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Predictors of recurrence after paclitaxel drug-coated balloon use for treating femoropopliteal in-stent restenosis

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Abstract

Objective: Paclitaxel drug-coated balloon (PDCB) angioplasty has been shown to be an effective treatment of in-stent restenosis (ISR) at the femoropopliteal (FP) arteries. Long-term studies, however, have shown a progressive decrease in the patency rates following PDCB. The aim of this study was to determine the predictors of stenosis recurrence after PDCB treatment of FP-ISR, and its immediate and mid-term outcomes.

Methods: This prospective, non-randomized study included all chronic lower extremity ischemia patients of Rutherford class 3–6 who underwent PDCB angioplasty to treat >50% FP-ISR between June 2017 and December 2019. The primary endpoint was primary patency, defined as freedom from binary restenosis and freedom from clinically driven target lesion revascularization (CD-TLR) at 12 months. Secondary endpoints included 12-months freedom from CD-TLR and major adverse events (MAEs).

Results: A total of 73 symptomatic chronic limb ischemia patients (73 limbs including 63 with limb threatening ischemia) underwent PDCB angioplasty of FP-ISR lesions (13.7% Tosaka class I, 54.8% class II, and 31.5% class III). The mean ISR lesion length was 121.8 ± 52.7 mm. Technical success was achieved in 70 (95.9%) patients. Kaplan–Meier estimate of the 12-months rates of primary patency and freedom from CD-TLR was 76.1% and 87.4%, respectively. At one year, MAEs occurred in eight patients (11.0%) including two deaths (2.7%), one major amputation (1.4%), and six (8.2%) surgical revascularizations. Multivariable analysis showed that Tosaka class III ISR (HR 4.51, CI: 1.31–15.53, $p < 0.001$) and reference vessel diameter (HR 0.38, 95% CI: 0.18–080, $p = 0.01$) were independently associated with recurrent ISR.

Conclusions: PDCB is safe and effective treatment of FP-ISR lesions. Occlusive ISR lesions and reference vessel diameter were independently associated with recurrent ISR stenosis after PDCB treatment.

Keywords

In-stent restenosis, paclitaxel drug-coated balloon, peripheral arterial disease, drug-eluting balloon, femoropopliteal arteries

Introduction

In patients undergoing endovascular treatment of femoropopliteal (FP) artery disease, implantation of self-expandable stents has been progressively used to treat early shortcomings of balloon angioplasty (PTA), such as residual stenosis, elastic recoil, and flow-limiting dissection.[1] Although stenting has improved the primary patency rates, the mechanical stress due to stent deployment has shown to contribute to an inflammatory response at the treated arteries which can precipitate in the development of neointimal hyperplasia and subsequent restenosis.[2] Occurrence of in-stent restenosis (ISR) has become a growing problem complicating up to 37% of successfully stented femoropopliteal arteries within the first year of treatment.[3–5]

Several endovascular strategies have been evaluated in the treatment of ISR including repeat standard plain old balloon angioplasty (POBA) with or without re-stenting,

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catheter-based atherectomy, and scoring or drug-coated balloon angioplasty. Paclitaxel drug-coated balloon (PDCB) angioplasty has been shown to be one of the best options for treatment of ISR in the FP arteries with a clear advantage in reducing recurrent stenosis at one year.[6–8] Long-term data on PDCB treatment of FP-ISR, however, were inconsistent, and despite its reported lower recurrent restenosis rates at five years as compared to POBA, there was a progressive decrease in the patency rates after the second year of treatment.[9] In another study with more complex patient and lesion characteristics, the clinical benefit of PDCB was totally lost after the first year of follow up.[10] Therefore, studying the predictors of recurrent ISR after PDCB angioplasty of FP artery disease may help determine patients at a higher risk for treatment failure who can benefit from more frequent surveillance and perhaps preemptive intervention.

The aim of the present study was to determine the predictors of stenosis recurrence, and immediate and mid-term outcomes after PDCB treatment of FP-ISR.

