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The clinical data were achieved with ELUTAX "3", Emperor or previously with ELUTAX SV a product, which was identically in construction or equivalent with the actual product.

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ORIGINAL ARTICLE

Drug-Coated Balloon Treatment in Symptomatic Intracranial High Grade Stenosis

A Retrospective Study of 33 Patients

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Abstract

Purpose Endovascular therapy (EVT) represents an alternative treatment modality for symptomatic intracranial high-grade atherosclerotic stenosis (sICAS); however, periprocedural complication rates as well as midterm restenosis rates represent relevant limitations of EVT. Drug-coated balloon percutaneous transluminal angioplasty (DCB-PTA) may overcome some of these shortcomings. The aim of this study was to assess feasibility and safety as well as the stroke recurrence rate in 33 patients.

Methods A retrospective, monocentric cohort study of sICAS patients treated with DCB-PTA. Outcome measures were the periprocedural intracranial complication rate, the recurrent stroke rate and mortality during follow-up.

Results This cohort study included 33 patients with 35 sICAS treated with DCB-PTA. The median age was 72 years (interquartile range, IQR 66–77 years); median clinical and mean radiological follow-up time was 9 months (IQR 3–22 months). Median preprocedural degree of stenosis (WASID) was 80% (IQR 73–80%) and median postprocedural residual stenosis degree (WASID) was 50% (IQR 33–60%). Intracranial periprocedural complications occurred in 2 (6%) patients. The overall restenosis rate was 15% ($n=5$). In four patients a symptomatic ischemic re-event occurred within 7 months after the initial treatment. None of the patients died.

Conclusion This DCB-PTA cohort study showed a relatively low intracranial complication rate of 6% with a symptomatic recurrence rate of 12%. Larger trials are needed to validate these promising observations.

Keywords Drug-coated balloon (DCB) · Percutaneous transluminal angioplasty (PTA) · Intracranial atherosclerotic disease (ICAD) · Ischemic stroke · Intracranial stenosis

Introduction

Intracranial atherosclerotic disease (ICAD) is a common cause of stroke worldwide with a high stroke recurrence rate despite best medical treatment [1, 2]. Endovascular treatment (EVT) of ICAD is associated with a high restenosis rate (up to 30%) for both percutaneous transluminal angioplasty with stenting (PTAS) and percutaneous transluminal angioplasty (PTA) [3, 4], which is a major midterm to long-term limitation of this treatment modality. To overcome this shortcoming, drug-eluting stents (DES) and drug-eluting balloons (DCB) have been developed, which have been successfully used to treat atherosclerotic heart disease in interventional cardiology [5].

The drug-coated balloons (DCB) are mostly semicompliant balloons coated with an antiproliferative drug and a complex excipient enabling a rapid delivery of the active drug upon inflation to the vessel wall [6, 7]. These antiproliferative drugs inhibit smooth muscle cell prolifer-

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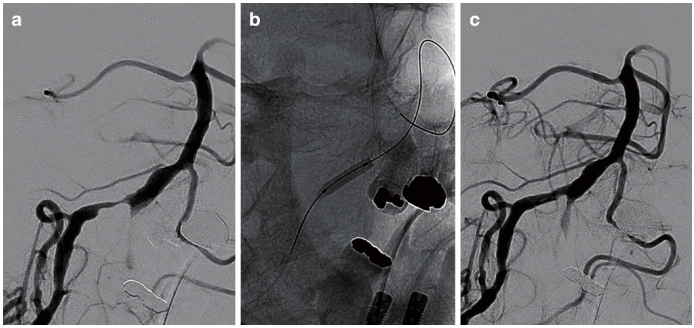

Fig. 1 Illustrative case. A 71-year-old patient with transient ischemic attacks (TIA) with dysarthria and dizziness due to a high-grade stenosis of the right intracranial vertebral artery. In his medical history, he already suffered from a cerebellar stroke and was under antiplatelet treatment and lipid-lowering treatment. **a** Preprocedural angiogram of this symptomatic, high-grade (Warfarin Aspirin in Symptomatic Intracranial Disease [WASID] trial stenosis grading criteria >95%), distal V4 segment vertebral artery stenosis of the right side. **b** The target lesion was treated with a single run paclitaxel drug-coated balloon (DCB) (2.0 mm × 10 mm Sequent Please NEO; b.braun, Melsungen, Germany) PTA without predilatation using submaximal angioplasty technique. **c** Postprocedural angiogram of this symptomatic V4-segment vertebral artery stenosis with a residual stenosis (WASID <40%)

ation, which occurs after the PTA causes microinjuries due to natural immune inflammatory response [8].

In recent years, first cohort studies have shown feasibility and safety of DCB in symptomatic intracranial high-grade atherosclerotic stenosis (sICAS) ([9–11]; Fig. 1); however, the experience with DCB is limited since data are based on small patient numbers and short follow-up periods.

The aim of this study was to assess the feasibility and safety of DCB PTA in 33 patients.

Methods

Patient Selection

This retrospective monocenter cohort study at a tertiary stroke center was approved by the local ethics committee (EKNZ 2018-01204) with waived informed consent for the data analysis. Prior to the intervention, patients gave their informed consent to the DCB-PTA. Patients (≥18 years) with symptomatic, intracranial high-grade stenosis (WASID ≥70%) and electively (≥1 day after index event) treated with DCB-PTA between 2014 and 2019 were included in this retrospective data analysis. Patients with hyperacute (0–24 h) stroke or additional extracranial tandem stenosis, as well as patients with asymptomatic stenosis and without follow-up were excluded.

Study Devices

In this study two different Paclitaxel coated DCB-PTA systems, either the Neuro Elutax SV (Aachen Resonance GmbH, Aachen, Germany) or the SeQuent Please NEO (B Braun medical, Melsungen, Germany), were used [12, 13]. The Neuro Elutax SV represents the first CE certified DCB-PTA system specifically designed for neurovascular use. The SeQuent Please NEO is one of the latest cardiovascular DCB-PTA systems. The use of this DCB PTA system represents an off-label use. The decision on the type of DCB was at the discretion of the treating interventionalist.

Procedure

All procedures were performed with the patient under general anesthesia. Prior to the intervention, all patients were either under dual antiplatelet therapy (DATP) with aspirin and clopidogrel or under an oral anticoagulant (OAC) combined with an antiplatelet monotherapy ($n = 3$, 9%). An additional heparin bolus was administered, adjusted for body weight according to the activated coagulation time (ACT) blood test. In almost all cases a retrograde approach of the right common femoral artery was performed. A retrograde distal brachial artery access was obtained in only one patient. All interventions were performed on a biplane angiography system (Allura Xper, Philips, Amsterdam, The Netherlands). For the exact sizing of the DCB, the precise length and diameter of the stenosis was assessed by a 3D DSA prior to the PTA procedure. Under fluoroscopic guidance, the lesions were first explored by a microwire (synchro, Stryker Neurovascular, Kalamazoo, MI, USA), followed by the delivery of the DCB-PTA system in monorail technique. After careful positioning of the DCB over the lesion, the DCB was inflated for 30–60 s and a submaximal angioplasty maneuver was performed as described

elsewhere [14, 15]. If necessary, repeated angioplasty was done. No predilatation with a conventional angioplasty balloon or an additional stent deployment was performed.

Postprocedurally, the systolic blood pressure was kept at ≤140–160 mm Hg. Thus, patients were monitored on a neurological intermediate care unit or intensive care unit (ICU) for 24 h. Most of the patients were kept on DAPT or OAC combined with a mono-antiplatelet therapy for 3 months. In 9 patients an immediate change to a monotherapy (aspirin [ASS] or clopidogrel alone) was done. In one case DAPT was reduced to ASS because of SAH. All patients were under a lipid lowering therapy and underwent medical modification of the cerebrovascular risk factors.

Imaging

Cerebral angiography was used for the exact assessment of the preprocedural and post-procedural degree of intracranial stenosis according the WASID criteria. Within 24 h postprocedural, all patients underwent an ultrasound (US) monitoring restenosis assessment. This US served also as a follow-up examination baseline. On each clinical follow-up, patients underwent an ultrasound control.

Outcome Measures

Primary outcome parameters for safety and efficacy were the periprocedural symptomatic stroke rate (day 0–30), the stroke recurrence rate in the respective vascular territory and residual stenosis patency at follow-up assessed by a trained vascular neurologist. Restenosis was defined as a change in the US finding at follow-up that led from no stenosis or ≤50% stenosis to a >50% stenosis degree with/or without clinical symptoms in the respective vascular territory during the follow-up period.

Furthermore, we looked at periprocedural complication rate, mortality rate and favorable clinical outcome, defined as modified Ranking scale score ≤2 within 90 days.

Results

This cohort comprised 33 treated patients with 35 lesions (Table 1). Median clinical and radiological follow-up was 9 months (interquartile range, IQR 3–22 months, range 1–56 months). In half of the patients ($n=16$) a follow-up of more than 12 months was available. Median age was 72 years (IQR 66–77 years). Most of the patients were men. Hypertension and dyslipidemia were the most common vascular risk factors. Median NIHSS on admission was 1 (IQR 0–2). Median time from index event to intervention was 12 days (IQR 5–16 days). Most treated lesions were located in the posterior circulation. In two patients, serial lesions of the vertebral and basilar artery were treated. Median preinterventional degree of stenosis (WASID) was 80% (IQR 73–80%). The most commonly used DCB-PTA system was the SeQuent Please NEO PTA system.

Table 1 Population, stenosis and technical characteristics

Population Characteristics	$N=33$
Age in years, median (IQR)	72 (66–77)
Sex male, no. (%)	27 (82%)
Hypertension, no. (%)	28 (85%)
Dyslipidemia, no. (%)	27 (82%)
Diabetes mellitus type II, no. (%)	10 (30%)
Obesity, no. (%)	17(52%)
Atrial fibrillation, no. (%)	3 (9%)
Smoker, no. (%)	10 (30%)
Previous stroke, no. (%)	9 (27%)
NIHSS score on admission, median (IQR)	1 (0–2)
Time from index event to intervention in days, median (IQR)	12 (5–16)
Follow-up period in months, median (IQR)	9 (3–22)
Intracranial stenosis characteristics	
Left side, no. (%)	11 (16%)
Preprocedural stenosis degree in percentage WASID, median (IQR)	80 (73–80)
Intradural vertebral artery, no. (%)	10 (30%)
Basilar artery, no. (%)	10 (30%)
Distal intracranial carotid artery, no. (%)	9 (27%)
Middle cerebral artery, no. (%)	6 (18%)
Technical characteristics	
General anesthesia, no. (%)	33 (100%)
Neuro Elutax SV (Aachen Resonance, Aachen, Germany)	7 (21%)
Sequent Please NEO (bbraun, Melsungen, Germany)	26 (79%)

IQR interquartile range, *NIHSS* National Institute of Health Stroke Scale, *no* number, *WASID* warfarin aspirin in symptomatic intracranial disease

Mean postprocedural stenosis degree (WASID) was 50% (IQR 33–60%) (Table 2).

A minor ischemic event with bilateral ischemic lesions occurred within 24 h after the intervention in only one patient. In one patient, a dissection of the intradural vertebral artery with consecutive subarachnoid hemorrhage occurred during the interventional maneuver. Fortunately, the patient recovered completely from this incident. Furthermore, a hemodynamic relevant groin hematoma at the puncture side occurred that needed vascular surgery but there was no vasospasm, vessel perforation or in-hospital or out-of-hospital deaths during the follow-up reported. The 24 h postprocedural US and the follow-up US results remained stable with no evidence of stenosis in 37% and 42% of the cases, ≤50% stenosis in 42% and 40% and >50% stenosis in 21% and 18%, respectively. On follow-up, the overall restenosis rate was 15% ($n=5$). Of these 5 patients with

Table 2 Summary of outcome measures

Outcome measures	*N* = 33
Modified Ranking Scale (mRS) score at follow-up, median (IQR)	1 (0–1)
Postprocedural stenosis degree in percentage (WASID), median (IQR)	50 (33–60)
Overall restenosis rate, no. (%)[a]	5 (15%)
Symptomatic ischemic re-events, no. (%)	4 (12%)
Relevant asymptomatic restenosis rate, no. (%)	1 (3%)
Intracranial periprocedural complications, no. (%)	2 (6%)
Extracranial periprocedural complications, no. (%)	1 (3%)
Death rate within the follow-up period, no. (%)	0 (0%)

IQR interquartile range, *NIHSS* National Institute of Health Stroke Scale, *mRS* modified Ranking Scale Score, *no* number, *WASID* warfarin aspirin in symptomatic intracranial disease

[a]This overall restenosis rate consists of the relevant asymptomatic re-stenosis rate as well the restenoses with symptomatic ischemic re-events

restenosis symptomatic ischemic re-events occurred in 4 (12%) with a median intervention to re-event interval of 7 months (IQR 7–9.5 months). Median degree of restenosis (WASID) of these 4 symptomatic patients, who received conventional cerebral angiography when presenting with new symptoms, was 80% (IQR 78–83%). All of these 4 patients had a postprocedural degree of stenosis (WASID) of ≥50% after DCB-PTA for the index event. In addition, all of them had a history of smoking and 2 out of 4 patients suffered from diabetes mellitus. In addition, in one case a severe asymptomatic restenosis occurred after 6 months without clinical symptoms. Finally, 4 of these patients were successfully retreated with DCB-PTA.

Discussion

This retrospective cohort study demonstrated the feasibility and safety of DCB-PTA treatment with a low intracranial periprocedural complication rate of 6% and a symptomatic recurrence rate of 12%.

Only limited data on DCB-PTA in sICAD patients are available [9–11]. Treatment of sICAD patients with high-grade stenosis (≥70–99%) remains challenging as the only approved treatment regimen (best medical treatment) revealed a disappointedly high stroke recurrence rate with 21% within 1.8 years [16]. Endovascular treatment in these patients is limited due to the high periprocedural complication rate as well as the high restenosis rate in the follow-up period; however, the high periprocedural complication rates [17] have recently been challenged by the results of the WAEVE trial (2.6%) [18]. In addition, data from a few DCB-PTA cohort studies revealed comparatively low periprocedural complication rates ranging from 0% to 6.5% that are supported by our findings with an intracranial complication rate of 6% [9–11]. The reason for the lower complication rates may be due to the advances of material technology enabling a better maneuverability and navigability, the growing experience of the treatment of intracranial lesions since the era of endovascular stroke treatment and careful patient selection [19].

A known long-term complication is restenosis secondary to neointimal hyperplasia induced by mechanical microinjuries during dilatation or stent deployment [20]. Under the assumption that a restenosis with ≥50% luminal loss may provoke cerebral ischemic events again [21], the prevention of such lesions is of utmost importance. Despite promising results [22], DES have never become a standard procedure in the neurovascular field. The PTA alone revealed a similar periprocedural complication rate compared to PTAS but seems to have better long-term results regarding re-events compared to PTAS [23]; however, large RCT are lacking. Nevertheless, these results might also indicate an advantage in the long-term efficacy for DCB-PTA. Recent data from DCB PTA studies have shown convincing results in the treatment of sICAD patients [9–11]. Our findings support these results. Within a median follow-up of 9 months (IQR 3–22 months), 12% symptomatic re-events occurred, which is lower than the natural course with 21%, as reported in cohorts of sICAS patients treated with best medical treatment (BMT) only [16]. The reoccurrence of ischemic symptoms usually occurred around 7 months after the intervention, which has also been described for patients treated with PTAS [21]. All of these patients were smokers and half of them also suffered from diabetes, while the original cohort consisted of only 30% smokers and 30% diabetes patients. This observation is not surprising, as diabetic patients in particular tend to develop restenosis after cardiological PTA [24]. Interestingly, the pathophysiological influence of smoking on the development of restenosis after percutaneous coronary intervention has not yet been defined [25]. Nevertheless, our data suggest that these two vascular risk factors may promote stenosis in cerebral vessels. Furthermore, due to our submaximal angioplasty technique, the initial median residual stenosis of 50% may be too high in these cases. Probably, the residual stenosis should be lower in these cases.

Limitations are the retrospective nature of this cohort and the relatively small number of patients due to the fact that DCP-PTA is still an off-label use in the neurovascular setting. Additionally, the radiological follow-up control with US only enables an approximate assessment of the treated stenosis; however, US follow-up is only justified because it is non-invasive and does not expose patients to additional radiation or possible complications of endovascular surgery. Furthermore, it is cost-effective.

Conclusion

Drug-coated balloon (DCB) angioplasty in symptomatic intracranial high-grade stenosis shows a relatively low intracranial complication rate of 6% with a symptomatic recurrence rate of 12%. Larger trials are needed to further validate these promising observations.

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Author Contribution LR was responsible for the conception and design of the work, revising it critically for important intellectual content and final approval of the version to be published. MD, JB made substantial contributions to the conception and design of the work and revising it critically for important intellectual content. TK, JA, KN revising it critically for important intellectual content. PG was responsible for the conception and design of the work as well acquisition, analysis, and interpretation of data and writing the manuscript.

Compliance with ethical guidelines

Conflict of interest L. Remonda, M. Diepers, J. Berberat, T. Kahles, J. Anon, K. Nedeltchev and P. Gruber declare that they have no competing interests.

