significant difference of primary and secondary patency rates at 24 months in Kaplan-Meier curve (Figs 4 and 5). Moreover, the difference was statistically significant regarding the rate of restenosis and vessel occlusion at the same period (*P*=0.05) between DCB and BMS group. Moreover, the postprocedural ABI shows highly significant difference between both groups at 24 months (*P*<0.001).

Table 7 Life table analysis of secondary patency rate

Interval	At risk	Failed during interval	Withdrawn during interval	Interval failure rate	Cumulative patency rate	S
DCB						
0–3	47	0	1	0.000	100%	0%
3–6	46	0	0	0.000	100%	0%
6–9	46	1	0	0.021	97.8%	2.2%
9–12	45	1	1	0.023	95.7%	3.1%
12–15	43	1	1	0.024	93.6%	3.7%
15–18	41	2	1	0.050	91.4%	4.2%
18–24	38	0	0	0.000	91.4%	4.5%
BMS						
0–3	45	0	2	0.000	100%	0%
3–6	43	0	0	0.000	100%	0%
6–9	43	2	0	0.047	95.4%	3.1%
9–12	41	2	2	0.050	91.1%	4.3%
12–15	37	1	1	0.027	86.3%	5.3%
15–18	35	4	2	0.117	75.5%	6.3%
18–24	29	0	0	0.000	75.5%	6.9%

BMS, bare-metal stent; DCB, drug-coating balloon.

Figure 4



Kaplan–Meier plot of primary patency rate.

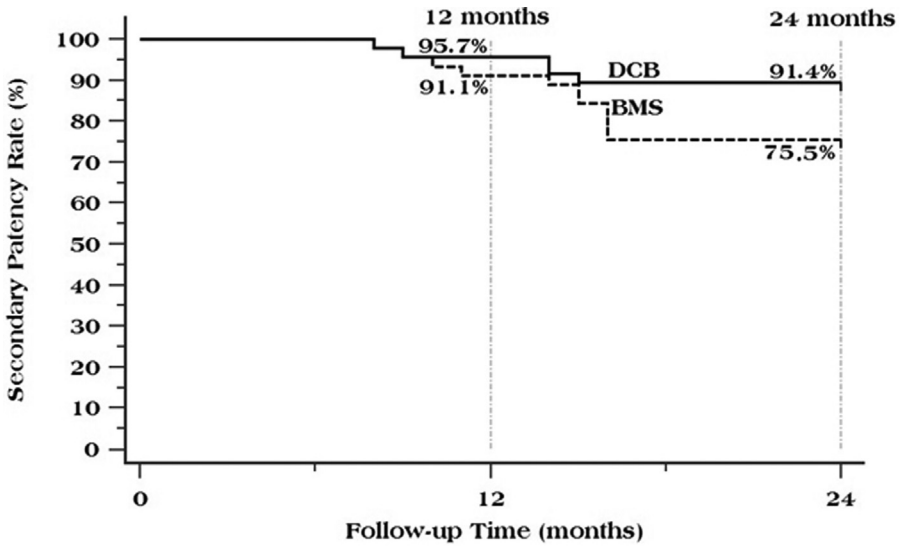
Discussion

CTO is one of the most complex lesions to be treated with endovascular approaches, especially when difficult to be crossed intraluminally, and plaque burden and calcification may result in elastic recoil and dissections after PTA [16]. Maintaining the status of patency of recanalized vessels remains the Achille's heel of endovascular treatment and the primary goal of newly developed endovascular devices and techniques. BMS of recanalized vessels and drug-coating devices are one of these techniques. Despite BMS has improved the outcome of the procedure in comparison with standard balloon angioplasty, its broader use is limited by stent fractures and the high occurrence of ISR in complex femoropopliteal lesions [17–20].

Only a few studies for DCB have reported findings after 1 year of follow-up. Micari *et al.* [21] recorded 83.7 and 72.4% patency rates at 1 and 2 years, respectively, for a short lesion length of about 7.6 cm. To date, few randomized, controlled trials have compared DCBs with stents in long, complex femoropopliteal lesions, and legitimate competitors will be the current generation of stents with novel designs or drug coatings; these implants tend to be ideal for the treatment of complex, calcified lesions, but the permanent metal implant still has drawbacks [22,23].

In the current study, 1-year primary patency rate by Kaplan–Meier estimate was 87.2% for DCB group with a mean lesion length of 18.5 cm and 75.6% for BMS group, with a mean lesion length of 17.8 cm,

Figure 5



Kaplan–Meier plot of secondary patency rate.

which is nearly similar to 12-month primary patency by the IN.PACT Global Study of 85.3% in the overall CTO cohort (mean length 22.8 cm), which was higher when compared with 77% for the prospective research of direct stenting [24–26], 78% in the prospective trial of PTA with stents (mean length 24.5 cm) [19], 79% in the retrospective analysis of PTA with stents [20], 80% in a prospective PTA study with stent grafts [24], and in a prospective PTA analysis with stent graft for long (>20 cm, mean length 26.5 cm) TASC IIC and D lesions (92.9% of which were CTO), and 1 year primary patency by Kaplan–Meier estimate was even as low as 67% [27]. Exception to this pattern is SUPERSUB 34-subject (SUPERA stent after subintimal crossing) research that dealt with long TASC C/D CTOs and 1-year primary patency of 94.1% was demonstrated with a mean length of 27.9 cm [26]; this better outcome may be owing to the associated use of the atherectomy device. Moreover, Pacifier study [28,29] shows better 1-year primary patency rate of 90% in spite of marked calcification and total occlusion percentage; this is probably because of vessel preparation with high-pressure balloon before using DCB.