Patients and Methods

This is a prospective, two-center, non-randomized study that included all adult chronic lower extremity ischemia patients of Rutherford[11] class 3–6 who underwent PDCB angioplasty to treat >50% ISR at superficial femoral or proximal (P1) segment of the popliteal artery between June 2017 and December 2019. The IN. PACT Admiral DCB (Medtronic, Santa Rosa, CA), which has a paclitaxel concentration of 3 μg/mm^2, was used exclusively in this study.

Ankle-brachial pressure index (ABI) measurements and duplex ultrasound examination were obtained in patients before endovascular treatment. Preoperative assessment of the degree of ISR was determined by peak systolic velocity ratio (PSVR) > 2.4 within a previously deployed FP stent to treat de novo atherosclerotic lesions. Patients with acute limb ischemia, ISR ≤50%, and untreated ipsilateral iliac artery stenosis were excluded from the present study. The study protocol was conducted in accordance with the Declaration of Helsinki and was approved by the local institutional review board of Assiut Faculty of Medicine (approval number 17,300,830). Written informed consents were obtained from all patients.

Procedures

All interventions were done by vascular surgeons in a hybrid operating room under local anesthesia. Unless the patient was already taking clopidogrel, a 300 mg loading dose was administered one day before the intervention. The access site was ipsi- or contra-lateral common femoral artery according to the lesion location and the condition of the access artery. After placement of 6-Fr introducer sheath, 5000 IU of unfractionated heparin were injected into the sheath. Intraluminal passage of 0.018-inch guidewire (V18; Boston Scientific, Marlborough, MA) was first attempted to cross in-stent occlusion. If the wire could not cross the lesion, a loop-wire technique was done using a 0.035-inch angled stiff wire (Radifocus; Terumo Medical, Somerset, NJ), supported by a 5-Fr Bern catheter (Boston Scientific). In case of failed antegrade approach, retrograde wire passage via tibial arteries was our last option before the procedure is considered a technical failure.

After crossing the ISR lesion, POBA (Admiral Xtreme Balloon; Medtronic) was done to predilate the lesion with a balloon size of 0.8:1 to the reference vessel diameter and a suitable length to the lesion. Successful POBA was followed by PDCB angioplasty for 3 min (Figure 1). The balloon size was 1:1 to the vessel diameter with a length that covers the whole ISR and 10 mm beyond the proximal and distal stent edges. When more than one PDCB was needed, a 5-mm balloon overlap was allowed.

If flow-limiting dissection or >30% residual stenosis was detected, a nitinol self-expanding stent (EvereFlex; Medtronic) was deployed. Treatment of the concomitant inflow or outflow lesions was performed in the same or another session according to the clinical findings and surgeon discretion. Hemostasis was done using manual compression. All patients were prescribed dual antiplatelet therapy in the form of daily aspirin (75 mg/day) indefinitely and clopidogrel (75 mg/day) for six months.

Follow up

All patients were followed up after discharge at 1, 3, 6, 9, and 12 months for clinical assessment, ABI measurement, and duplex ultrasound examination. Late clinical events such as all-cause death, repeat revascularization, and major amputation were also recorded. Patients with recurring symptoms underwent angiography as clinically indicated (generally within one week from presentation), and re-interventions were performed only if a target lesion diameter stenosis was >50%.

Definitions and study points

The ISR lesions were classified by visual estimate on angiography using the Tosaka classification.[12] Class I (focal, ≤50 mm in length) included lesions located in the stent body, at the stent edge, or a combination of these sites. Class II referred to diffuse (>50 mm long) ISR lesions in the stent body or at the stent edges. Class III was a totally occluded stent.