Ethical standards The ethical approval was given by the local ethics committee (EKNZ 2018-01204). There was a waived informed consent modus for this study

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Transcranial duplex ultrasound monitoring of intracranial arterial stenosis treated with ELUTAX "3" drug-eluting balloon

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Abstract

We report the results of transcranial ultrasound monitoring in three patients with intracranial arterial stenosis of the middle cerebral artery treated with the only drug-eluting balloon certificated for intracranial use in highly symptomatic intracranial arterial stenosis, ELUTAX "3" (AR Baltic Medical). We performed transcranial Doppler ultrasounds 24 h, 72 h, 10 days, 15 days and 30 days after the angioplasty, thereby measuring mean flow velocity (MFV) in the maximum stenosis area in patients with symptomatic steno-occlusive disease of the middle cerebral artery treated with ELUTAX "3". Two patients were treated during mechanical thrombectomy (MT) due to acute ischemic stroke and one patient was treated on elective basis due to symptomatic pre-occlusive stenosis, with recurrent transient ischemic attacks (TIAs) refractory to medical therapy. In Case 1, the first transcranial Doppler ultrasounds evidenced MFV of 348 cm/s, with progressive MFV reduction until 15 days post-treatment, with MFV of 177 cm/s. In Case 2, 24 h after angioplasty had an MFV of 258 cm/s, decreasing to 103 cm/s at 30 days. Case 3 had an MFV of 436 cm/s before angioplasty that immediately decreased after the procedure to 364 cm/s, with a final MFV of 260 cm/s at 30 days. We have recorded a progressive MFV reduction in intracranial arterial stenosis, with better outcomes in patients treated during MT. In our experience, the use of ELUTAX "3" for the treatment of symptomatic intracranial arterial stenosis achieves a progressive improvement of stenosis, evident in the first weeks, to a higher extent in cases of occlusive thrombosis. More studies are needed to provide more information about this device.

Keywords

Intracranial stenosis, angioplasty, drug-eluting balloon, ELUTAX "3"

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Introduction

The first-line treatment for intracranial arterial stenosis (ICS) is currently medical therapy, as clinical trials such as SAMMPRIS show that percutaneous transluminal angioplasty and stenting involves a high percentage of periprocedural complications (14.7%) and up to 34% recurrences, most of them due to restenosis.[1]

A drug-eluting balloon (DEB) has been recently developed specifically for intracranial use, consisting of paclitaxel (ELUTAX "3"), a potent lipophilic anticancer agent with antiproliferative action on endovascular smooth muscle cells, that reduces intimal hyperplasia and, therefore, restenosis.[2] It is the only DEB with CE mark (*Conformité Européenne*, CE) for intracranial use in highly symptomatic ICS,[3] but to date there are no follow-up studies available that describe the hemodynamic changes occurring in ICS following treatment with intraarterial paclitaxel.

A simple, useful tool to monitor hemodynamic changes in intracranial arterial flow is transcranial Doppler ultrasounds (TCD).[4] This non-invasive technique can be used to measure mean flow velocity (MFV) in the area of maximum stenosis and, therefore, correlate it with the ICS degree.[5,6]

We report the results of ultrasound monitoring in three patients with intracranial stenosis of the middle cerebral artery (MCA) treated at our site with ELUTAX "3" (AR Baltic Medical).

Methods

Patients with symptomatic steno-occlusive disease of the MCA treated in our site with ELUTAX "3" were screened.

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In all cases, the target lesion was crossed using a Traxcess 0.014″ microwire (MicroVention, Tustin, California, USA) and a microcatheter was advanced distal to the lesion to perform an initial. We used Trevo Pro 18 (Stryker Neurovascular, Kalamazoo, MI, USA) as it is part of the standard equipment for the treatment of the stroke in our hospital. With the tip of the guidewire in a distal branch of the target artery, ELUTAX "3" was then advanced with monorail technique over an exchange system by adding a docking wire.

The size and length of the balloon was chosen based on the characteristics of the lesion.

We performed control ultrasound studies 24 h, 72 h, 10 days, 15 days and 30 days after the angioplasty, thereby measuring MFV in the maximum stenosis area.

The studies were performed at the neurosonology laboratory of a tertiary hospital by transcranial color-coded ultrasonography, under baseline conditions, through the temporal window with probe at 1–4 MHz (Philips CX50), with the patient lying on his back, at rest and with normal blood pressure values. In case of insufficient temporal acoustic window, it was allowed to use the echo-enhancer, which was used in the rest of the tests in this patient.

Results

Two patients were treated with ELUTAX "3" during mechanical thrombectomy (MT) due to acute ischemic stroke, in the first case for impossibility to perform it with the previous thrombus aspiration device, with suspected arterial occlusion due to intracranial atherosclerosis, and in the second case due to progressive restenosis after thrombus aspiration.

Patient 3 was treated on an elective basis due to symptomatic pre-occlusive stenosis of the left MCA, with recurrent TIAs, refractory to aggressive medical therapy.

Table 1 shows the demographic and clinical characteristics of the patients treated with ELUTAX "3".

Patient 1 is a 70-year old man with a history of left carotid stroke six months before in his country of origin treated with primary MT, with residual modified Rankin Scale of 1 due to intracranial atheromatosis. He suffered a new stroke of the left MCA (occlusion of M1 segment) treated with primary TM due to the uncertain onset. During the procedure, moderate to severe focal residual stenosis was

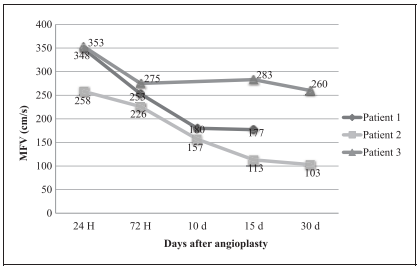

Figure 1. Hemodynamic changes after ELUTAX "3" in ICS measured with TCD. MFV: mean flow velocity.

Table 1. Demographic and clinical characteristics of the patients treated with ELUTAX "3".

	Patient 1	Patient 2	Patient 3
Age (years)	70	66	41
Sex	Male	Male	Male
Vascular risk factors	HT, DLP	HT, DLP, active smoker (40 years-pack)	HT, obesity, OSAS
Treatment on admission	Clopidogrel 75 mg, Carbasalate calcium 100 mg, Atorvastatin 40 mg	Pravastatin 40 mg	Acetyl salicylic acid 150 mg
Clinical signs	Ischemic stroke left MCA	Ischemic stroke right MCA	Recurrent TIAs
History of stroke/previous TIA	Yes	No	Yes
National Institute Health Stroke Scale on admission (points)	15	18	0
ICS site	Left proximal MCA	Right proximal MCA	Left proximal MCA
Treatment with ELUTAX "3"	During MT	During MT	Deferred. TIAs refractory to medical treatment
ICS degree in DSA after immediate treatment	DSA: ICS 50–69%	DSA: ICS 50–69%	DSA: ICS >90%
Antithrombotic treatment post-ELUTAX "3"	– 3 months clopidogrel 75 mg + acetyl salicylic acid 100 mg – Atorvastatin 80 mg		
One month modified Rankin Scale	3	1	0

MCA: middle cerebral artery; ICS: intracranial arterial stenosis; MT: mechanical thrombectomy; HT: hypertension; DLP: dyslipidemia; OSAS: obstructive sleep apnoea syndrome; TIA: transient ischemic attack; DSA: digital subtraction angiography.

evidenced in the proximal segment of M1 of the left MCA with a trend to reocclusion and difficulty to advance the guide, for which angioplasty was performed with ELUTAX "3", achieving complete revascularization with modified Thrombolysis in Cerebral Infarction (mTICI) 3.

The first TCD control performed at 24 h evidenced MFV of 348 cm/s, with progressive MFV reduction until the last TCD performed at 15 days post-treatment, with MFV of 177 cm/s. No subsequent ultrasonographic controls are available as he returned to his country (see Figures 1 and 2).

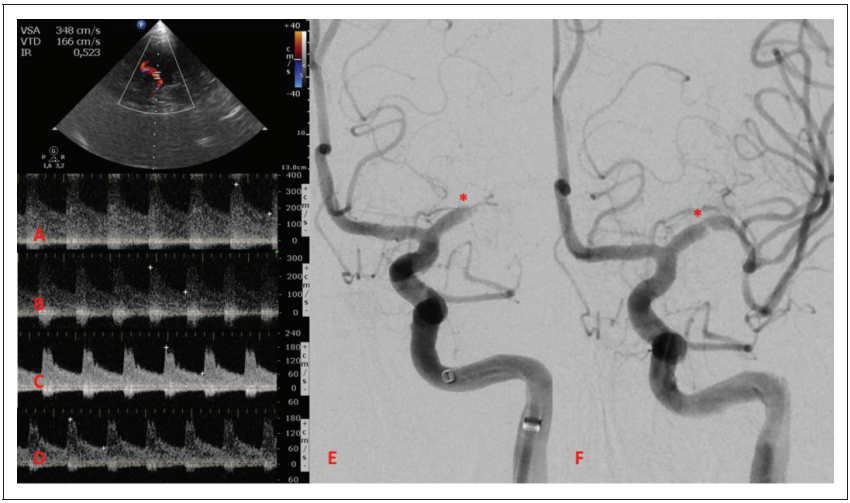

Figure 2. TCD control in Patient 1 at 24 h after angioplasty with ELUTAX "3" (a), 72 h (b), 10 days (c) and 15 days (d) after treatment. (e) and (f) correspond to DSA studies during MT: (e) shows left M1 occlusion (*) and (f) shows the residual stenosis (*) after angioplasty with the DEB.

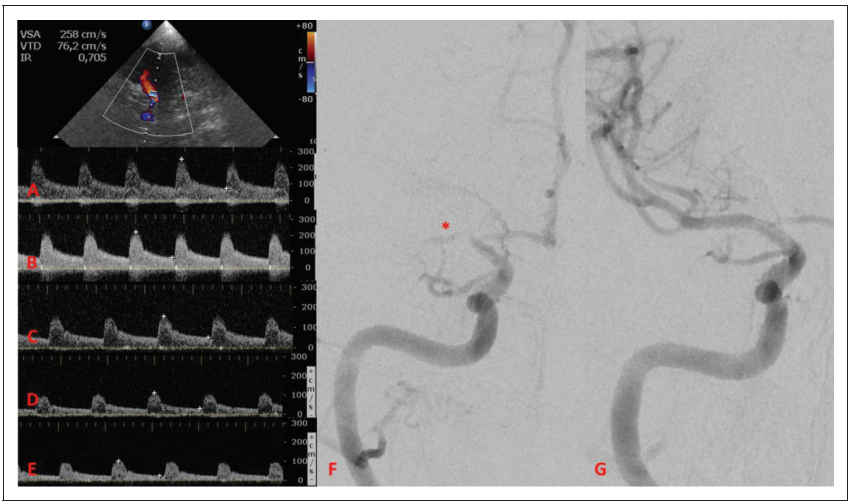

Figure 3. TCD control in Patient 2 at 24 h after angioplasty with ELUTAX "3" (a), 72 h (b), 10 days (c), 15 days (d) and 30 days (e) after treatment. (f) and (g) correspond to DSA studies during MT: (f) shows right proximal M1 occlusion (*) and (g) shows the recanalization after angioplasty with the DEB.

Patient 2 is a 66-year old man with ischemic stroke of the right MCA due to atheromatous occlusion of the M1 segment, treated with fibrinolysis iv and rescue TM, initially achieving partial revascularization with high-grade residual stenosis, performing angioplasty with ELUTAX "3" and achieving complete revascularization (mTICI 3).

Initially at 24 h after ELUTAX "3", he had MFV measured with TCD of 258 cm/s, decreasing to 103 cm/s at 30 days (see Figures 1 and 3). The patient had a progressive clinical improvement, with National Institute Health Stroke Scale 2 points at 30 days.

Patient 3 is a 41-year old man with finding of preocclusive stenosis in proximal segment of the left MCA after study of recurrent left carotid TIAs. The patient had two to three TIAs daily despite the accurate hemodynamic control and the aggressive medical therapy with dual antiplatelet treatment and high-dose statin. The last two TIAs occurred a few hours before angioplasty with ELUTAX "3", and he has been asymptomatic since then.

Before the treatment, a neurosonologic study was performed, finding in the left MCA an area of narrowing of the flow with aliasing and murmur and MFV of 436 cm/s, consistent with severe stenosis at this level (which required administration of echo-enhancer due to the absence of transtemporal window in all the tests). Immediately after the angioplasty (1 h post-treatment), a MFV reduction to 364 cm/s was shown. In the next controls, a progressive reduction was identified in the MFV, with final MFV of 260 cm/s at 30 days (see Figures 1 and 4). There were no immediate complications in any patient after the procedure. No patient had more ischemic events in the first months after the procedure.

Discussion

ELUTAX "3" is the only CE-marked DEB for the treatment of ICS and its use is indicated in symptomatic, high-grade ICS. Several studies have shown that the restenosis rate is lower with ELUTAX "3" than

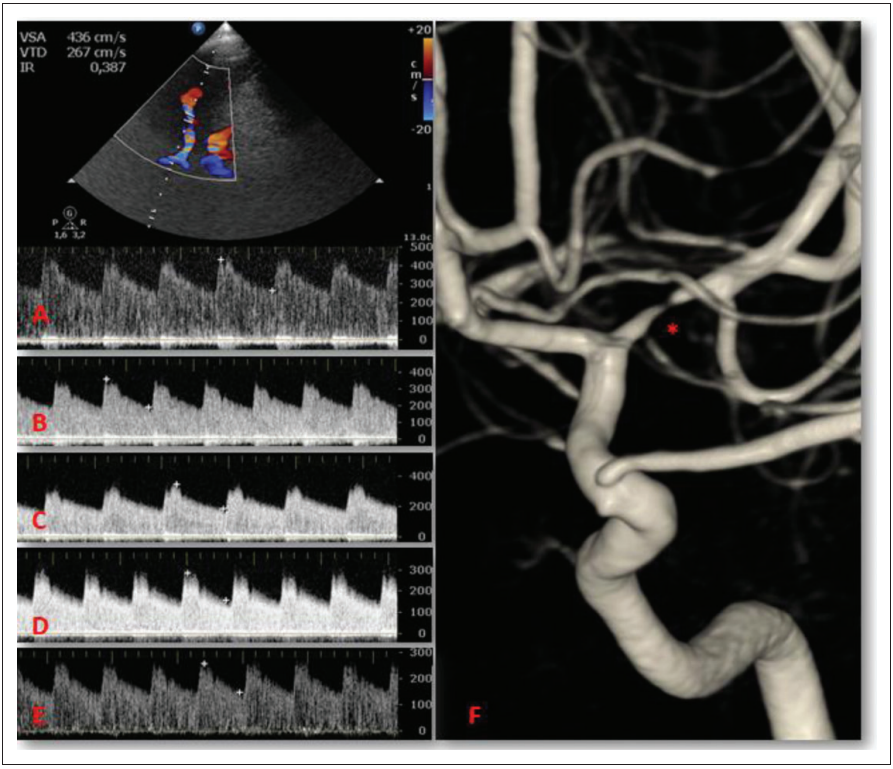

Figure 4. TCD control in Patient 3 before angioplasty with ELUTAX "3" (a), 1 h (b), 24 h (c), 72 h (d) and 30 days (e) after treatment. (f) corresponds to 3D DSA study of the same patient, with critical left MCA stenosis (*).

with conventional metal stents, but they are limited to case series or cohort studies with a small sample size.[1–3,7–10]

As far as we know, this is the first article that describes the time course of hemodynamic changes caused by ELUTAX "3" in the ICS, measured by TCD. We have used this DEB in two patients coming to our site with acute ischemic stroke of the MCA with severe residual ICS and in one patient with high-grade symptomatic drug-resistant stenosis of the MCA.

We have recorded a progressive MFV reduction of ICS, probably due to, on the one hand, the immediate mechanical effect of angioplasty over ICS (enlargement of ICS that we saw in one patient where we could perform TCD before the angioplasty and immediately after it) and, on the other hand, to the antiproliferative endovascular effect occurring over the long term, though it is already evident in the first weeks.

We have also seen better outcomes in the MFV reduction in patients treated during MT with ELUTAX "3" (Patients 1 and 2) than in the patient with chronic ICS (Patient 3). This can be due to the characteristics of the most chronic plaques, possibly with more calcification and more fibroblastic and/or cellular content, which would lead the MFV improvement to be evidenced later. In addition, the latter patient had a higher degree of ICS initially and therefore higher MFV, which can also affect the results.

We have no control TCD at 10 days due to the difficulty for Patient 3 to travel to our site.

In our experience, the use of ELUTAX "3" for the treatment of symptomatic ICS achieves a progressive improvement of stenosis, which becomes evident in the first weeks, to a higher extent in the case of occlusive thrombosis. Larger sample studies, with a longer follow-up time, are required to provide more information about this new device.

Declaration of conflicting interests

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Technical notes & surgical techniques

Treatment of acute occlusion due to intracranial atherosclerosis by angioplasty with ELUTAX "3″ drug-eluting balloon

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A B S T R A C T

Background: Intracranial atherosclerotic disease is an important cause of ischemic stroke due to large vessel occlusion. The acute management of these occlusions is challenging and associates an important risk of complications, especially when mechanical thrombectomy does not achieve vessel recanalization. In this context, the ELUTAX "3″ drug-eluting balloon has been designed for neurological procedures. Nevertheless, there is not enough clinical evidence of this balloon. We report our experience with ELUTAX "3" during mechanical thrombectomy, explaining the technical details and the outcome of the procedure, the subsequent management and the clinical evolution of the patients.

Methods: We report four cases of patients with acute stroke due to intracranial atherosclerosis who were treated with the Elutax "3″ drug-eluting-balloon.

Results: Using the Elutax "3″ we achieved a complete recovery of the occluded arteries caliber (mTICI 3) and a good performance status of our patients on discharge, with the only remarkable complication of a mild asymptomatic subarachnoid bleeding in one of them. The 90-days mRS in those patients was less or equal than 2, and they have not experienced recurrence of the strokes in the long term follow-up.