In this study, comparing the patency rate between both groups, the DCB group exhibited higher rates of 1-year primary patency (87.2 vs. 75.6%; *P*=0.15), 2-year primary patency (76.6 vs. 57.8%; *P*=0.05), 1-year secondary patency (95.7 vs. 91.1%; *P*=0.43), and 2-year secondary patency (91.4 vs. 75.5%; *P*=0.05). This statistically significant difference of primary and secondary patency at 24 months between DCB and BMS is owing to the presence of metal foreign body, which induce inflammatory reaction and intimal hyperplasia, causing ISR; moreover, stent fracture may stand behind this result. So, the results are so better in DCB when compared with BMS group. However, in a study done by Meng *et al.* [7] that enrolled 94 patients who received a DES (*n*=24) or BMS (*n*=70) between 2009 and 2014, when comparing DES with BMS group, the DES group exhibited higher rates of 1-year primary patency (87.5 vs. 71.4%; *P*=0.169), 2-year primary patency (79.2 vs. 61.4%; *P*=0.139), 1-year secondary patency (100 vs. 94.3%; *P*=0.569), and 2-year secondary patency (100 vs. 87.1%; *P*=0.106), although the differences were nonsignificant.

The 12-month incidence of thrombosis was low in DCB group (4.3%) in a study performed by Tepe *et al.* [4], which was similar to that in the present study at which the rate of acute thrombosis in BMS is higher than DCB (11.1 vs. 4.3%, respectively) but the differences were statistically insignificant between the two groups (*P*=0.26). The presence of metal foreign body and induced inflammatory reaction by it may stand behind this result.

In the current analysis, the 2-year TLR rate in the DCB group was lower than that in the BMS group (14.9 vs. 17.7%); however, the difference was nonsignificant (*P*=0.67). Moreover, in a study done by Meng *et al.* [7], the 2-year TLR rate in the DES group was lower than that in the BMS group (20.8 vs. 38.6%), also with nonsignificant difference (*P*=0.139).

In our study, no device-related deaths occurred, and the 2-year all-cause mortality rate was 2.1% in the DCB

group and 4.4% in BMS group, and there was no significant difference in overall mortality rate between the two groups (P=1.00). Moreover, in a study done by Dake *et al*. [30], balloon and stent reported no device-related deaths, and the 2-year mortality rates were 3.4 and 7.6% in PTA and primary DES groups, respectively. These rates did not differ significantly between both groups (P=0.12). Major target limb amputation within 24 months after our procedure occurred in 6.3% of the DCB group and 11.1% in the BMS group (P=0.48), but the differences were nonsignificant between the two groups. However, the outcome of major target limb amputation after the procedure done by Bausback *et al*. [10] was 8% of cases in DCB group and 7% of cases in DES group (P=0.77).Both DCB and BMS treatment methods were particularly challenged in long and CTO, with multiple of patency failures. As predicted, the length of the lesion and the existence of complete occlusion were significant predictors of restenosis in statistical analysis. A relatively high percentage of restenosis and patency failures are observed following BMS treatment (25% at 12 months and 43% at 24 months) in our study. A number of previous registries reported findings with a self-expanding nitinol stent (BMS) in longer lesions. A 12-month Japanese study reported a primary patency of 86% for 907 femoropopliteal lesions with a mean length of about 14.7 cm [31]. Another Japanese registry (ZEPHYR [Zilver PTX for Femoropopliteal Artery]; mean lesion length 17 cm) registered restenosis of 37% after 1 year in 831 femoropopliteal lesions [32].

Reintervention for ISR is associated with both decreased technical success and patency rates, whereas reintervention after DCB treatment is relatively simple and gives the chance to a wider range of endovascular options for further treatment. This in turn can result in a potentially superior effect on long-term secondary patency. In our patients undergoing repeated angiography, we also found that restenosis after DCB was usually shorter and more focal, simplifying retreatment [13].

Clinical data on safety and efficacy of endovascular therapy for femoropopliteal CTO are limited and should invite multiple trials for investigating and developing the best endovascular modality. The goal of use of DCB may be leaving nothing in the vessel, which is better to the long-term persistence of a foreign body for improving long-term patency. An important advantage of the DCB, other than its patency rate, which was established for short lesions and still under investigation for complex lesions, is leaving the door open to a wider range of possibilities of endovascular treatment options. Limitations to the data presented in our analysis contain an insufficient number of patients to make more statistically significant differences to be found between the two groups, and the short follow-up period of 2 years.

Conclusion

Our 2-year outcomes showed superior efficacy, higher safety, and greater clinical benefits of DCB than BMS for the treatment of complex femoropopliteal lesions. A statistically significant lower rate of restenosis and occlusions and a statistically significant higher 2-year primary and secondary patency rates were observed in the DCB group than in the BMS group. However, more studies with a larger sample and long-term follow-up are required.

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Conflicts of interest

There are no conflicts of interest.

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