Technical success was defined as the ability to perform PDCB angioplasty with a residual stenosis of <30% of the reference diameter. Binary restenosis was defined as a >50%

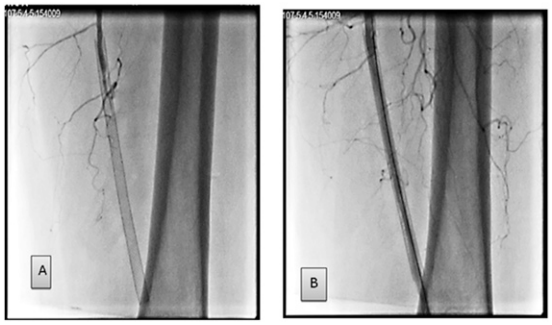

Figure 1. (a) A case of Tosaka class III in-stent restenosis, (b) angiography after successful treatment with paclitaxel drug-coated balloon angioplasty demonstrating patency of the target lesion.

diameter stenosis by angiography or a peak systolic velocity ratio (PSVR) > 2.4 by duplex at any location within the stent(s) or the adjacent proximal and distal 5-mm segments.[13] Early ISR is occurrence of ISR within six months after stenting.

The primary endpoint of the study was primary patency, defined as freedom from clinically driven target lesion revascularization (CD-TLR) and freedom from binary restenosis. Secondary endpoints included: (a) CD-TLR, defined as any reintervention at the target lesion(s) due to symptoms or drop of ABI by ≥ 20% or >0.15 compared to post-procedural baseline values, (b) procedural complications, defined and categorized according to criteria of the Society of Interventional Radiology criteria,[14] (c) major adverse events (MAEs) included all-cause mortality, major target limb amputation, and surgical intervention at the target lesion site.

Statistical analysis

Descriptive statistics were used, with continuous variables expressed as mean ± standard deviation (SD) and/or median and interquartile range (IQR), and categorical variables as frequency and percentage. Kaplan–Meier survival curves were used to estimate primary patency rate, and CD-TLR, reported as proportion ± standard error (SE). Univariable analysis was performed on potential predictors of recurrent ISR, including patients' demographics, clinical presentation, reference vessel diameter, diameter stenosis, early ISR, stent characteristics (type, number, diameter, length, fracture), and lesion characteristics (location, Tosaka class, length, calcification, run-off vessels). Multivariable Cox proportional hazard regression was then performed including predictors with a p value <0.05 in the univariable analysis, in a stepwise approach, and results were presented as hazard ratio (HR) and 95% confidence interval (CI). A p value <0.05 was considered the threshold of statistical significance. Statistical analysis was performed using SPSS 24.0 (IBM Corp, Armonk, NY, USA), and MedCalc 16.8 (MedCalc Soft ware, Ostend, Belgium).

Results

Baseline characteristics and immediate outcomes

The present study included 73 symptomatic chronic limb ischemia patients (73 limbs) with >50% ISR of the superficial femoral or proximal popliteal artery who underwent PDCB angioplasty. The mean age of the study patients was 64.5 ± 6.4 years who were mostly males (76.7%), diabetic (71.2%), and presenting predominantly with chronic limb threatening ischemia (86.3%). Patients' demographics, severity of ischemia, and clinical characteristics are listed in Table 1.

The overwhelming majority of ISR lesions were located at the superficial femoral artery (94.5%) and the remaining 5.5% involved the proximal popliteal artery. The mean ISR lesion length was 121.8 ± 52.7 mm. According to Tosaka classification, 10 patients (13.7%) had class I, 40 patients (54.8%) had class II, and 23 patients (31.5%) had class III.

Lesion and procedure characteristics are summarized in Table 2. Technical success was achieved in 70 patients (95.9%), including 14 patients (19.2%) who required adjunctive stenting. The failed three procedures (4.1%) were due to inability to cross the ISR lesion and were successfully treated with bypass surgery. No other major adverse events or reinterventions occurred during hospitalization. Postoperative ABI values significantly increased from 0.39 ± 0.13 to 0.82 ± 0.07 (p < 0.0001). Other procedure-related complications included distal embolization (two patients) and access site small hematoma (two patients) and were all treated conservatively.