Conclusions: In our experience, the Elutax "3″ might be a safe and effective therapeutic option in acute large vessel occlusion secondary to intracranial atherosclerotic disease. However, further studies will be necessary to evaluate the efficacy and safety of this device.

1. Introduction

ICAD is a major cause of ischemic stroke due to LVO worldwide, especially in Asian countries, where it is more common than cardioembolic strokes [1–3].

The management of acute LVO secondary to ICAD is technically more challenging and associates greater risk of recurrence of the stroke. Although endovascular therapy has demonstrated to be superior to standard medical treatment in anterior circulation LVOs [4], in ICAD-related strokes MT often leads to re-occlusion, procedure complications and residual stenosis [5].

Following the results of the SAMMPRIS and VISSIT studies, aggressive medical treatment has been established as therapy of choice in chronic symptomatic ICAD [6,7]. However, acute management of ICAD-related strokes is controversial, especially when MT is not able to recanalize the vessel. Different approaches, such as performing an angioplasty with or without placing a stent [8,9] or using glycoprotein IIb/IIIa inhibitors[10–12] have been proposed. Neither of them are exempt of complications, and their effectiveness is not well established. Hence, new treatment strategies have been searched for.

In this context, the ELUTAX "3″ DEB (AR Baltic Medical) has been recently designed. It is a hydrophilic device created specifically for neurological procedures. This balloon has a 360° and 2.2 μg/mm^2 paclitaxel coating and, after placing it in the area of maximum stenosis, it is inflated with a maximum pressure of 6 ATM for at least 30 s, releasing the drug film. Paclitaxel then coats the surface of the stenosis for 12 additional weeks, preventing restenosis thanks to its cytostatic effect on the intimal vascular layer. This is a new therapeutic option with some interesting advantages: the patient does not need dual antiplatelet therapy, comparing to conventional stents, ant the device has a local

Abbreviations: ACA, anterior cerebral artery; ASA, acetyl salicylic acid; ASPECTS, Alberta Stroke Program CT Score; ATM, atmosphere; BA, basilar artery; CT, Computed Tomography; DAPT, Dual anti-platelet therapy; DEB, Drug-elutig balloon; ICA, Internal Carotid Artery; ICAD, Intracranial atherosclerotic disease; ICH, intracranial hemorrhage; LVO, Large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin Scale; MT, Mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institute Health Stroke Scale; TCD, transcranial Doppler

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Table 1
Characteristics of the patients, arterial occlusions, outcome of the procedures, complications, clinical evolution and management.

	Patient 1	Patient 2	Patient 3	Patient 4
Age	70 years old	66 years old	53 years old	75 years old
Gender	Male	Male	Female	Male
Baseline mRS	1	0	0	1
Baseline NIHSS	15	18	10	10
Occlusion	Left M1	ICA + MCA	Right M1	BA
mTICI	3	3	3	3
Complications	No	No	Mild subarachnoid bleeding	No
Anti-platelet therapy	Dual antiplatelet therapy for 3 months	Dual antiplatelet therapy for 3 months	Single antiplatelet therapy	Dual antiplatelet therapy for 3 months
NIHSS at discharge	6	7	0	2
90-days mRS	1	0	0	2

effect on the intracranial stenosis, avoiding systemic complications. Nevertheless, there is not enough clinical practice information yet.

We report our initial experience in four patients with acute ICAD-related LVO stroke, treated with ELUTAX "3″ DEB, explaining the technical details and the outcome of the procedure, the subsequent management and the clinical evolution of the patients (Table 1).

Case 1:. A 70-year-old man with previous left hemispheric ischemic stroke treated by primary MT with mRS 1. He experienced a new stroke of uncertain onset due to occlusion of the left M1 segment with a penumbra area in perfusion-CT throughout the MCA territory and a NIHSS of 15.

Under general anesthesia, the puncture of the femoral artery was performed and a 8F introducer was placed. A NeuronMAX 088 sheath (Penumbra Inc, Alameda, CA, US) was positioned in the petrous segment and a Catalyst 6 catheter (Stryker Neurovascular, Kalamazoo, MI, US) was positioned in the cavernous segment of the ICA performing angiographic series (Fig. 1A). The MT was attempted by contact aspiration with an ACE 68 catheter (Penumbra Inc, Alameda, CA, US), which did not achieve the recanalization of the vessel. Then, after several attempts to cross the occlusion, a Traxcess 0.014″ microguidewire (MicroVention, Tustin, California, US) could be advanced, and a TrevoPRO 18 microcatheter (Stryker Neurovascular, Kalamazoo, MI, US) was positioned distally in the MCA. This difficulty to cross the occlusion led to suspecting it was a LVO caused by ICAD, so, using an exchange guidewire, the ELUTAX "3″ was advanced and an angioplasty was performed directly with an ELUTAX "3" 2.75 × 15 mm DEB. The latter was inflated performing slow gradual increase in pressure inflation, as recommended (1 ATM every 30 s) (Fig. 1B) to reach its nominal pressure of 6 ATM, using a 50% mixture of iodinated contrast and saline (the same solution was used to purge it). In control angiographic series, recanalization of the affected vessel and its branches, mTICI 3, was seen, with persistent severe stenosis in the M1 segment (Fig. 1C). After 24 h, a control brain CT was performed, showing no evidence of ICH, and DAPT was started. The TCD and angio-CT (Fig. 1D) evidenced residual focal stenosis of over 50%. The patient was discharged 16 days later with a NIHSS of 6 points, maintaining DAPT for 3 months. The 90-days mRS was 1. After one year of follow-up, he has not experienced new strokes.

Case 2:. A 66-year-old man, smoker, with hypertension, dyslipidemia and a baseline mRS of 0 points. The patient experienced an ischemic stroke due to a right MCA occlusion in its proximal M1 segment, with a NIHSS score of 18 points, a plain CT with ASPECTS of 5 points and a perfusion CT with a penumbra area of over a 40% of the MCA territory.

After intravenous fibrinolysis with alteplase, and under general anesthesia, a puncture of the femoral artery was performed, placing a 8F introducer. A NeuronMAX 088 sheath was placed in the petrous segment and a Catalyst 6 catheter was placed in the cavernous segment of the ICA, performing diagnostic angiographic series (Fig. 2A). The MT was attempted by contact aspiration with an ACE 68 catheter achieving partial revascularization of the vessel due to high-grade stenosis in the terminal segment of the ICA (Fig. 2B), which in control angiographic series progressed to complete occlusion of the MCA. To cross the occlusion area, a Traxcess 0.014″ microguidewire and a TrevoPRO 18 microcatheter were used, subsequently replaced with a rapid exchange by an ELUTAX "3″ 2.5x10mm balloon. Slow gradual inflation was performed to reach its nominal pressure (6 ATM). Recanalization of mTICI 3 (Fig. 2C) was achieved, with persistent severe stenosis in the origin of the ACA (Fig. 2D). Twenty-four hours later, a control brain CT was performed, without ICH findings, and DAPT was started. The control TCD and the angioCT evidenced residual focal stenosis of 50–69%. The patient was discharged 7 days later with a NIHSS of 7 points, and maintaining DAPT for 3 months. The 90-days mRS was 0, as well as the mRS after one year of follow-up, and he has not experienced new ischemic events.

Case 3:. A 53-year old woman, with hypertension, type 2 diabetes, dyslipidemia, obesity and previous diagnosis of ICAD in the proximal segment of the right MCA in 2016, under follow-up with TCD and angioCT and with persistent subocclusive stenosis, treated with acenocoumarol and ASA. The patient experienced a stroke of uncertain onset on the right MCA territory, with NIHSS score of 7 points and a perfusion CT with penumbra area throughout this territory.

Under general anesthesia, a puncture of the femoral artery was performed, obtaining angiographic series, which evidenced severe stenosis in the right supraclinoid ICA and the origin of both the ACA and the MCA (Fig. 3A). The proximal segment of the MCA was accessed through a tri-coaxial system comprising a Neuron 6F 90 cm catheter (Penumbra Inc, Alameda, CA, US), a Sofia 5F 115 cm intermediate catheter (MicroVention Inc, Aliso Viejo, CA, US) and an Echelon 0.017″ 150 cm catheter (Medtronic, Dublin, Ireland). For intracranial navigation of the system, a Traxcess 0.014″ microguidewire was used. The microcatheter exchange was performed using a Traxcess Docking wire adapter (MicroVention Inc, Aliso Viejo, CA, US) of 115 cm, positioning on the supraclinoid ICA stenosis an ELUTAX "3″ balloon of 2.5x10 mm (Fig. 3B), and dilating it slowly to its nominal pressure (6 ATM). A Gateway balloon (Stryker Neurovascular, Kalamazoo, MI, US) of 1.5 mm was then progressed to distal M1 segment and three progressive dilations were performed proximally to the origin of the MCA. The final controls evidenced complete recovery of the vascular caliber of the MCA and the ICA (Fig. 3C), with severe residual stenosis in the origin of the ACA. Twenty-four hours later a brain CT was performed, which evidenced a subarachnoid bleeding in the sulci of the right convexity and no signs of restenosis in the angioCT (Fig. 3D). Antiplatelet therapy was started with ASA 100 mg and the patient was discharged with NIHSS of 0, maintaining treatment with simple antiaggregation and removing anticoagulation. The 90-days mRS was 0. After one year of follow-up, asymptomatic restenosis was seen in a control angioCT, starting DAPT, but she did not experience new strokes.

Case 4:. A 75-year old man, smoker, with hypertension, diabetes and a

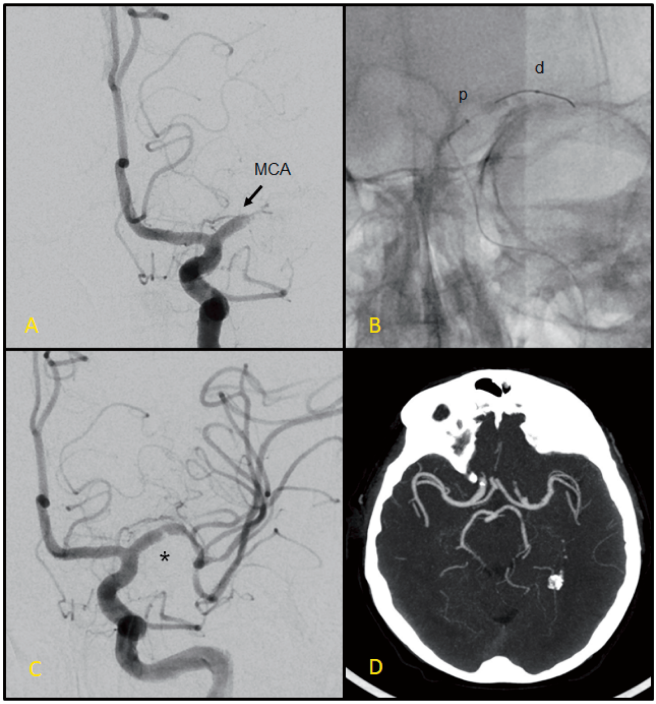

Fig. 1. A: PRE-ANGIOPLASTY Selective digital subtraction arteriography of the left ICA in anteroposterior view. Occlusion in segment M1 of the MCA. B: ANGIOPLASTY Image of arteriography without subtraction in anteroposterior view. After progressing through the occlusion, the angioplasty balloon is partially inflated, observing its proximal (p) and distal (d) mark. C: POST-ANGIOPLASTY Recanalization of the MCA, with persistent severe focal stenosis in segment M1 (*). D: CONTROL ANGIOCT. Recanalized MCA with moderate-severe residual stenosis.

baseline mRS 1, who experienced a stroke about 12 h before due to complete occlusion of the BA in its middle third and previous occlusion of right V4, with a NIHSS score of 10 points.

Under general anesthesia, a NeuronMAX 088 sheath was placed in the left V1 and diagnostic angiographic series were performed (Fig. 4A). An attempt was made to perform MT by aspiration with ACE 68 catheter, without achieving any recanalization after two contact aspirations. A Traxcess 0.014″ microguidewire was used to cross the occlusion area and, after checking the permeability of the distal branches by contrast injections with a microcatheter, a Tigertriever 4x32 mm stent (Rapid Medical, Yokneam, Israel) was placed. A run was performed together with simultaneous local aspiration (Fig. 4B), achieving the opening of the intracranial stenosis and evidencing a distal thrombus that occluded the left P1 segment (Fig. 4C). An ELUTAX"3″ balloon of 3x10 mm was positioned centered in the stenosis and inflated slowly to its nominal pressure (6 ATM), achieving the recovery of the vascular caliber. Then, the stenosis point was crossed with an ACE 68 aspiration device to the level of BA bifurcation. After one contact aspiration, the posterior circulation could be completely recanalized (Fig. 4D). A load of 250 mg intravenous ASA was administered during the procedure. Twenty-four hours later, a control brain CT was performed, which evidenced infarction in the right hemicerebellum, with no ICH findings, and DAPT was started. The patient was discharged 7 days later with NIHSS of 2 points. The 90-days mRS was 2. Ten months after the procedure, he has not experienced neither restenosis nor focal symptoms.

2. Discussion

Acute treatment of ICAD-related strokes is still controversial and challenging. Vessel re-occlusion during MT is a common complication, and studies have not demonstrated the superiority of glycoprotein IIb/IIIa inhibitors or angioplasty alone or with self-expanding stents over other treatments. On the other hand, these therapies have an important risk of intracranial bleeding, vessel rupture or stent thrombosis. Therefore, new therapies have been searched for, some of them following the results of coronary flow studies, since coronary artery occlusions are usually caused by local thrombosis of atherosclerotic vessels, with a similar mechanism of intracranial atherosclerotic-related occlusions.

Considering primary percutaneous transluminal coronary angioplasty has the highest recommendation in acute myocardial infarction, and the complications related to stent-retriever MT, Yang et al. have compared primary angioplasty and/or stenting with conventional stent-retriever MT. They have reported favorable functional outcomes and lower asymptomatic ICH rates in the angioplasty and/or stenting group [13]. However, most of the patients in this group had an ICA occlusion and better collateral flow. Hence, these results may not be applicable to MCA occlusions.

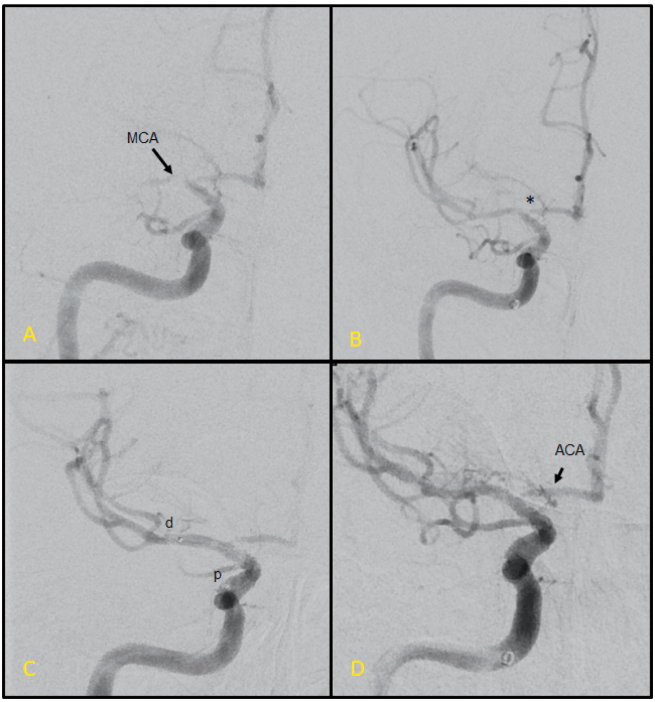

Fig. 2. A: PRE-TREATMENT Selective digital subtraction arteriography of the right ICA in anteroposterior view. Occlusion in the origin of the MCA. B: POST-ASPIRATION. After a run of mechanical aspiration, severe focal stenosis was seen in the terminal segment of the ICA (*), that affects the origin of the MCA and ACA. C: ANGIOPLASTY Angiographic series following angioplasty with ELUTAX "3″ balloon in segment M1 of the MCA and terminal segment of the right ICA. The balloon is deflated and the distal (d) and proximal (p) mark can be seen. D: POST-ANGIOPLASTY Complete recovery of the MCA caliber, with persistent severe stenosis in the origin of the ACA.

Bradley et al. have proposed the use of balloon-mounted stents as an alternative to self-expanding conventional stents, due to their advantage of a swift single pass. Nevertheless, in their series an important percentage of patients suffered *peri*-procedural complications, including symptomatic ICH and stent thrombosis. Their results were, therefore, worse than those seen for patients undergoing MT for LVO secondary to embolic disease [14].

In randomized studies on coronary flow, a reduction in the restenosis and clinical event rates has been shown with the use of paclitaxel-eluted balloons compared to conventional balloons [15]. Thus, the use of these devices in the intracranial circulation has been considered for the treatment of chronic ICAD, including the ELUTAX "3″ DEB.

As we know, there is evidence of the use of other DEBs as secondary prevention in patients with symptomatic ICAD [16]. Gruber et al. have been the first to compare ELUTAX "3″ to the Wingspan stent (Stryker Neurovascular, Kalamazoo, MI, US) in symptomatic ICAD, obtaining better outcomes in terms of recurrence of stroke/TIA or restenosis, without any statistically significant differences in evolution, complications or mortality [17]. However, to our knowledge, our patients are the first patients with ICAD-related LVO strokes treated with the ELUTAX "3" DEB in an acute phase.