Mid-term outcome measures

The 12-months follow up data were available for 69 patients (94.5%). Two patients died at three and six months due to cardiac causes resulting in one-year all-cause mortality rate of 2.7%, while two patients lost follow up. Major amputation was performed in one patient (1.4%) after a failed attempt of endovascular recanalization of thrombosed stent followed by failed femorotibial bypass surgery.

Kaplan–Meier estimate of the 12-months primary patency rate was 76.1% (Figure 2), and freedom from CD-TLR was 87.4% (Figure 3). CD-TLR was needed in six patients (8.2%) including the patient who required limb amputation after failed endovascular and open surgical attempts. The remaining five patients were successfully treated with PDCB (n = 3) or successful bypass surgery (n = 2). At one year, MAEs occurred in eight patients (two deaths, one major amputation, and five surgical

Table 1. Patients' demographics and clinical characteristics.

Age, years	
Mean ± SD	64.5 ± 6.4
Median (IQR)	64 (59–69)
Male gender	56 (76.7)
Diabetes	52 (71.2)
Hypertension	22 (30.1)
Current smoking	36 (49.3)
BMI, kg/m^2	—
Mean ± SD	23.1 ± 3.1
Median (IQR)	23 (20.5–25.5)
CAD	14 (19.2)
CVD	9 (12.3)
CKD	12 (16.4)
COPD	8 (11.0)
Dyslipidemia	19 (26.0)
Rutherford stage	—
Stage 3	10 (13.7)
Stage 4	24 (32.9)
Stage 5	33 (45.2)
Stage 6	6 (8.2)

Continuous data are presented as the means ± standard deviation (SD) and/or median and interquartile range (IQR); categorical data are given as the counts (percentage). Abbreviations: BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease (defined as eGFR <60 mL/min/1.73 m^2); CVD, cerebrovascular disease; COPD, chronic obstructive pulmonary disease.

revascularization of the treated limb) with a cumulative MAE rate of 11.0%.

Exploratory univariate analysis identified Tosaka class III ISR lesions (HR 10.16, 95% CI: 1.35–16.52, $p = 0.03$), early occurrence of ISR (HR 4.89, 95% CI: 1.73–13.84, $p = 0.003$), reference vessel diameter (HR 0.47, 95% CI: 0.22–0.99, $p = 0.04$), and length of ISR lesion (HR 1.01, 95% CI: 1.00–1.04, $p = 0.04$) as possible predictors of recurring ISR. Multivariate analysis of those risk factors, however, showed that Tosaka class III ISR (HR 4.51, CI: 1.31–15.53, $p = <0.001$) and reference vessel diameter (HR 0.38, 95% CI: 0.18–080, $p = 0.01$) were the only variables that are independently associated with recurrent stenosis after PDCB treatment.

Discussion

Although several endovascular options have been attempted to avoid surgical treatment of FP-ISR, it continues to be a challenging clinical problem among vascular surgeons. Theoretically, covered stents may offer a barrier to the development of neointimal hyperplasia with a reported improved primary patency rates in de novo[15] or ISR lesions.[16] However, occurrence of edge stenosis at the interface between the covered stent and the treated vessel, and the related loss of collateral vessels

Table 2. Lesion and procedure characteristics.

Reference vessel diameter, millimeter	
Mean ± SD	5.9 ± 0.6
Median (IQR)	6 (5.5–6.5)
Diameter stenosis, %	—
Mean ± SD	74.5 ± 12.6
Median (IQR)	75 (65–80)
Stent type	—
Protègè EverFlex	31 (42.5)
E-Luminexx	26 (35.6)
Absolute Pro	16 (21.9)
Stent no.	—
Mean ± SD	1.4 ± 0.5
Median (IQR)	1 (1–2)
Stent diameter, millimeter	—
Mean ± SD	6.1 ± 0.6
Median (IQR)	6 (6–7)
Stent total length, millimeter	—
Mean ± SD	185.6 ± 64.4
Median (IQR)	180 (150–240)
Stent fracture	6 (8.2)
Lesion location	—
SFA	69 (94.5)
Proximal popliteal artery	4 (5.5)
Lesion length, millimeter	—
Mean ± SD	121.8 ± 52.7
Median (IQR)	120 (90–140)
Tosaka classification	—
Class I	10 (13.7)
Class II	40 (54.8)
Class III	23 (31.5)
Early ISR	7 (9.6)
Grade 3/4 PACSS	14 (19.2)
Run-off vessels	—
1 vessel	37 (50.7)
2 vessels	24 (32.9)
3 vessels	12 (16.4)
PDCB diameter, millimeter	—
Mean ± SD	6.2 ± 0.5
Median (IQR)	6 (6–7)
PDCB no.	—
Mean ± SD	1.3 ± 0.5
Median (IQR)	1 (1–2)
PDCB cumulative length, millimeter	—
Mean ± SD	159.2 ± 27.8
Median (IQR)	170 (140–180)
Adjunctive stenting	14 (19.2)
Stent fracture	4 (5.5)
Stent extension	8 (11)
Stent-in-stent	2 (2.7)
Treated concomitant lesions	17 (23.3)

Continuous data are presented as the means ± standard deviation (SD) and/or median and interquartile range (IQR); categorical data are given as the counts (percentage). Abbreviations: DCB, drug-coated balloon; ISR, in-stent restenosis; PACSS, Peripheral Artery Calcium Scoring System.

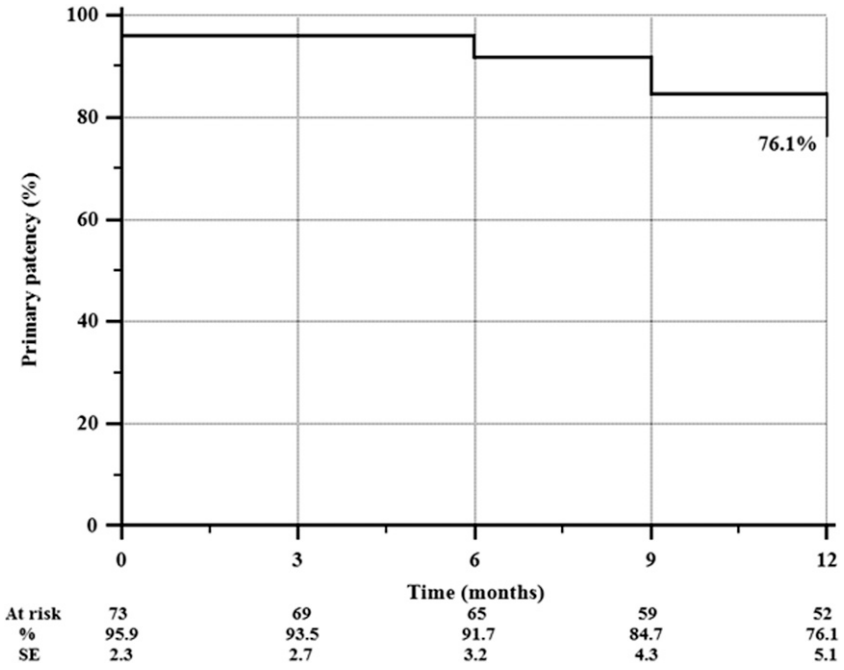

Figure 2. Kaplan–Meier curve of the 12-months primary patency rate of study patients.