Our preliminary experience with these four cases shows that it is an easy navigation device, which reduces intimal hyperplasia, the main cause of restenosis in patients with ICAD. A tri-axial support system was used in all cases since the initial intention was to perform a conventional MT. Then, once the diagnosis of ICAD-related stroke was made, a microcatheter was first advanced distal to the lesion to perform an initial angiogram to assess the vascular anatomy of major branch-vessel as well as determine the length of the lesion to be treated. The size and length of the balloon were chosen based on the characteristics of the lesion. The entire lesion length should be covered by the balloon, and the diameter should be smaller than the normal vessel size. Then, over an exchange microguidewire, the Elutax "3″ was easily advanced and positioned to cover the stenosis, slowly inflated to its nominal pressure. Besides, once the purge of the balloon is done correctly, the visibility is excellent.

These procedures allowed us to achieve a mTICI 3 recanalization in all the patients, with a residual stenosis inferior to 70% and a good performance status on discharge, which are all of factors of good prognosis to prevent restenosis and future ischemic events. In addition, the only remarkable complication was a mild asymptomatic subarachnoid bleeding in one of the patients. As for mid-term results, the mRS after 90 days for those patients was less than or equal to 2, and after one year of follow-up they have not reported new ischemic events.

On the other hand, it must be highlighted that, using the Elutax "3″ DEB, subsequent DAPT is not required. Thus, in patients receiving alteplase it does not increase the risk of ICH. However, in our case we maintained DAPT for at least three months in three of the patients due to the lack of experience with this new device and because of the persistent, at least 50%, residual stenosis.

3. Conclusions

Based on the results described, we consider this might be a therapeutic option to take under consideration in acute LVO secondary to

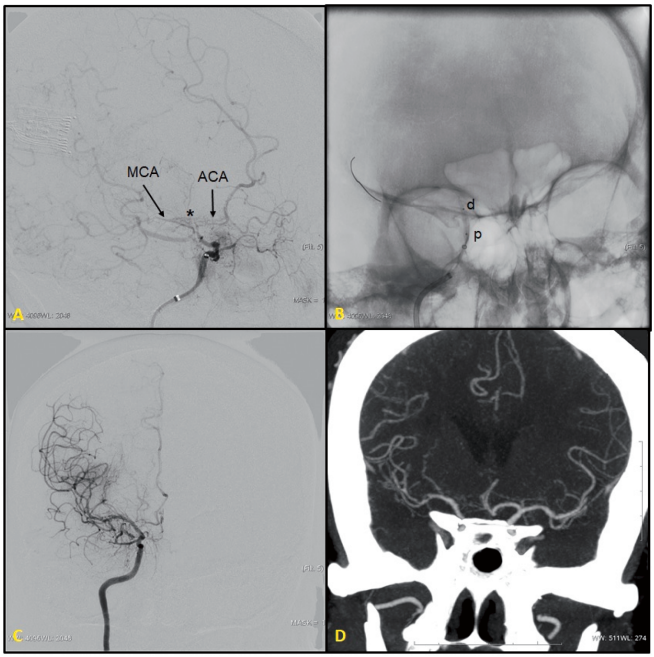

Fig. 3. A: PRE-TREATMENT Selective brain arteriography of the right ICA. Subocclusive stenosis of the supraclinoid ICA with minimum passage of filiform contrast to MCA and ACA. Moyamoya type arteriolar network around the bifurcation (*). B: ANGIOPLASTY Once the stenosis has been crossed an ELUTAX "3" balloon of 2.5x10 mm is centered in the maximum stenosis point (p, proximal mark; d, distal mark). C: POST-ANGIOPLASTY Recovery of the vascular caliber in the MCA and supraclinoid ICA, with severe residual stenosis of the origin of ACA. D: CONTROL ANGIOCT No restenosis is seen in the segments treated. Adequate compensation of the vascular territory dependent on the right ACA from the left side.

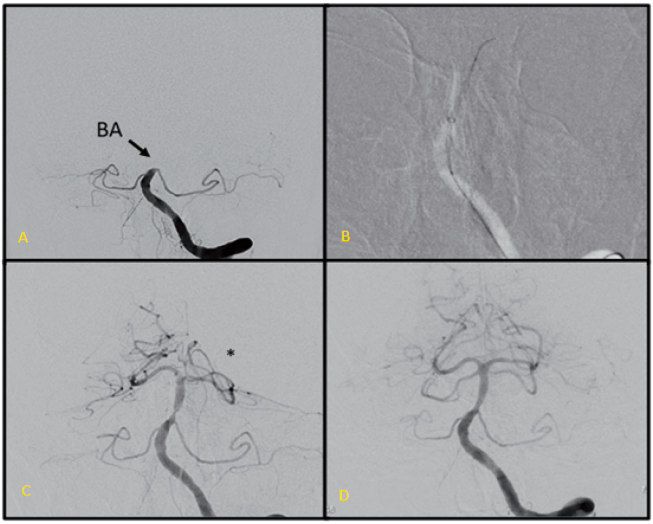

Fig. 4. A: PRE-TREATMENT Selective cerebral arteriography of the left vertebral artery. Complete occlusion of the middle third of the BA. B: After performing two contact aspirations, no recanalization was achieved, which increased the suspicion of intracranial stenosis. A Tigertriever stent extractor was placed, centered in the occlusion together with simultaneous aspiration by ACE 68. C: POST-THROMBECTOMY Recanalization of the basilar artery is seen, together with significant stenosis of the middle third due to atheromatous stenosis and distal occlusion of the proximal segment of the left posterior cerebral artery (P1) (*). D: FINAL CONTROL Complete recanalization of the posterior circulation and recovery of vascular caliber after two angioplasties with ELUTAX "3" coated balloon in the intracranial stenosis of the BA.

ICAD, when MT is not effective or possible. However, further studies with a higher number of patients are required to evaluate the efficacy and safety of this device.

4. Contributorship statement

All the authors from the author list above have contributed to the design and the writing of this manuscript, have revised it critically for important intellectual content, have given the final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Blanca Serrano Serrano: Writing - original draft, Visualization. **Francisco Hernández Fernández:** Writing - review & editing. **Nicolás López Hernández:** Writing - review & editing, Supervision. **Elena Elvira Soler:** Writing - review & editing. **Giorgio Barbieri:** Writing - review & editing. **Juan D. Molina Nuevo:** Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REVIEW

Device profile of different paclitaxel-coated balloons: Neuro Elutax SV, Elutax '3' Neuro and SeQuent Please NEO for the treatment of symptomatic intracranial high-grade stenosis: overview of their feasibility and safety

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ABSTRACT

Introduction: Intracranial atherosclerotic disease (ICAD) is highly prevalent and probably the most common cause of stroke worldwide. Despite best medical treatment (BMT), the rate of recurrent stroke in symptomatic ICAD patients is elevated, especially in those with high-grade stenosis. Thus, alternative treatment options are needed. So far, endovascular ICAD treatment has been considered a second-line therapy. However, recent progress in the endovascular acute stroke treatment challenges this issue. Drug-coated balloon (DCB) – percutaneous transluminal angioplasty (PTA) represents a promising alternative to BMT alone.

Areas covered: In this review, current clinical studies on paclitaxel-coated DCB-PTA in symptomatic high-grade ICAD patients will be presented and discussed. Furthermore, technical profile of the different paclitaxel-coated DCB, which has been used for intracranial use (Neuro Elutax SV, Elutax '3' Neuro, and SeQuent Please NEO) are being presented.

Expert opinion: Despite limited data and its experimental (off-line) use, DCB-PTA has been demonstrated to be feasible and safe in selected ICAD patients with symptomatic high-grade stenosis. DCB-PTA offers several advantages compared to alternative endovascular therapy option as well as BMT alone. Consequently, DCP-PTA might be a promising candidate for the future armamentarium in ICAD treatment.

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Drug-coated balloon; Elutax '3' Neuro; intracranial atherosclerotic disease; Neuro Elutax SV; paclitaxel; percutaneous transluminal angioplasty; ischemic stroke; SeQuent Please NEO

1. Introduction

1.1. Intracranial atherosclerotic disease – a medical treatment challenge

Intracranial atherosclerotic disease (ICAD) is highly prevalent and is probably the most common cause of stroke worldwide since the incidence in the Asian, Hispanic and African populations is high [1,2]. It has been shown that ICAD patients with high-grade stenosis (≥70–99%) are at increased risk of recurrent stroke [3,4]. Current guidelines recommend an adequate antiplatelet treatment combined with consequent treatment of vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, and nicotine abuse [5]. Despite this treatment regimen, the stroke recurrence rate remains disappointingly high, as the GESICA or WASID studies have shown [4]. There is therefore a need for other treatment options in symptomatic ICAD patients. The endovascular treatment of ICAD patients has a long tradition and dates back to the early 1980s [6]. Despite promising results from several mono-center studies, case series and cohort studies either using percutaneous transluminal angioplasty (PTA) alone or percutaneous angioplasty with stenting (PTAS), the large-randomized SAMMPRIS trial comparing PTAS with the self-expanding Wingspan stent system (StrykerNeurovascular, Fermont, CA, USA) with aggressive medical treatment failed to show the effectiveness of PTAS in symptomatic ICAD patients [7]. Furthermore, the VISSIT trial that compared PTAS using the balloon-mounted Pharos Vitesse stent system (Codman&Shurtleff, Raynham, Massachusetts, USA) compared to best medical treatment (BMT) alone was prematurely terminated and demonstrated the inferiority of PTAS in ICAD patients [8]. These results are mainly due to the high peri-procedural complication rate in the intervention arms (14.9% in the SAMMPRIS and 36.2% in the VISSIT trial, respectively) [7,8]. Recently, these data were challenged by the results of the post-marketing, mono-cohort, multi-center WAEVE trial that looked at peri-procedural complications within 3 days after PTS using the Wingspan Stent system demonstrating a complication rate of 2.6% being significantly lower than SAMMPRIS or the VISSIT trial, therefore comparable to BMT alone [9]. These promising results are mainly due to the rigorous selection criteria and the fact that only comprehensive stroke centers with abundant experience in endovascular ICAD treatment could participate in this trial.

1.2. Mid- to long-term complications in PTA and PTAS

Besides the above-mentioned limitations there are also mid- to long-term complications in both PTA and PTAS, respectively, concerning the restenosis rate. This issue is well known and has been described in several series for both PTA and PTAS with recurrent stenosis rate of up to 30% [10–12]. The main cause of restenosis is neointimal hyperplasia (NIH).

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Article highlights

- Intracranial atherosclerotic disease (ICAD) is highly prevalent and probably the most common cause of stroke worldwide.
- Current guidelines recommend the best medical treatment (BMT) as first-line therapy. Despite BMT, the stroke recurrence rate is elevated in symptomatic ICAD patients with high-grade stenosis.
- Drug-coated balloon percutaneous trans-luminal angioplasty (DCB-PTA) might offer an efficient alternative treatment option.
- Despite its current experimental use, DCB-PTA is feasible and safe in well-selected ICAD patients.
- Neuro Elutax SV and SeQuent Please NEO have been proven to be feasible and safe in ICAD patients with symptomatic high-grade stenosis.
- Large randomized trials are needed to prove the concept that DCB-PTA is effective in ICAD patients.
- To our opinion, DCB-PTA has the potential to play an important role in the endovascular treatment of ICAD.

Both PTA and PTAS lead to (micro-) lesions of the endothelium and the intima portion of the vessel wall due to the mechanical stress during dilatation. These lesions induce a complex cascade of repair mechanism that finally results in excessive smooth muscle and connective tissue proliferation. To overcome this major disadvantage of PTA and PTAS, several anti-proliferative, as well as immune-modulatory agents, have been evaluated [13]. The highly lipophilic anti-proliferative microtubule-stabilizer paclitaxel has been proven to be effective inhibitor of NIH in vitro as well in vivo [14]. Clinical evidence for the efficacy of drug eluted stents (DES) as well as drug-coated balloon (DCB) is mainly derived from the peripheral endovascular field. Feasibility, safety, and efficacy have been widely shown in interventional cardiology studies for both DES and DCB, respectively [15,16]. Recent encouraging results from the Basket Small II trial demonstrated superiority of DCB (SeQuent Please and SeQuent Please NEO) compared to DES in *de novo* small coronary artery disease [17].

Currently, data on the use of DES as well as DCB in neurovascular patients are limited. Promising data on DES has been published in the early 2000 [18–21], but the interest on PTAS and PTA dramatically decreased after the negative SAMMPRIS and VISSIT trial [22].

2. Drug-coated balloon in the neurovascular field – a potential candidate device for ICAD treatment

Given the high incidence of ICAD worldwide, as well as the high risk of recurrent strokes – especially in ICAD patients with symptomatic high-grade stenosis – there is a need for new treatment concepts in addition to BMT alone [23]. DCB might be a real alternative treatment modality to BMT alone and offers several advantages compared to PTAS [24,25]. PTA in ICAD patients has been shown to be feasible and safe due to the advance of material technology over the last two decades. Furthermore, the introduction of submaximal angioplasty technique that intends to prevent PTA from feared vessel dissection and the so-called 'snow-plow' effect (the involuntary occlusion of perforator vessel by plaque dislodgment during PTA) [26] increased peri-procedural safety. In addition, DCB-PTA enables a positive remodeling of the treated vessel wall and keeps natural vessel vasomotion compared to PTAS. There is no foreign material left in the vessel lumen compared to PTAS, thus preventing long-term inflammatory reactions caused by the foreign material. DCB-PTA leads to a more efficient and homogeneous drug distribution over the treated vessel wall compared to DES that covers only 15% of the vessel lumen with drug due to stent-strut geometry [27]. There are no stent-related limitations for additional treatment. Since there is a low risk of incomplete neointimal healing and delayed endothelialization in DCB-PTA compared to DES [28], the duration of dual antiplatelet therapy (DAPT) could be shortened in patients treated with DCB-PTA compared to patients treated with DES as recommended for cardiac patients with 1 month [29]. Due to the high risk of intracranial hemorrhage in the neurovascular field, long-term and aggressive anti-aggregation should be avoided. Making DCB-PTA an even more attractive treatment option since there are many ICAD patients with additional co-morbidities such as atrial fibrillation. Nevertheless, the post-procedural antiplatelet therapy in DCB-PTA treated patients has to be elucidated for the neurovascular field since there is no data available.

Economically, DCB-PTA might be more cost-effective compared to PTA or PTAS using DES as it has been demonstrated for the endovascular treatment of femoro-popliteal artery disease [30]. Accordingly, providing another advantage of DCB-PTA technique.

The disadvantages of DCB-PTA are the potential early recoil and a larger degree of post-procedural residual stenosis compared to DES.

Currently, all data regarding DCB-PTA in ICAD patients correspond to paclitaxel-coated DCB-PTA systems. To the best of our knowledge, there are no publicaly available data concerning other drug-coating, such as Sirolimus – coated balloons.

3. Current studies on paclitaxel-coated balloon-PTA in the neurovascular field

In 2018, first reports on DCB-PTA for *de novo* symptomatic high-grade ICAD patients were published (Table 1). We retrospectively compared a cohort of symptomatic high-grade ICAD patients either treated with the first CE-certified DCB for neurovascular use (Neuro Elutax SV) (n = 8) or treated with the Wingspan – Stent System (n = 11) with a median follow-up of 9.5 and 10.0 months, respectively [31]. The results showed a significantly lower symptomatic and asymptomatic recurrence rate with a lower complication rate in DCB-treated patients compared to Wingspan stent patients. Another study reported excellent feasibility and safety on a mono-cohort of 10 symptomatic ICAD patients treated with the SeQuent Please NEO (b.braun, Melsungen, Germany) DCB – a latest coronary DCB-PTA system [32]. In both studies, submaximal angioplasty technique was performed for balloon deployment. Of note, we did not perform any pre-dilation using a conventional balloon PTA system. A third Chinese study on symptomatic high-grade *de novo* ICAD patients demonstrated good results in 30 patients treated with SeQuent Please (b. braun Melsungen, Germany) – the previous DCB-PTA model of

Table 1. Summary of current studies of paclitaxel-coated balloon (pDCB)-PTA in symptomatic high-grade stenosis.

Publication	N. of DCB treated patients	Type of study	DCB-PTA system	Follow-up period in months	DCB deployment technique	Post-procedural stenosis degree	Peri-procedural complications	Asymptomatic restenosis	Symptomatic restenosis
Gruber P. et al. JNIS 2018 [31]	8	Retrospective comparison of pDCB-PTA vs Wingspan-PTAS	Neuro Elutax SV (Aachen Resonance)	9.5	Submaximal angioplasty	37.5% (20–60)	0	1 (13%)	0
Gruber P. et al. JNIS 2018 [32]	10	Retrospective monocohort study	Sequent Please NEO (b.braun)	3	Predilatation with conventional	50% (45–53)	0	0	0
Han J et al. JNIS 2018 [33]	30	Retrospective monocohort study	SeQuent Please (b. braun)	9.8	Submaximal angioplasty	20% (10–40	2 (6.5%)	1 (3.5%)	0

pDCB, paclitaxel drug-coated balloon; N., number; PTA, percutaneous transluminal angioplasty; PTAS, percutaneous transluminal angioplasty with stenting.

the SeQuent Please NEO [33]. In contrast to our reported practice, all stenoses were pre-dilated with a Gateway balloon.

Recently, another study demonstrated the successful use of paclitaxel-coated DCB-PTA (SeQuent Plaese, b.braun, Melsungen, Germany) in 14 patients with non-acute total occlusion of the middle cerebral artery. In contrast to our studies, DCB-PTA was performed after predilation with a conventional balloon [34]. DCB-PTA has also been successfully used in intracranial restenosis of ICAD patients initially treated with PTAS [35].