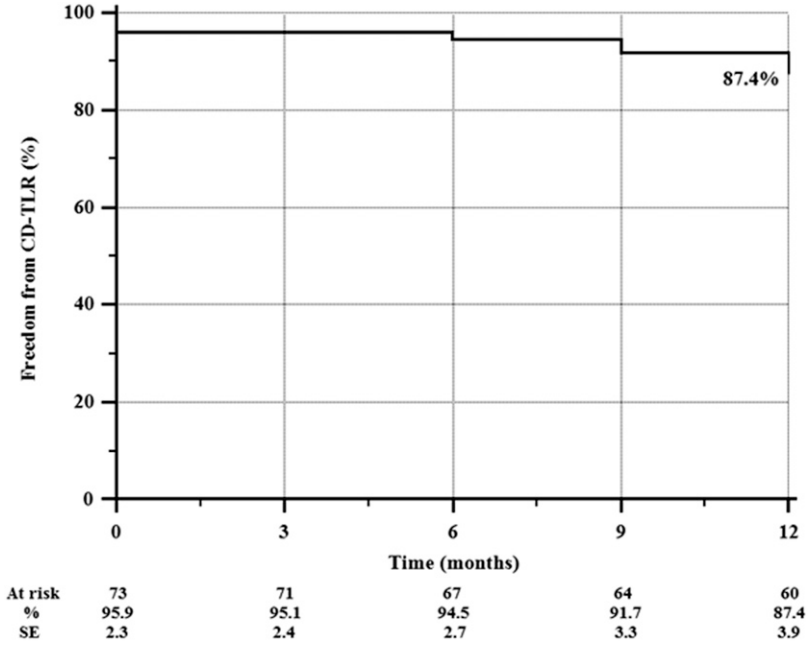

Figure 3. Kaplan–Meier curve of 12-months freedom from clinically driven target lesion revascularization (CD-TLR) of study patients.

causing a potential for acute limb ischemia in case of thrombosis of the covered stent are still valid concerns with their use in the treatment of arterial occlusive disease.[17] Combined POBA with mechanical debulking, including laser[18] or excisional atherectomy,[19] have also shown favorable results in the treatment of FP-ISR but they are not widely available in Egypt. Drug-eluting stents for FP-ISR lesions also showed promising results,[20,21] but the limited available evidence along with the preference of many surgeons to avoid repeat stenting (unless indicated for a flow-limiting dissection) did not support their wide use.

Randomized controlled trials have shown that PDCB for FP-ISR lesions was associated with less restenosis and TLR than POBA at one year[6–8] and at two years.[22] The results of the present study have also demonstrated the benefit of PDCB treatment of FP-ISR lesion with a 12-month primary patency and freedom from CD-TLR of 76.1% and 87.4%, respectively, which are also comparable to the corresponding rates reported by DEBATE-ISR study (81.5% and 86.4%, respectively)[6] and the FAIR study (70.5% and 90.8%, respectively).[7] Better rates, however, have been reported by the PLAISIR (83.7% and 90.2%, respectively)[23] and Stabile et al.[24] (92.1% and 92.1%, respectively). The observed differences among the different studies regarding the mid-term outcomes of PDCB treatment of FP-ISR could be attributed to several factors. The authors of the PLAISIR study suggested that the similarity in the mean lesion length between their study (86 mm) and Stabile et al. study (82.9 mm) could have resulted in the comparable primary patency and TLR rates, while the longer lesions in the DEBATE-ISR (132 mm) may have contributed to the better outcomes of the PLAISIR study. This may also explain the comparable one-year primary patency and CD-TLR rates of the present study (lesion length 121.8 mm) and the DEBATE-ISR study (lesion length 132 mm).

Also, the type of ISR lesion has been found to be one of the factors that may affect recurrence of ISR and the success of subsequent intervention. At one-year follow-up, after POBA of FP-ISR lesion, Tosaka et al.[12] reported a significantly higher incidence of recurrent ISR in Tosaka III lesions by 2.8 and 2.2 times of that in Tosaka I and II lesions, respectively. In the DEBATE-ISR study, treatment of type III lesions was associated with significantly worse rates of TLR in both PDCB and POBA groups.[10] Presence of Tosaka class III ISR lesions in about one-third of our patients and in about half of the DEBATE-ISR patients can be another reason for the equivalent rates of primary patency and CD-TLR in both. Although type III ISR was not associated with increased rates of recurrent restenosis in Stabile et al. study,[24] their two-year follow-up data showed that both class II and III ISR lesions were associated with significantly increased rates of recurrent restenosis compared to type I lesions (33.3% and 36.3% vs 12.5%, respectively).[25] The smaller prevalence of occlusive ISR lesions in Stabile et al. study (20.5% vs 31.5%) along with the shorter lesion length (82.9 mm vs 121.8 mm) may justify their improved primary patency and TLR rates compared to the present rates.