Current data suggest that the use of DCB-PTA in selected patients with symptomatic high-grade intracranial stenosis is safe and feasible. However, further randomized studies are required to also prove its efficacy.

4. Profile of the different paclitaxel-coated balloons

4.1. Neuro Elutax SV

One retrospective study reported on the use of the Neuro Elutax SV (Aachen Resonance, Aachen, Germany) being the first CE-certified DCB for neurovascular purpose [36]. Neuro Elutax SV DCB is a 360-degree Paclitaxel-coated DCB (2.2 µg/mm^2) consisting of a complex three-layer matrix that allows uniform drug release and prevents from the rubbing effect – the friction of losing Paclitaxel during the passage throughout the body vessels by a seal layer. Additionally, there is a target deposition modus (TDM) ensuring that paclitaxel will only be released at a certain inflation pressure (6 atm) and only when there is contact to the vessel. The recommended balloon inflation time is 30 s. In certain circumstances, we extend it to a maximum of 60 s. There is no pre-dilation needed.

The Neuro Elutax has a 0.017-inch tip profile and is available from length sizes of 10 to 30 mm as well as diameters ranging from 1.5 to 4 mm. The working length is limited to 135 cm, which has to be extended at least to 150 cm to reach more distant lesions. Neuro Elutax has a 5F-guiding catheter as well as 0.014-inch guidewire compatibility. This DCB is navigable, flexible and offers a good pushability. This DCB-PTA system has a hydrophilic shaft coating. In our hands, Neuro Elutax SV has proven to be effective in more proximal lesions. However, in distal and very tortuous vessels it requires some technical improvements since the balloon is to a certain amount rigid and the PTA-catheter system is only available in working length of 135 cm. Unfortunately, the CE certificate has expired and is currently under reevaluation.

4.2. Elutax '3' Neuro

The Elutax '3' Neuro (AR Baltic Medical, Vilnius, Lithuania) DCB-PTA system is currently the only available CE-certified DCB-PTA system for neurovascular use representing a kind of successor to the Neuro Elutax SV [37]. This DCB has a modified drug-coating surface layer with a three-dimensional dextran-paclitaxel formation. This specific coating intends to minimize drug-loss during the DCB navigation through the body vessels. Similar to Neuro Elutax SV, this possesses also a TDM, allowing Paclitaxel to be released only upon contact with the vessel wall and at a certain balloon inflation pressure (6 atm). The recommended balloon inflation time is 15 s and thus shorter compared to Neuro Elutax SV (30 s) or SeQuent Please NEO (30 s). Similar to Neuro Elutax SV no pre-dilation is necessary.

The Elutax '3' Neuro is compatible with 5F guiding catheters and 0.014-inch guidewires. The Elutax '3' Neuro is in various balloon sizes available: nominal diameter from 1.5 to 4.0 mm as well as nominal balloon length from 10 mm to 40 mm. Furthermore, this DCB-PTA system has a hydrophilic shaft coating and is also available in a working length of 144 cm that represents an advantage to reach distal lesions. Currently, clinical data of Elutax '3' Neuro are very limited.

4.3. SeQuent Please NEO

SeQuent Please NEO (b.braun, Melsungen, Germany) is a latest-generation coronary DCB-PTA [38]. The coating of SeQuent Please NEO consists of a complex, polymer-free Paclitaxel and Iopromide matrix (3 µg/mm^2). Similarly to Neuro Elutax SV, SeQuent Please NEO enables a rapid drug transfer from the balloon matrix to the vessel wall within 30 s. No pre-dilation is needed.

This DCB is also available in various balloon sizes. Therefore, the balloon length ranges from 10 to 40 mm and the balloon

diameter from 2.0 to 4.0 mm. SeQuent Please NEO is compatible with 5F-guiding catheters as well as 0.014-inch guidewires. This DCB-PTA has a hydrophilic shaft coating and the working length is up to 145 cm, which enables reaching more distant lesions. The navigability, the flexibility, and pushability of this DCB are good. In our hands, more distant lesions as well as more tortuous vessel could be treated using the SeQuent Please NEO DCP-PTA system. Additionally, the SeQuent Please NEO has recently proven its efficacy in small (≤3 mm) coronary artery disease [17].

5. General technical considerations

DCB-PTAs are usually performed under general anesthesia. Prior to the intervention, patients have to be under DAPT (aspirin and clopidogrel). Activated clotting time (ACT) test is performed and body weight-adjusted bolus of intravenous heparin is given prior to the procedure.

Intervention is recommended to be performed on a biplane angiography system. We prefer to gain access via the right common femoral artery using a 7F long-sheath. Rarely is a brachial access used for DCB-PTA – especially in posterior circulation stenosis – but this has so far been without any clinical evidence.

Prior to the intervention, we perform a four-vessel angiogram to assess the general vessel conditions and in particular the targeted vessel lesions. Under fluoroscopic guidance, we prefer to advance a 6F-guiding catheter for the anterior circulation in the cervical segment of the internal carotid artery and for the posterior circulation in the proximal segment of the subclavian artery. The targeted lesion will be explored using a 0.014-inch guidewire. The tip of the guidewire will be positioned distal to the lesion. In monorail technique, the DCB-PTA system will be advanced and precisely centered over the target lesion. We do not perform pre-dilation and we do not use any kind of protection device. During the angioplasty maneuver, the DCP will be slowly inflated performing submaximal angioplasty technique [26], thus preventing from dissection and perforator branch occlusions ('snow-plow' effect). Before deflation, the DCB stayed submaximally inflated for 30 s. We do always a control angiogram after angioplasty to assess the immediate effect of DCB. If it is needed, we repeat the DCB-PTA maneuver.

Feared adverse events of the DCB-PTA technique are early recoil of the stenosis that would need additional DCB-PTA runs or bailout stenting, as well as dissection of the vessel or distant embolic ischemic events or perforator ischemic events due to mechanical manipulation of the atherosclerotic lesion [39]. Thus, submaximal angioplasty technique intends to diminish these adverse events as shown by Dumont et al. with a 5% major periprocedural complication rate [26]. But, as already stated by McTaggart, a problem of DCB-PTA will be the balance of submaximal angioplasty and the attempt of whole drug coverage of the vessel wall [25], leading to a less effective drug delivery and a potential higher restenosis rate.

Besides these potential major adverse events of DCB-PTA, generic complications of endovascular therapy such as access site complications (i.e. groin hematoma around 1–9%, dissection, fistula) contrast agent reaction as well as allergic reactions can occur [40].

6. Conclusion

Given the high incidence of ICAD worldwide and the high risk of stroke recurrence despite BMT alone, there is a need for alternative treatment options. Recent data suggested that DCB-PTA using a paclitaxel-coated DCB is feasible and safe in selected ICAD patients with symptomatic high-grade stenosis. Therefore, DCB-PTA might be a promising candidate for the future endovascular treatment alternative in patients with symptomatic high-grade stenosis.

Of note, these first clinical experiences of DCB-PTA in symptomatic ICAD patients are still rather preliminary and has to be currently regarded as experimental. However, given the promising results and high potential of this technique, more research on that topic should be carried out in order to strengthen the evidence of the efficacy of that technique. Thus, large randomized controlled trials should be prompted to prove the efficacy of DCP-PTA in this setting.

7. Expert opinion

These first studies on DCB-PTA show feasibility and safety in patients with symptomatic high-grade ICAD. Since the rapid technological and clinical advances in endovascular acute stroke treatment in the last decade, there is a growing interest on ICAD treatment. However, the dogma of conservative treatment of ICAD patients as first-line therapy might only be challenged if the efficacy of DCB-PTA is proven. Therefore, large randomized studies are needed to clarify this important question. In view of the positive results of the WAEVE trial, it might be realistic to expect that endovascular ICAD treatment will regain popularity. The key areas are the technological improvement of DCB-PTA systems to adapt to the specific needs of the neurovascular field. An important issue is the flexibility of the DCB that facilitates the navigability of these DCBs. Further, the working lengths for the DCB-PTA systems have to be adapted for intracranial use, i.e. preferably longer than ≥145 cm.

As certain concerns have recently been raised about paclitaxel-coated devices, alternative coating strategies such as other neointimal antiproliferative drugs (e.g. Sirolimus, Zotarolimus, or Everolimus) and coating matrices for intracranial application need to be evaluated. In addition, little data are available to date on the safety of drug-coated devices in brain tissue. Further pre-clinical and clinical data are needed.

Future research could help establish DCB-PTA as a real treatment option for the neurovascular field – especially for ICAD. In addition, this research will contribute to a better understanding of the mechanism effect of DCB treatment in the cerebral vasculature and improve the clinical selection of patients. Therefore, next trials in this area should answer the question whether DCB-PTA in symptomatic ICAD patients will be efficient. We believe – given the high prevalence of ICAD and the high rate of stroke recurrence despite the BMT – that endovascular procedures for the treatment of

ICAD patients will regain popularity. Since DCB-PTA treatment in ICAD patients is still experimental in nature, it remains to be elucidated whether DCB-PTA – especially paclitaxel-coated DCB – will become established as a standard treatment in 5 years. Nevertheless, the DCB-PTA technique is a very promising candidate for the future endovascular armamentarium of ICAD treatment.

7.1. Five-year view

Due to the high incidence of ICAD worldwide (particularly in Asia) and the additional high risk of recurrent ischemic events despite BMT, alternative treatments are needed for symptomatic ICAD patients. Despite the currently rather experimental character of DCB-PTA in symptomatic ICAD patients, we believe that DCB-PTA will be a real treatment option and accordingly a promising candidate for the future armamentarium of ICAD treatment. However, it might take some time before the concerns about endovascular therapy in ICAD patients are partially or completely resolved. However, DCB-PTA offers several advantages over PTAS, such as no foreign bodies remaining in the vascular lumen, uniform drug coverage of the entire vessel lumen, positive remodeling, and even a shorter DAPT duration.

Of course, despite the promising results of several small studies, large randomized controlled trials are mandatory to shed light on the effectiveness of this DCP-PTA technique in ICAD patients. In addition, the current DCB-PTA systems require additional modifications in navigability, pushability and working length in order to adapt these systems perfectly to the specific needs of the neurovascular field, since the vessels are usually tortuous and technically demanding. There is also a need to define who among symptomatic ICAD patients will benefit most from such endovascular therapy. Possibly symptomatic ICAD patients with hemo-dynamically relevant stenoses as well as patients with unstable plaques could be good candidates for this endovascular treatment [1].

In conclusion, preliminary data have demonstrated the feasibility and safety of DCB-PTA in small cohort studies. Despite its current rather experimental character, DCB-PTA offers several advantages over PTAS and BMT alone, hence DCB represents a promising candidate for the future ICAD treatment.

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ORIGINAL RESEARCH

Neuro Elutax SV drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience

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ABSTRACT

Background Intracranial atherosclerotic disease is a well-known cause of ischemic stroke. Following the SAMMPRIS trial, medical treatment is favored over stenting. Drug-eluting balloons (DEB) are widely used in coronary angioplasty, showing better results than bare-surface balloons. There is little evidence of DEB employment in intracranial stenosis, especially of paclitaxel-eluted balloons (pDEB). The Neuro Elutax SV (Aachen Resonance) is the first CE certificated pDEB for intracranial use.

Objective To compare pDEB Neuro Elutax SV (ElutaxDEB) with the Wingspan/Gateway stent system (WingspanStent).

Materials and methods A single-center, open-label, retrospective cohort study of 19 patients with symptomatic atherosclerotic intracranial high-grade stenosis treated with either ElutaxDEB or WingspanStent from a tertiary stroke center in Switzerland.

Results Eight patients (42%) received ElutaxDEB. Median clinical follow-up was 10 months for the WingspanStent and 9.5 months for ElutaxDEB (P=0.36). No differences were found in the clinical baseline characteristics, with a median stenosis grade of 80% for the WingspanStent and 81% for the ElutaxDEB (P=0.87). The compound endpoint 'ischemic re-event and/or restenosis' was significantly lower for ElutaxDEB (13% vs 64%; P=0.03, OR 0.08 (95% CI 0.007 to 0.93; P=0.043) than for the WingspanStent.

Conclusions The ElutaxDEB may be a promising alternative treatment for patients with symptomatic high-grade intracranial stenosis showing a significantly lower rate of ischemic re-events or restenosis in comparison with the WingspanStent-treated patients with a similar safety profile. Further studies will be needed to definitively elucidate the role of pDEB in the management of symptomatic intracranial high-grade stenosis.

INTRODUCTION

Intracranial atherosclerotic disease (ICAD) is a well-known cause of stroke and is responsible for approximately 5–10% of all strokes and up to 50% in the Asian population, with an estimated 1-year stroke-free survival rate of 88%.[1] Despite best medical care, the annual risk of recurrent stroke in symptomatic ICAD is around 9–12%.[2] Therefore, ICAD has to be regarded as a serious medical condition with a high risk of strokes. In order to improve the poor outcome in ICAD, endovascular revascularization using percutaneous transluminal angioplasty with stenting (PTAS) was developed in the 2000s.[3 4] As a result of the SAMMPRIS trial[2], medical treatment rather than stenting is regarded as first-line therapy because of the high incidence of periprocedural complications (14.7%).[5] Restenosis is an additional major drawback in stent-treated patients, with a recurrence rate of up to 34%. In the post-SAMMPRIS era, there is still a debate about stenting as a possible alternative treatment,[6–8] because despite best medical treatment recurrence rates in symptomatic high-grade stenosis are still considerable.

Following the first randomized clinical trial (RCT) in 2006,[9] recanalization using drug-eluting balloons (DEB) became a well-established technique in coronary angioplasty. However, there is little evidence for the deployment of DEB in ICAD. Several single-center case series have shown the technical feasibility and safety of different drug-eluting stents or DEB.[10–13] Several different DES are available, such as Cipher (Cordis, Miami Lakes, Florida, USA), Taxus Express (Boston Scientific, Natick, Massachusetts, USA) or the Endeavor (Medtronic, Minneapolis, Minnesota, USA), which are not primarily designed for neurovascular procedures and therefore considered off-label use.[14] The Neuro Elutax SV (Aachen Resonance) is a CE certificated, hydrophilic balloon— specifically designed for neurovascular application—with an even 360° coating of 2.2 µg/mm^2 paclitaxel, a highly hydrophilic anticancer drug (figure 1).

The aim of this study was to assess the feasibility, safety, and efficacy of PTA/Neuro Elutax SV DEB compared with PTAS using the WingspanStent system in patients with high-grade ICAD.

MATERIALS AND METHODS

Patient selection

This retrospective study with an open-label cohort design was carried out at a tertiary stroke center and approved by the local ethic committee.

We initially identified 40 patients with symptomatic intracranial high-grade stenosis who had been treated endovascularly at our institution between January 2009 and September 2016. Endovascular treatment was indicated in patients with symptomatic high-grade intracranial artery stenosis (≥70% in conventional cerebral angiography) with

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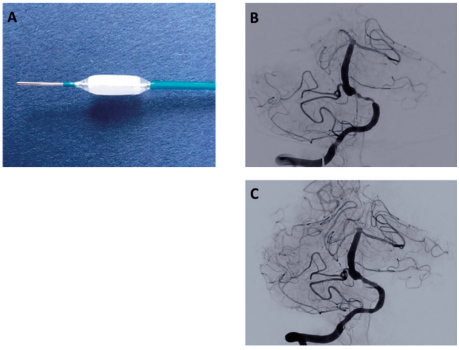

Figure 1 (A) Neuro Elutax SV balloon catheter—CE certificated—specifically designed for neurovascular applications, with a 360° coating of paclitaxel, a common anticancer drug inhibiting intimal hyperplasia. (B,C) Illustrative case of a patient with a symptomatic right-sided V4 segment 70% stenosis of the vertebral artery treated with the Neuro Elutax SV; before (B) and after (C) procedural cerebral angiography. A reduction of stenosis from 70% to 20% was achieved.

recurrent or progressive stroke/transient ischemic attack (TIA) despite medical treatment. Most patients had at least one platelet inhibitor or oral anticoagulant and received high-dose statins. Furthermore, lifestyle modification and/or drug treatment was established for reduction of risk factors for secondary stroke prevention.

All eligible patients had to be over 18 years and were recanalized either with PTA with Neuro Elutax SV paclitaxel DEB or PTAS using the well-described and approved Wingspan stent system consisting of the WingspanStent and Gateway balloon. Patients treated with other stent systems or other device combinations were excluded. This stringent selection process was used to define two homogeneous treatment groups and resulted in 19 patients fulfilling all the above-mentioned criteria (PTA n=8, PTAS n=11).

Procedures

Most of the interventional procedures were performed under general anesthesia (n=16, 84%). All procedures were performed on a Philips Allura Xper FD20/20 biplane angiography system (Philips Medical System, Best, the Netherlands) according to departmental protocol, with intraprocedural modification if required. Briefly, access was achieved through the right common femoral artery, where a 7F long-sheath system was placed. After conventional catheter-based angiography an interventional procedure was performed with the following two device systems: Neuro Elutax SV (Aachen Resonance, Luxembourg)—a CE-certificated DEB specifically designed for neurointerventional procedures—with length 10–30 mm and diameters from 1.5 to 4 mm; and Wingspan stent system (Boston Scientific, Natick, USA) with Gateway PTA balloon catheter (Stryker Neurovascular, Fremont, California, USA)—a Food and Drug Administration approved angioplasty system specifically designed for the neurovascular arteries—as the standard and reference PTAS system.

For the Wingspan stent system the over-the-wire technique was used. The Neuro Elutax SV DEB is a monorail system. Submaximal angioplasty technique was performed for DEB deployment with a balloon inflation time of 30 s.[15]

The decision about which device to use was at the discretion of the neurointerventionalist in charge. Dual antiaggregation with aspirin and clopidogrel was initiated for at least 6 months in all patients treated with PTAS. In patients treated with pDEB Elutax, two patients received therapeutic anticoagulation owing to atrial fibrillation, three aspirin/clopidogrel, and three aspirin alone.

Imaging

The degree of stenosis before and after intervention was determined according to NASCET criteria in cerebral digital subtraction angiography (DSA).[16] The follow-up stenoses were assessed according to the underlined follow-up imaging technique.

Outcome measures

The primary outcome was the compound endpoint of recurrent stroke/TIA and/or restenosis. Restenosis was defined as radiological evidence of postinterventional stenosis of >50% measured by ultrasound, MRI, CT angiography or cerebral angiography during a median follow-up period of 4 months (range 1–9) for the Wingspan and 3 months (range 3–3.5) for the Elutax patients. Any focal neurological symptom related to the corresponding vascular territory occurring within the follow-up period was considered as recurrent stroke or a TIA. Secondary outcomes were stroke or any death within 30 days and good clinical outcome (modified Rankin Scale (mRS) score ≤2) at follow-up.

Statistical analysis

Epidemiological, clinical and radiological data were acquired from the medical records.

All data were anonymized and reviewed by the authors. All statistical analyses were performed by using the STATA/IC 14.1 software (StataCorp LLc, Texas, USA). Study parameters were compared between the two patient groups using either a two-tailed t-test for continuous variables or the Wilcoxon rank sum test for categorical variables. Logistic regression analysis was performed. For all results, a P value <0.05 was considered statistically significant.

RESULTS

A total of 19 patients (9 (47%) female) with 20 lesions (one tandem lesion) were eligible for this study. Eight patients (42%) were treated with a pDEB Elutax SV and; 11 patients (58%) with a Wingspan stent system. The median clinical follow-up was 9.5 months (IQR 4.5–27) for the Elutax patients and 10 months (IQR 6–58) for the PTAS patients, respectively (P=0.36). There were no significant differences in the epidemiological and clinical baseline characteristics between the two groups (table 1). Median age was 68.5 years (IQR 52–76) for the Elutax patients and 67 years (IQR 59–73) for the Wingspan patients (P=0.86). Both groups had similar distributions of vascular risk factors, such as hypertension, diabetes, dyslipidemia, smoking and atrial fibrillation (table 1). Median National Institute of Health Stroke Scale (NIHSS) score was 0 (IQR 0–4) for the Elutax patients and 2 (IQR 0–6) for the PTAS patients (P=0.28). Seventy-five percent of the Elutax patients and 45% of the Wingspan patients had TIAs as initial presenting symptom (P=0.21). Nearly all patients (90%) were on antiplatelet or anticoagulant therapy and received an anti-lipid agent before admission.

Table 1 Demographic, clinical baseline and target lesion characteristics

Characteristics	Elutax (n=8)	Wingspan (n=11)	P value
Gender, female, n (%)	3 (38%)	6 (55%)	0.47
Age (years), median (IQR)	68.5 (52–76)	67 (59–73)	0.86
Clinical follow-up (months), median (IQR)	9.5 (4.5–27)	10 (6–58)	0.36
NIHSS score on admission, median (IQR)	0 (0–4)	2 (0–6)	0.28
Vascular risk factors			
Hypertension, n (%)	6 (75%)	8 (73%)	0.81
Diabetes, n (%)	1 (13%)	4 (36%)	0.26
Dyslipidemia, n (%)	3 (38%)	7 (64%)	0.28
Coronary artery disease, n (%)	4 (50%)	3 (27%)	0.53
Smoking, n (%)	1 (13%)	2 (18%)	0.74
Peripheral artery occlusive disease, n (%)	0 (0%)	1 (9%)	0.39
Atrial fibrillation, n (%)	1 (13%)	1 (9%)	0.82
History of stroke, n (%)	3 (38%)	4 (36%)	0.96
Medication on admission			
Aspirin, n (%)	3 (38%)	7 (64%)	0.27
P2Y12 inhibitor, n (%)	1 (13%)	1 (9%)	0.82
Dipyridamole, n (%)	0	1 (9%)	0.39
Dual antiplatelet therapy, n (%)	1 (13%)	1 (9%)	0.81
Vitamin K antagonist, n (%)	1 (13%)	0 (0%)	0.24
NOAC, n (%)	1 (13%)	0 (0%)	0.24
Anti-lipid agent, n (%)	6 (75%)	6 (55%)	0.51
Severity of stenosis			
Degree of stenosis (%) before intervention, median (IQR)	81% (72.5–92.5)	80% (72–100)	0.87
Degree of stenosis (%) after intervention, median (IQR)	37.5% (20–60)	10% (10–50)	0.23
Localization of target lesions			
Internal carotid artery, n (%)	0 (0%)	1 (9%)	0.39
Middle cerebral artery, n (%)	3 (38%)	5 (45%)	0.74
Vertebral artery, n (%)	3 (38%)	3 (27%)	0.64
Basilar artery, n (%)	2 (25%)	2 (18%)	0.73

IQR, Interquartile range; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NOAC, novel oral anticoagulant.

The overall severity of stenosis in this study was 80% (median; IQR 75–95). The degree of stenosis was reduced from 81% (median; IQR 72.5–92.5) to 37.5 (median, IQR 20–60) in Elutax patients and from 80% (median, IQR 72–100) to 10% (median, IQR 10–50) in Wingspan patients (P=0.23) (table 1). Localization of the target lesions was quite similar in both groups (table 1).

For the primary outcome (table 2), the compound endpoint of recurrent stroke/TIA and/or restenosis within the follow-up period of 9.5 months for the Elutax and 10 months for the Wingspan patients, respectively, was significantly lower for the Elutax patients (n=1, Wingspan n=7, P=0.03; logistic regression OR=0.08, CI 95%: 0.007 to 0.93, P=0.043). No other correlation with demographic or baseline characteristics was found (data not shown).

No clinical re-events—defined as TIA or stroke in the vascular territory of the formerly treated stenosis within the follow-up period—were reported for Elutax patients, whereas 5 (3645%) of Wingspan patients had new clinical symptoms in the corresponding vascular territory (TIA n=4, minor stroke n=1). Of those patients, four out of five underwent conventional DSA; three of them needed immediate interventional procedure with angioplasty or intra-arterial thrombolysis. Median time to recurrent stroke/TIA was 3 months (IQR 1.5–4) after the intervention.

Table 2 Clinical and technical outcome measures

Outcome measures	Elutax (n=8)	Wingspan (n=11)	P value
Good clinical outcome (mRS score ≤2) at follow-up	5 (63%)	9 (82%)	0.36
mRS score on follow-up, median (IQR)	1 (0-3)	1 (0-2)	0.95
Stroke or death within 30 days, n (%)	1 (13%)	0 (0%)	0.24
Technical success*, n (%)	5 (63%)	7 (64%)	0.96
Transient ischemic attack, n (%)	6 (75%)	5 (45%)	0.21
Compound recurrence rate, n (%)	1 (13%)	7 (64%)	0.03
Clinical re-event, n (%)	0 (0%)	5 (45%)	0.03
Restenosis, n (%)	1 (13%)	6 (55%)	0.068
Specific complications, n (%)	0 (0%)	2 (18%)	0.21
Generic complications, n (%)	0 (0%)	1 (9%)	0.39
Technical failure, n (%)	1 (13%)	0 (0%)	0.24
Number of devices used, median (IQR)	1 (1–2)	3 (2–4)	0.003

*Technical success; defined as <50% residual stenosis at the end of the intervention.
mRS, modified Rankin Scale.

Restenosis rate—defined as any radiological evidence of stenosis degree >50%—tended to be higher in Wingspan treated patients (n=6) than in the Elutax patients (n=1, P=0.068).

One death occurred owing to fatal vertebrobasilar stroke not related to the intervention (table 2).

Technical success—defined as <50% residual stenosis at the end of the interventional procedure—was achieved in 63% of the Elutax patients and 64% of the Wingspan patients (P=0.96). Furthermore, significantly fewer different devices were needed for successful recanalization in the Elutax group which required one device (median, IQR 1–2) for each case compared with three devices (median, IQR 2–4) for each case in the Wingspan group (P=0.003) (table 2).

There were no intraprocedural complications in 15/19 patients. Overall technical failure was 5% due to unsuccessful deployment of a pDEB because of difficult local anatomical conditions in an Elutax patient (Elutax: 13%; Wingspan: 0%, P=0.24). Generic complications were reported for only one Wingspan patients (9%) due to a groin hematoma at puncture site, which had to be surgically evacuated. Specific complications were seen in two Wingspan-treated patients: one had an intraprocedural in-stent thrombosis and the other had a consecutive hyperperfusion syndrome with transient neurological deterioration. No other procedure-related neurological complications, such as vessel perforation, dissections, subarachnoid hemorrhage, intracranial hemorrhage, or ischemic events, were found (table 2).

Finally, there were no differences between the two groups in good clinical outcome (modified Rankin Scale (mRS) score ≤2, (table 2), with a median mRS of 1 (IQR 0–3) for the Elutax patients, and a median mRS of 1 (IQR 0–2) for the Wingspan patients, respectively (P=0.95).

DISCUSSION

To our knowledge, this is the first cohort study reporting a pDEB specifically dedicated to neurovascular application (Elutax SV) and the Wingspan stent system in patients with intracranial symptomatic high-grade atherosclerotic arterial stenosis. During a median follow-up period of 9.5 months (Elutax) and 10 months (Wingspan), recurrent stroke/TIA was significantly lower in Elutax-treated patients than in the Wingspan group. Likewise, restenosis tended to be lower in Elutax patients. There was no significant difference in complication rate and outcome at follow-up.

ICAD is a common cause of ischemic stroke and patients with high-grade intracranial stenosis (70–99%), in particular, are at high risk of developing an ischemic event in the vascular territory of the stenosis.[17] These lesions may be amenable to intracranial angioplasty, but several concerns have been raised about this technique.

Evidence derived from cardiology has proved the efficacy and safety of DEB in coronary angioplasty. Since the first RCT of pDEB in coronary angioplasty for in-stent thrombosis, which found a significantly lower restenosis rate in the pDEB group (5% vs 43%, P=0.002),[9] the benefit of pDEB has become evident and the superiority of pDEB over conventional balloon catheters has also been proved in long-term follow-up studies.[18 19]

Conversely, the role of DEB, and especially pDEB, in the neurovascular setting is still unclear. Since the publication of the SAMMPRIS trial in 2011,[2] best medical care is regarded as the preferred treatment for ICAD because of the high periprocedural complication rate of 14.7%. This rate was considerably higher than in previously published data— for example, data from the European INTRASTENT multicentric registry, which had an intrahospital event rate of 7%.[20] Furthermore, a high incidence of recurrent stenosis of up to 31% appears to be a major problem with intracranial stenting, despite growing experience in procedural feasibility, safety, and durability of revascularization.[21 22] These restenoses may result in up to 39% of patients having a TIA or stroke.[23] Therefore, enthusiasm for using intracranial stenting has declined over the past years.

A review of intracranial angioplasty showed a relatively low incidence of 30-day major complications of ≤6%, but the rate of symptomatic and angiographic restenosis after 6 months was still 5–30%.[24] By using drug-eluted devices for the ICAD treatment, the rate of restenosis and clinical re-events may be reduced, as was shown in early studies.[11–13] However, their efficacy has not yet been totally confirmed in ICAD. So far, a study of a large cohort of 95 patients with ICAD treated with a sirolimus-coated coronary DES system (Coroflex Plaese Stent) has reported promising results, with a low restenosis rate of 3.9% and a low periprocedural complication rate of 0.9%.[10] In our study, a paclitaxel-coated balloon specifically designed for neurovascular application was used. Restenosis is mainly caused by intimal hyperplasia. Paclitaxel is a highly lipophilic anticancer drug and has an antiproliferative effect. By inhibiting the proliferation of smooth muscle cells, paclitaxel reduces intimal hyperplasia.[25] Thus, paclitaxel has been proved to be a potent agent to prevent restenosis.[26]

Preliminary good results with pDEB have been shown in different small case series for the treatment of restenosis in internal carotid artery stenosis.[27 28] But, experience of pDEB treatment in ICAD is limited to only one case series of 51 patients with ICAD, demonstrating a significantly lower restenosis rate than with a conventional stent system (9% vs 50%) during a mean follow-up of 6.5 and 7.5 months, respectively.[29] Our results support these findings that pDEB-treated patients have less restenosis and fewer cerebrovascular re-events than patients treated with conventional bare-metal stent and uncoated balloon catheters. The relatively high rate of restenosis of 36% in our Wingspan group is not surprising and is in-line with previous reports of up to 34%.[24]

Interestingly, despite the submaximal angioplasty technique with greater residual stenosis, the restenosis rate remained low. This is of special interest, because there are concerns about the effective interaction of the drug-coated surface of the DEB and the targeted vessel walls when the submaximal angioplasty technique is applied.[24]

Furthermore, the technical success rate was lower for both groups (Elutax vs Wingspan) with 63% and 64%, respectively, compared with previous studies with success rates of 70–100%.[22] Our results might be related to the submaximal angioplasty technique and low patient number. Despite the small number of patients, the technical failure rate was comparably low, with only one unsuccessful pDEB deployment in an anatomically difficult lesion. The deployment failure might be due to the greater rigidity and stiffness of the balloon because of the coated surface. Subsequent technical advances in catheter design may overcome this problem in the future, and may lead to softer and more flexible balloons.

No other severe incidents, such as vessel perforation, dissections, subarachnoid hemorrhage, or intracranial hemorrhage, occurred either in the short or long term. Therefore, the overall safety for the pDEB patients was good and lower as reported for PTAS patients in a recent meta-analysis.[30] Thus, a large sample size is needed, to definitively confirm the success rate and safety profile of the Neuro Elutax SV.

Finally, clinical outcome was favorable, with a median mRS score of 1 in both groups. However, there are differences in the initial NIHSS and clinical presentation in the two groups with insignificant, but a higher proportion of TIAs in the pDEB patients than in the PTAS patients, which might have biased the outcome for each group.

Major limitations are the retrospective design, lack of randomization and the small number of eligible patients because following the SAMMPRIS trial, patients with ICAD are primarily treated with platelet inhibitors without mechanical recanalization. Furthermore, the follow-up was relatively short. Because of the retrospective design, routine follow-up DSA to describe the treated stenosis at 90 days is not a common procedure at our institution, thus follow-up imaging is always based on ultrasound or other non-invasive imaging techniques. In addition, these data are obtained from only one experienced high-volume single center and thus may not be generally applicable.

Finally, our observations suggest that drug-eluting balloon angioplasty might be a valid option for patients with ICAD with intractable disease despite best medical care, because the technical advances of newer DEB generations has led to a lower complication rate with an overall good clinical and radiological outcome. Thus, large-scale, prospective studies are needed.

CONCLUSION

The pDEB Neuro Elutax SV may be a promising alternative treatment for highly selected patients with ICAD, showing a lower recurrence rate than with the PTAS Gateway/Wingspan with a similar safety profile and technical success rate. Despite a significant difference in the recurrence rate, conclusions have to be reached with caution owing to the limitations of this study. Further studies will be needed to clearly elucidate the role of pDEB in the management of symptomatic intracranial high-grade stenosis.

28

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ELSEVIER

Clinical Research

Angioplasty Using Drug-Coated Balloons in Ostial Vertebral Artery Stenosis

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Background: Ostial vertebral artery stenosis (OVAS) is a relevant cause of acute ischemic posterior circulation stroke. Percutaneous trans-luminal angioplasty (PTA) might offer a promising treatment modality, but restenosis rate is high. So far, little is known about recanalization using drug-coated balloons (DCB) in OVAS. We aimed to show feasibility and safety of DCB-PTA in OVAS.

Methods: Retrospective, monocenter case series of 12 patients with ostial vertebral artery stenosis (≥50%) treated with PTA using a drug-coated balloon.

Results: Median age was 69.5 years (IQR 57–78.5) with a female rate of 41%. Patients were treated either with a SeQuent Please NEO or Neuro Elutax SV DEB. Median preinterventional stenosis degree was 75% (IQR 70–85) with a median lesion length of 4.5 mm (IQR 4–7.5). Median postinterventional stenosis degree was 40% (IQR 27–50). All treated vessels remained patent. No major complications such as dissection, vessel perforation, hemorrhage, or ischemic events occurred. Moreover, we did not detect any restenosis during a median follow-up period of 6.1 months. The clinical outcome was excellent with median mRS scale of 0 (IQR 0–1).

Conclusions: PTA using drug-coated balloons is feasible and safe in patients with ostial vertebral artery stenosis.