There are several risk factors known to impact the primary patency after endovascular treatment of ISR, including hemodialysis,[26] stent fracture,[26] TASC II C/D lesions,[8,26] diabetes mellitus,[8] lesion length,[8] reference vessel diameter,[12] early ISR,[27] and Tosaka type III ISR lesion.[6,12,28] In the present study, multivariate analysis of all studied patient and lesion variables showed that Tosaka type III ISR and reference vessel diameter were the only variables that are independently associated with recurrent ISR after PDCB treatment. Similar to the findings from other studies, treatment of Tosaka III ISR lesion in our study remained a strong independent predictor of recurrent stenosis or occlusion with more than four-fold increased risk.[6,12,28] Conversely, multivariate analysis in PACUBA trial did not demonstrate differences between stenotic and occlusive ISR lesions regarding the primary patency or freedom from TLR.[8]

Safety outcomes through the 12-months follow-up of the present study showed comparable all-cause mortality rate to the corresponding rates from Stabile et al.,[24] PLAISIR,[23] and FAIR[7] studies (2.7% vs 2.6%, 4.0%, and 4.3%, respectively). Our one-year major amputation rate (1.4%) was also comparable to that of the PLAISIR study (1.8%),[23] but higher than the 0% rate reported from other studies.[6,7,24]

On the other hand, our 8.2% rate of surgical revascularization was substantially higher than that reported in the PLAISIR (3.8%) study.[23] The rate of bypass surgery after PTA treatment of ISR lesions was reported to be significantly higher in occlusive than stenotic types, urging some authors to suggest bypass surgery as the favorable treatment of occlusive ISR.[12] This may justify our higher surgical intervention rates with the higher prevalence of occlusive ISR lesions in the present study than in the PLAISIR (31.5% vs 2%). The FAIR trial, however, had occlusive lesions in about quarter of their patients, yet their surgical intervention rate is also markedly lower than ours (2.1% vs 8.2%).[7] This may suggest that the rate of surgical intervention following PDCB treatment of ISR lesions cannot be solely influenced by the type of ISR lesion. The prominent differences between the present study and the FAIR trial in both the prevalence of critical limb ischemia (86.3% vs 4.8%) and the mean lesion length (121.8 mm vs 82.3 mm) display the more complex nature of the arterial disease in our patients which may have led to increased need for bypass surgery. Our increased surgical intervention rate has notably contributed to the increased cumulative MAE rates in the present study compared to the FAIR trial (11.0% vs 8.5%).

The present study has some limitations including the study design with lack of a control group that may limit conclusive assessment of efficacy and safety of PDCB treatment of ISR lesions. In the analysis of PDCB outcomes to treat ISR lesions, most trials have used POBA, the first and most used endovascular option, for comparison, which has now shown to be ineffective especially in the complex long lesions seen in our patients.[29,30]

The relatively small number of patients may have affected the statistical power to identify other risk factors associated with recurrent ISR after PDCB treatment. Lack of independent core laboratory analysis of images, including duplex ultrasonography and angiography is another

limitation of this study. Finally, the present study did not ascertain functional outcomes including patients' quality of life or cost analysis of PDCB treatment which merit further investigation.

Conclusions

Despite the abovementioned limitations, we are able to conclude that PDCB is a safe treatment option of FP-ISR lesions with satisfactory immediate and mid-term outcomes in terms of one-year primary patency and freedom from CD-TLR. Occlusive ISR lesions and reference vessel diameter were independently associated with recurrent ISR stenosis after PDCB treatment.

Declaration of conflicting interests

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