INTRODUCTION

Approximately 20–25% all of ischemic strokes occur in the posterior circulation, and 10–20% of the patients with ostial vertebral artery stenosis (OVAS) will suffer from a stroke.[1,2] Furthermore, patients with a vertebrobasilar transient ischemic attack (TIA) due to OVAS (≥50%) have a 5-year risk of stroke recurrence of 30%.[3] In addition, the risk of stroke or death is six times higher in OVAS patients than in patients without OVAS.[4]

Nevertheless, there is an ongoing debate on the treatment modalities for OVAS patients whether patients benefit from endovascular or from best-medical treatment alone since the VIST, VAST, and CAVATS trial.[5–7] Today, best medical treatment using antiplatelet agents is considered first-line treatment of OVAS.[8] However, endovascular OVAS treatment might be considered especially in patients with hemodynamic vertebrobasilar insufficiency, bilateral >70% vertebral artery stenosis (VAS) and in patients with unilateral VAS with contralateral hypoplastic or occluded vessels.[9] Initial good clinical results and high success rates have been reported for percutaneous angioplasty with or without stenting. However, the restenosis rate was reported as high as 10–67%.[10,11]

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During the last decade, drug-eluting stents (DES) and drug-coated balloons (DCB) have been established in the field of interventional cardiology with convincing short- and long-term results.[12] In line with these observations, several case series as well as cohort studies in OVAS patients treated with DES have been published and demonstrated feasibility and safety with high technical success rates of 98.8% and low morbidity.[8] DES in patients with high-grade OVAS appear to have lower restenosis rates compared to the previously used bare-metal stents (BMS).[13,14] Data on treatment of high-grade OVAS with DCB is scarce.[15] DCB offers the opportunity to prevent restenosis through a drug-coated matrix that releases antiproliferative drugs inhibiting neointimal hyperplasia[16] on one hand and omits the permanent deployment of extraneous material on the other hand.

In this case series, we assessed feasibility and safety of DCB-PTA in patients with OVAS (≥50%) using Neuro Elutax SV (Aachen Resonance, Aachen, Germany) and SeQuent Please NEO (B. Braun Melsungen, Germany).

METHODS

Patient Selection

In this retrospective monocenter case series, we screened our stroke database for patients (≥18 years) with OVAS (≥50%) treated with DCB-PTA within the last 3 years. The OVAS degree was based on a multimodality imaging approach (CTA, MRA, and or US) that has to be confirmed by conventional angiography.

We identified 12 patients with either symptomatic OVAS ($n = 10$) or treatment of OVAS in order to improve the collateral situation in two patients suffering from complex occlusive vasculopathies with additional high-grade stenosis of the internal carotid arteries, as well as stenosis or occlusion of the contralateral vertebral artery. Thus, our indications were high-risk patients with recurrent TIAs or manifest strokes in the posterior circulations and additional OVAS, as well as patients with complex occlusive, supra-aortic vasculopathies with concomitant high-grade OVAS and with insufficient collateral circuits.

The local ethics committee (Ethikkommission Nordwest und Zentralschweiz, EKNZ, 2018-01,204) approved the study.

Procedure

Preinterventionally, patients received either a dual antiplatelet therapy (DAPT) with aspirin 100 mg and clopidogrel 75 mg ($n = 9$; 75%) or in case of concomitant atrial fibrillation anticoagulation with rivaroxaban 15 mg and antiplatelet therapy with clopidogrel 75 mg ($n = 3$; 25%) according to the PIONEER-AF trial.[17] Prior to the intervention, an additional heparin bolus (range 2,500—5,000 I.E) adjusted for body weight was administered according to activating clotting time (ACT) blood test. Most of the procedures were performed under general anesthesia ($n = 9$; 75%).

All endovascular procedures were performed on a biplane angiography system (Allura Xper, Philips, the Netherlands). The tip of 6F guiding catheter was placed via a 7F femoral access sheath into the proximal part of the subclavian artery. Under roadmap guidance, a flexible 0.0014-inch microwire (Synchro2, Stryker Neurovascular, USA) was directed across the lesion. The tip of the microwire was always placed into the distal part of the extracranial vertebral artery. By monorail technique, a properly sized Neuro Elutax SV or a SeQuent Please NEO DCB was placed across the lesion covering at least the plaque lesion length. Then, DCBs were gently inflated to subnominal pressure (first run with first device: median 9 bar, interquartile range IQR 6—10 bar) according to submaximal angioplasty technique as described elsewhere and kept inflated for 30—60 sec.[18] In all cases, a final postprocedural angiography was performed to document the final result as well to exclude vessel dissection, distal embolization, or vessel perforation. Within 24 hours after the procedure, patients were controlled for immediate restenosis with ultrasound. These results served also as a baseline examination for follow-up imaging.

Postprocedurally, one patient initially on DAPT was newly diagnosed with atrial fibrillation and was switched to rivaroxaban 15 mg and clopidogrel 75 mg/d. In addition, another four patients initially on DAPT were switched to aspirin only directly after the intervention. Furthermore, all patients were under lipid-lowering medication, and vascular risk factors were controlled and treated if necessary.

Outcome Measurements

We measured postprocedural angiographic stenosis degree according to the VOTE method criteria,[19] as well as the postprocedural short-term (within 24 hours) and long-term ultrasonographic stenosis degree according to the nomogram of Ranke et al.[20] Additionally, all periprocedural complications as well as clinical follow-up (mRS) were assessed.

Table I. Cohort characteristics and outcome parameters of the study

	N = 12
Clinical characteristics	
Age in years (yrs), median (IQR)	69.5 yrs (57–78.5)
Sex (female), *n* (%)	5 (41)
Hypertension, *n* (%)	12 (100)
Dyslipidemia, *n* (%)	10 (83)
Diabetes mellitus, *n* (%)	3 (25)
Heart disease, *n* (%)	7 (58)
Atrial fibrillation, *n* (%)	4 (33.3)
History of nicotine abuse, *n* (%)	8 (67)
NIHSS, median (IQR)	0 (0–0)
Lesion Characteristics	
Lesion side (left), *n* (%)	12 (100)
Preinterventional stenosis degree VOTE in percentage, median (IQR)	75% (70–85)
Lesion length in mm, median (IQR)	4.5 (4–7.5)
Most common clinical symptom: vertigo/dizziness	7 (58%)
Contralateral vertebral artery (VA)	
Hypoplastic V4-segment of the VA	2 (17%)
Occlusion/Pseudo-occlusion of the VA	2 (17%)
High-grade stenosis (≥70)	2 (17%)
Moderate stenosis (≤50%)	2 (17%)
Procedure Characteristics	
General anesthesia, *n* (%)	9 (75)
Neuro Elutax-SV as first DCB, *n* (%)	6 (50)
SeQuent Please NEO as first DCB, *n* (%)	6 (50)
Second larger-size DCB use, *n* (%)	4 (44)
Change to another DCB, *n* (%)	1 (11)
Outcome Measures	
Modified ranking scale score at follow-up, median (IQR)	0 (0–1)
Postinterventional stenosis degree VOTE in percentage – median (IQR)	40% (27–50)
Mean follow-up period in months	6.1
Recurrent clinical ischemic event, *n*	0
Restenosis rate at follow-up, *n*	0
Overall major periprocedural complications, *n*	0
Dissection, *n*	0
Vessel perforation, *n*	0
Hemorrhage, *n*	0
Distal ischemic event, *n*	0
Mortality, *n*	0

DCB, drug coated balloon; IQR, interquartile range; NIHSS, National Institute of Health Stroke Scale; no., number; VA, vertebral artery; VOTE, vertebral origin treatment with endovascular therapy method; yrs, years.

RESULTS

In this case series, median age was 69.5 years (IQR 66–76). There was a female rate of 41%. Most prevalent vascular risk factors were hypertension (*n* = 12; 100%), followed by dyslipidemia (*n* = 10, 83%) (Table I). Eleven patients were also under previous antiplatelet therapy (APT) (*n* = 7), dual antiplatelet therapy (DAPT) (*n* = 2), or anticoagulation (*n* = 1) as well as anticoagulation and APT (*n* = 1). Prior to the intervention, 11 patients were already under Statin therapy. All culprit lesions were located on the left side. In 33% (*n* = 4) of the patients, additional stenoses on the same side were found, of whom one patient with a concomitant high-grade V2/V3 segment stenosis of VA was additionally treated with PTA-DCB. In 67% (*n* = 8) of the patients, a moderate-to-severe contralateral vertebral artery lesion was found such as occlusion, bilateral OVAS, or hypoplastic vertebral arteries (Table I).

Preinterventional stenosis degree according to the VOTE method was 75% (IQR 70–85).

Neuro Elutax SV DCB and Sequent Please NEO DCB were equally used as first-line in three cases. In four cases, the initially used DCBs were changed

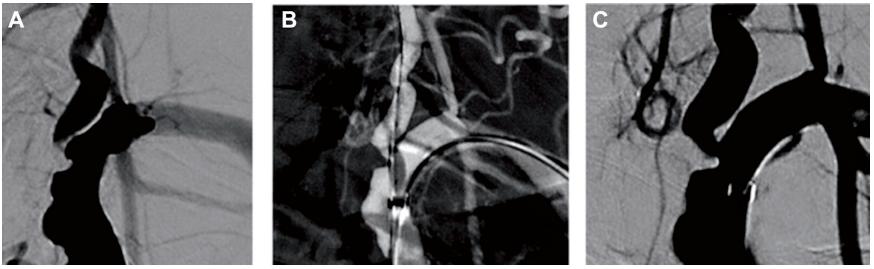

Fig. 1. Central illustration: Illustrative case of DCB use in ostial vertebral artery stenosis. Patient with known extensive atherosclerotic arteriopathy of supra-aortic arteries. **(A)** Preprocedural angiogram of a high-grade, excentric OVAS of the left vertebral artery. **(B)** Intraprocedural inflated angioplasty balloon (SeQuent Please NEO). four-time angioplasty with two times 2 mm × 10 mm SeQuent-Please NE0 and two times with a 3 mm × 10 mm SeQuent Please NEO. **(C)** Postprocedural angiogram with residual stenosis (50%) with good restoration of antegrade flow.

to larger sized DCBs of the same manufacturer. One patient required a switch from Neuro Elutax SV DCBs (attempt with two different sizes) to SeQuent Please NEO DCB). Final deployment of DCBs was technically successful in all cases.

Median postprocedural stenosis degree was 40% (IQR 27—50) and ultrasonographically the treated vessel remained open within the first 24 hours. There was no correlation between the initial lesion characteristics and outcome. The clinical outcome was excellent with median modified Ranking Scale (mRS) Score at follow-up of 0 (IQR 0—1).

We did not observe any major complication such as vessel dissection, vessel perforation, ischemic or hemorrhagic intracranial events.

During a mean follow-up period of 6.1 months, postprocedural ultrasound findings showed in 7 (58%) patients normalized flow profile and in 5 (42%) patients residual stenosis. During this follow-up period, no clinical recurrent strokes occurred.

DISCUSSION

Our findings showed that OVAS treatment with DCB in appropriately selected patients is feasible, safe, and revealed sustained short-outcome results (Fig. 1). These findings are in line with a previous case report of DCB in OVAS.[15]

Vertebral artery stenosis is the second most common stenosis in the extracranial vasculature after carotid artery stenosis and might have deleterious effect if it becomes symptomatic. There is still the question, which patients will benefit most from endovascular therapy.

Anatomical Considerations

Most of our patients had also pathoanatomical changes of the contralateral side and nearby all of these lesions—comprising high-grade OVAS, hypoplastic VA, or occluded VA—together with the culprit OVAS might also lead to vertebra-basilar insufficiency. Thus, these OVAS should be endovascularly treated as recommended by others.[9,21] Interestingly, all culprit lesions were located on the left side. As often reported in anatomical studies, the left VA diameter is commonly the larger one of both VAs.[22,23] This might have some hemodynamic implications in atherosclerotic VAs, because the left VA might be the dominant artery in this constellation. And, as soon as this VA will be severely affected by atherosclerosis, vertebrobasilar insufficiency will occur.

Technical Considerations

Since endovascular mechanical vessel treatment leads to vessel wall injuries, restenosis after endovascular OVAS treatment remains a medical challenge and was reported to be as high as 25—30% in stenting.[24] The underlying pathobiological mechanism is smooth muscle cell proliferation that causes neointimal hyperplasia and that is considered to be responsible for restenosis. Thus, DES/DCB use intents to deliver antiproliferative and immunemodulatory drugs that will prevent neointimal hyperplasia.[12] So far, DES has shown to be feasible,

safe, and effective[25–27] as well as superior over bare metal stents regarding restenosis rate as reported with 4.5% (DES) versus 19.1% (BMS) and in a meta-analysis of 442 OVAS patients with 4.7% (DES) and 11.6% (BMS),[14,28] since its first description in 2004.[29] Nevertheless, stenting has some shortcomings, which might be challenged by the use of DCB[30]: First, DCBs are more flexible compared to BMS/DES that may be of importance regarding the tortuous vessel anatomy mostly found in OVAS patients. Second, compared to DES (strut design), DCB covers the whole stenosis surface with a homogenous drug delivery and thus might better inhibit neointimal hyperplasia. Third, there is no residual foreign body left in the treated vessels and might enhance positive vessel remodeling. Fourth, multiple balloon use in the same lesion is possible. Fifth, since there is continuous mobility of the subclavian artery and tortuous anatomy of OVAS, restenosis could also be promoted by stent fracture or kinking due to mechanical stress, which could be detected up to 21.6% of cases,[13,31] a finding that cannot occur in DCB-PTA.

In addition, just recently, promising results have been shown for DCB treatment in symptomatic intracranial atherosclerotic disease (ICAD).[32,33] These results might even encourage the use of DCB also in the extracranial vasculature.

We observed no periprocedural complications. This finding is similar to that reported from different endovascular vertebral artery stenting studies with 0–5%,[8,10] supporting that endovascular treatment in OVAS is a relatively safe procedure. In addition, we did not use any distal protection device to prevent embolic events, as it has been described in some studies for OVAS stenting.[21] Additional devices in this mostly tortuous vessel anatomy of vertebral artery leads to additional complexity and might lead to higher complication rates.

Our technical success was also high, which is consistent with previous studies.[8,14] We had also no recurrent event, which has to be taken with caution because of low number and short follow-up.

There is a low risk of delayed endothelization and incomplete neointimal healing in DCB compared to DES. Thus, there is no late and very late thrombosis risk. Therefore, DCB patients might not need a prolonged duration of DAPT compared to DES patients in whom duration of DAPT is recommended up to 3–6 months.[34] In cardiac DCB patients, the duration of DAPT for 1 month was suggested to be sufficient.[35] Furthermore, in DCB studies using shorter durations of DAPT (1–3 months), there was no significant increase of major adverse cardiac events compared to longer DAPT durations observed.[12] Of note, this might also be an advantage for complex cardiovascular patients who need additional anticoagulation such as in patients with AF. Thus, in our cohort, 33.3% patients ($n = 3$) were under novel oral anticoagulant (rivaroxaban) combined with clopidogrel without any bleeding complications. The other nine patients received DAPT during the endovascular procedure, and clopidogrel was discontinued immediately after the intervention in four patients, after 2 months in three patients.

Limitations

Limitations are the small sample sizes and the lack of randomization, as well as the relatively short follow-up as it is known that in DCS, restenosis could appear even 42 months after implantation. Nevertheless, this case series might serve as a pilot study to encourage larger DCB-PTA studies in OVAS.

CONCLUSION

This study demonstrated the feasibility and safety drug-coated balloon PTA in ostial vertebral artery stenosis. Drug-coated balloons might be considered as a novel treatment option in patients with ostial vertebral artery stenosis.

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Are drug-coated balloons and drug-eluting stents the future in intracranial atherosclerotic disease?

1st February 2019 2401

Remonda L

Alternative treatment options for patients with intracranial atherosclerotic disease (ICAD) are needed, given its prevalence worldwide and the associated risk of recurrent ischaemic events. Here, Philipp Gruber and Professor Luca Remonda (Department of Neuroradiology at Cantonal Hospital Aarau, Aarau, Switzerland) look at previous studies to evaluate the viability of using drug-coated balloons (DCB) and drug-eluting stents (DES) in the treatment of intracranial atherosclerotic disease, and how they will play an increasingly important role in the not too distant future.

Intracranial atherosclerotic disease (ICAD) is responsible for 8–10% of strokes worldwide, its prevalence varies across populations, ranging from 10% in Caucasian up to about 40% in Asian populations. First-line therapy of symptomatic ICAD, in particular anti-platelet monotherapy, remains the best medical treatment. However, despite aggressive medical treatment, the annual risk of recurrent ischaemic events is still high with up to 18% in patients with >70% intracranial stenosis.[1] In particular, patients with high-grade stenosis (70-99%), patients with haemodynamically relevant stenosis —as shown in the natural history study GESICA[2]—and patients with unstable atherosclerotic plaque have an increased risk of stroke recurrence. Therefore, alternative treatment modalities are needed.

Endovascular treatment (EVT) for symptomatic ICAD treatment has been long debated since the first description of percutaneous transluminal angioplasty in a symptomatic basilar ICAD by Sundt et al in 1980.[3] Since the negative SAMMPRIS and VISSIT trials,[4] endovascular treatment of symptomatic ICAD—especially percutaneous transluminal angioplasty stenting—has been reluctantly used. Nevertheless, recent results from the WAEVE trial demonstrated a significantly lower periprocedural stroke and death rate of 2.9%,[5] which encourages consideration of EVT for symptomatic intracranial atherosclerotic disease.

Besides immediate periprocedural complications such as local dissection, subarachnoid haemorrhage or perforator ischaemia, EVT of intracranial atherosclerotic disease also carries the middle- to long-term issue of restenosis. The restenosis rate for both PTA as well as transluminal angioplasty stenting has been reported to be high. Both transluminal angioplasty stenting and percutaneous transluminal angioplasty lead to vascular wall injuries that induce a complex biological cascade of inflammatory responses and wound healing processes. These processes promote the proliferation of smooth muscle cells leading to neo-intimal hyperplasia. It has been recognised that neo-intimal hyperplasia is mainly responsible for restenosis.
To overcome this major limitation of stenting and percutaneous transluminal angioplasty, various anti-proliferative and immuno-modulatory drugs have been evaluated to prevent neo-intimate hyperplasia. Today, two different drug families are most commonly used: the limus drug family, consisting of mammalian target of rapamycin (mTOR) inhibitors (e.g. sirolimus) and calcineurin inhibitors (e.g. Tacrolimus), which are used in drug-eluting stents, and paclitaxel, a highly lipophilic anti-proliferative agent that is a microtubule stabiliser that inhibits mitosis, which is commonly used in DCB's. Anti-proliferative drugs are integrated into a carrier matrix attached to either a balloon or stent platform. After deploying the DES or while inflating the DCB, the drug can be administered locally at the lesion site.
Both DCB and DES have been very successfully used in interventional cardiology for more than a decade. Numerous studies have proven their efficacy and safety for cardiac atherosclerotic patients. In the neurovascular field, several case series and a few studies have shown that this technique in patients with the primary symptomatic ICAD is feasible, safe and might be effective, while no data were available for DCB until 2018.
DCB offers several advantages over DES. Using DCB, no residual foreign body, nor radial force wall stress is left after the intervention. This has a positive impact on local flow dynamic as well as feared late adverse material-tissue reaction. Furthermore, DCB allows homogeneous anti-proliferative drug coverage of the whole stenosis surface in contrast to DES, by which only 15% of the plaque surface can be coated with anti-proliferative drugs. DCB are more flexible compared to DES offering access to reach more lesions, especially in the tortuous neurovascular anatomy of ICAD patients. A shorter duration of recommended dual anti-platelet therapy (DAPT) might be possible for DCB since there is a lower risk of delayed endothelialisation and therefore lower late or very-late thrombosis compared to DES as shown in cardiac patients. Of course there are drawbacks of percutaneous transluminal angioplasty alone in comparison to stenting, such as immediate recoil phenomenon or higher residual stenosis degrees that might have an impact

on restenosis.

Recently, two case series and one study have reported positive results on preliminary experience with DCB use in symptomatic ICAD. Our retrospective single-center cohort study of 19 symptomatic ICAD patients compared Neuro Elutax SV (Aachen Resonance, Germany)—a DCB specifically designed for neurovascular use—with the Gateway/ Wingspan stent system (Boston Scientific, USA).[6,7] We showed that the use of this specific DCB was feasible and safe. In addition, we found that this DCB treatment was superior to the DES regarding asymptomatic and symptomatic recurrence over a median follow-up of nine and a half months. Very recently, Chinese group reported on their preliminary DCB experience of 30 symptomatic ICAD patients using SeQuent Please (b.braun, Germany) with a mean follow-up of nearly ten months—a DCB originally designed for cardiac use.[8] Their results support our findings regarding feasibility and safety and there was only one asymptomatic restenosis. At the same time, another case series of 10 symptomatic ICAD patients treated at our institution with SeQuent Please NEO—the latest generation of SeQuent Please, offering higher flexibility and better pushability—demonstrated convincing results regarding feasibility and safety, as well as good short-outcomes.[9]

Presently, DCB offer several advantages over DES as outlined above. But, several issues have to be addressed. A clear concept for patient selection should be established, and it has to be discussed which deployment technique should be performed, such as the submaximal angioplasty technique as we have used in our studies. Despite all the technical advances during the past decade, the devices have to be optimised and closely adapted to the neurovascular requirements. Finally, large randomised trials should be carried out to increase the power and reliability of data.

In conclusion, alternative treatment options for ICAD patients are needed since ICAD has a high prevalence worldwide and even with the best medical treatment the risk of recurrent ischaemic events is high. DCB is a feasible and so far safe endovascular technique for ICAD patients. Therefore, the DCB technique has the potential to play an important role in symptomatic ICAD treatment in the near future.

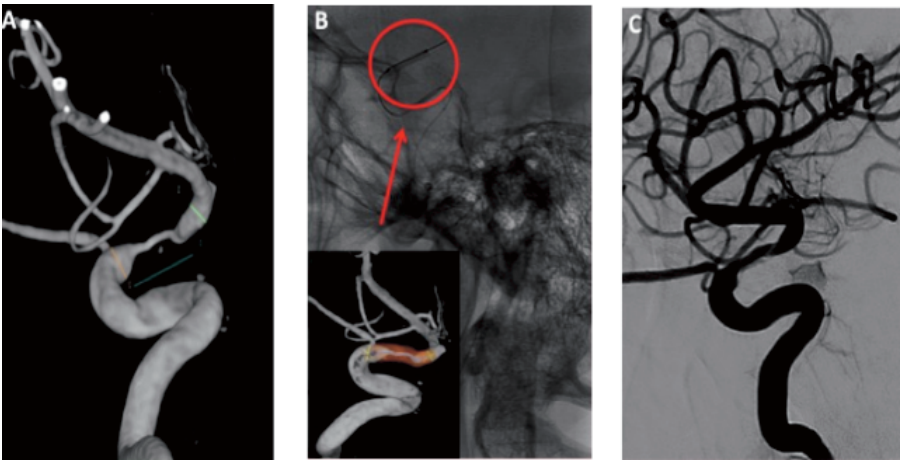

Figure 1: Illustrative Case of DCB use in a symptomatic ICAD patient

A patient with an ischaemic event in the posterior middle cerebral artery territory due to a symptomatic high-grade stenosis of the terminal internal carotid artery segment carotid artery stenosis on the same side.

1 Pre-interventional reformatted 3D-convantional angiogram showed a eccentric high-grade terminal internal carotid artery stenosis (80%).

2 SeQuent Please NEO (2.0mm x10mm) was successfully deployed over the lesion (red circle) and submaximally inflated with 8 bar.

3 Post-interventional control angiogram revealed a residual stenosis (50%).

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Drug-Coated Balloon Versus Drug-Eluting Stent for Small Coronary Vessel Disease

PICCOLETO II Randomized Clinical Trial

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ABSTRACT

OBJECTIVES This study sought to compare the performance of a novel drug-coated balloon (DCB) (Elutax SV, Aachen Resonance, Germany), with an everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) in patients with de novo lesions.

BACKGROUND Small vessel coronary artery disease (SVD) represents one of the most attractive fields of application for DCB. To date, several devices have been compared with drug-eluting stents in this setting, with different outcomes.

METHODS The PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) trial was an international, investigator-driven, multicenter, open-label, prospective randomized controlled trial where patients with de novo SVD lesions were randomized to DCB or EES. Primary study endpoint was in-lesion late lumen loss (LLL) at 6 months (independent core laboratory), with the noninferiority between the 2 arms hypothesized. Secondary endpoints were minimal lumen diameter, percent diameter stenosis at angiographic follow-up, and the occurrence of major adverse cardiac events at 12 months.

RESULTS Between May 2015 and May 2018, a total of 232 patients were enrolled at 5 centers. After a median of 189 (interquartile range: 160 to 202) days, in-lesion LLL was significantly lower in the DCB group (0.04 vs. 0.17 mm; $p = 0.001$ for noninferiority; $p = 0.03$ for superiority). Percent diameter stenosis and minimal lumen diameter were not significantly different. At 12-month clinical follow-up, major adverse cardiac events occurred in 7.5% of the DES group and in 5.6% of the DCB group ($p = 0.55$). There was a numerically higher incidence of spontaneous myocardial infarction (4.7% vs. 1.9%; $p = 0.23$) and vessel thrombosis (1.8% vs. 0%; $p = 0.15$) in the DES arm.

CONCLUSIONS In this multicenter randomized clinical trial in patients with de novo SVD lesions, a new-generation DCB was found superior to EES in terms of LLL as the angiographic pattern and comparable in terms of clinical outcome. (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment [PICCOLETO II]; NCT03899818) (J Am Coll Cardiol Intv 2020;■:■–■) © 2020 Published by Elsevier on behalf of the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

DCB = drug-coated balloon

DES = drug-eluting stent(s)

EES = everolimus-eluting stent(s)

HR = hazard ratio

LLL = late lumen loss

MACE = major adverse cardiovascular event(s)

MI = myocardial infarction

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

SVD = small vessel disease

TLR = target lesion revascularization

The overall complexity of interventions for coronary artery disease has progressively increased during the last 2 decades, due to epidemiological reasons and to the availability of devices with superior performance and long-term clinical efficacy (1,2). Drug-eluting stents (DES) especially experienced a dramatic improvement from the technological point of view, leading to the possibility to treat virtually any coronary lesion (3). However, despite the improved clinical outcome obtained with latest-generation DES, the total amount of stent length remains associated with an increase in late adverse events (4). This is 1 of the reasons why newer devices are required as potential alternatives to DES. Among them, drug-coated balloons (DCB) have been widely adopted in some specific settings, including in-stent restenosis and de novo lesions, particularly in small vessel disease (SVD). SVD is associated with a higher risk of restenosis and stent thrombosis after the use of DES (5–7). Accordingly, the possibility to treat SVD without the implantation of a permanent prosthesis by means of direct delivery of an antirestenotic drug with DCB has been considered appealing since the first results of this strategy were published 10 years ago (8,9).

However, it rapidly became evident how the addition of a drug to a balloon was not sufficient to produce an efficacious and homogeneous delivery of the drug to the vessel wall, and an effective and persistent antirestenotic effect. In fact, several DCB have been investigated so far, with mixed results, explaining why recent revascularization guidelines emphasize that there is not a class effect for DCB (10). The Elutax SV/Emperor (AR Baltic Medical, Vilnius, Lithuania) is a new-generation DCB eluting paclitaxel thanks to dextran as the drug carrier.

The aim of the PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) study was to assess the angiographic efficacy of this DCB as compared with Xience everolimus-eluting stent (EES) (Abbott Vascular, Santa Clara, California) in patients with SVD.

METHODS

STUDY DESIGN. The PICCOLETO II trial (NCT03899818) is an investigator-driven, prospective, randomized, multicenter, open-label clinical trial performed at 5 European centers. The study protocol was presented and accepted at the coordinating center (Fatebenefratelli Hospital, Milano, Italy) ethics committee in February 2015, and thereafter by the ethics committees of all the participating centers. First patient inclusion occurred in May 2015, and the last patient was enrolled in May 2018. The protocol was designed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided prior oral and written informed consent to be enrolled into the study.

PATIENT POPULATION. In order to be enrolled, the patient had to be hospitalized for stable coronary artery disease or an acute coronary syndrome, with an indication for percutaneous coronary intervention (PCI). The angiographic characteristics to enroll the patient were the following: coronary artery disease in a vessel with a diameter between 2.00 and 2.75 mm with a target lesion ≥70% (by investigator's judgment by visual estimation). The clinical exclusion criteria were as follows: inability to provide oral and written informed consent or unwillingness to come back for systematic angiographic follow-up; age <18 years; life expectancy <1 year; recent ST-segment elevation myocardial infarction (MI) (<72 h); left ventricular ejection fraction <30%; and creatinine clearance <30 ml/min. We also applied the following angiographic exclusion criteria: index lesion at left main stem; aorto-ostial lesion; presence of stent at target vessel; target lesion previously treated by means of any device; chronic total occlusion; severe calcification or tortuosity of the target vessel; untreatable thrombus at the target lesion; target lesion involving a major bifurcation; and lesion length >25 mm.

Periprocedural MI was defined according to the Third Universal Definition as type IV (11). All patients underwent electrocardiogram and cytonecrosis biomarker analyses the day following the intervention. Renal failure was defined as creatinine clearance between 30 and 50 ml/min calculated with the Cockroft and Gault formula.

INTERVENTION. Patients were enrolled just after diagnostic angiography but before the PCI procedure, and underwent open label randomization. Randomization was generated through randomly permuted blocks and randomization list was independently generated for each center and automatically integrated into an e-CRF website. Patients were randomized between Xience EES and Elutax SV/Emperor (experimental group) in a 1:1 fashion. In order to

reduce the confusion in event allocation, we decided to keep a maximum of 1 lesion per patient treated with any study device. If any additional lesion required treatment, the choice of intervention was left to the discretion of the operator.

In case of allocation to the DES arm, the investigator was left free to pre-dilate and prepare the lesion and post-dilate as required to ensure an optimal angiographic result. If the patient was randomized to the DCB arm, lesion preparation was strongly recommended, and in case of major dissection after predilatation, the investigator could decide to convert the intervention into a DES-based one. DCB inflation time had to be at least 30 s. In case of major, flow-limiting dissection or residual stenosis >50% after DCB use, the patient could be treated with DES; in this case, the stent length had to be inferior to the DCB (avoiding "geographic mismatch"), and the group allocation of the patient did not change (intention-to-treat analysis).

The PCI procedure was then performed according to current European Society of Cardiology guidelines (10). including the periprocedural and subsequent antithrombotic regimen. After DCB use, a minimum of 30 days of dual antiplatelet treatment was required (stable patients). In case of DES implantation, a minimum of 6 months was required. All patients with acute coronary syndrome received a 12-month prescription of 2 antiplatelet agents. All patients were discharged with a scheduled 6-month angiographic assessment and with 12-month and 24-month clinical visits.

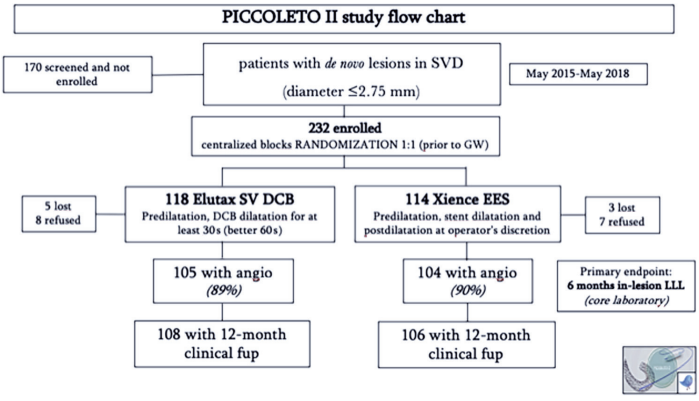
STUDY DEVICE. The technical characteristics of Elutax SV (also marketed as Emperor in some European countries) have been described previously (12). Briefly, this DCB elutes paclitaxel that is loaded on a folded balloon at dosage of ≅2.2 μg/mm^2 (tolerance of 1.4 to 3.00 μg/mm^2). The drug is added with dextran, which acts as an excipient to modulate paclitaxel diffusion in the vessel wall upon balloon inflation and to allow its persistence for the first 3 to 4 weeks. The drug uptake measured in different animal models is highest after 1 h and decreases slowly over days and weeks, with values at the beginning of around 250 μg/ml decreasing to around 100 μg/ml after 1 week to 10 μg/ml after 4 weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time, within the therapeutic window of paclitaxel; in a preclinical study by Lamichhane, only 10% to 20% of the total drug loaded was lost during transit, whereas ~80% was delivered during balloon inflation time.

STUDY ENDPOINTS. For the primary objective of PICCOLETO II, we hypothesized the noninferiority of the DCB arm versus the DES arm in terms of in-lesion late lumen loss (LLL). Angiographic success was defined as final stenosis <30% in the DCB arm and <20% in the DES arm, without major, flow-limiting dissections and Thrombolysis In Myocardial Infarction flow grade 3. This was caused by the intrinsic difference between a stent and a DCB, which is more prone to acute recoil due to the absence of scaffolding properties, especially for some types of de novo lesions. Procedural success was defined as angiographic success and the absence of in-hospital cardiovascular complications. Secondary angiographic endpoints were post-intervention minimal lumen diameter (MLD) and 6-month percent diameter stenosis, MLD, and binary restenosis. Clinical endpoints were major adverse cardiovascular events (MACE, a composite of cardiac death, MI, target lesion revascularization [TLR]) and the single components of MACE at 1 and 2 years.

ANGIOGRAPHIC ANALYSIS. Baseline and follow-up angiographies were assessed in an independent core lab (University of Ferrara, Ferrara, Italy). Study investigators were committed to perform at least 2 orthogonal views pre-procedurally, after the intervention, and during follow-up angiography, maintaining similar angulations. Additional views were requested for the correct localization of DCB and stent. Quantitative coronary artery analysis was performed using the Q-Angio XA system version 7.2 (Medis Medical Imaging Systems, Leiden, the Netherlands) by experienced operators.

STATISTICAL ANALYSIS. The study hypothesis was that PCI with Elutax SV was noninferior to PCI with the latest-generation DES for the treatment of native small coronary vessels, in terms of in-lesion LLL. Accordingly, the power calculation of the PICCOLETO II trial included the assumption of a LLL of 0.20 mm in the EES arm, with a delta of 0.35, alpha of 5%, power of 90%, and a noninferiority margin of 0.25 mm (5). The estimation of 0.20 mm of LLL in the control group was derived by previous studies with the same device, in a similar lesion setting. Therefore, we calculated a population of 99 patients per group. With an attrition rate for the angiographic follow-up of 10%, we decided to include a total population of 230 patients. In case the primary analysis confirmed the noninferiority hypothesis, a secondary analysis assessing superiority was predefined. We used Cox proportional hazards models

FIGURE 1 Study Flow Chart and Follow-Up of the PICCOLETO II Trial



angio = angiography; DCB = drug-coated balloon; EES = everolimus-eluting stent(s); fup = follow-up; GW = guidewire; LL = late lumen loss; PICCOLETO II = Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment trial; SVD = small vessel disease.

and Kaplan-Meier curves to analyze time-related events. Hazard ratios (HRs) were presented with 95% confidence interval (CI). For baseline characteristics, continuous variables were reported as mean ± SD (Mann-Whitney *U* test), and categorical variables as frequency with percentage, with 95% CI determined by the Wilson score method. A prespecified subgroup analysis was done for sex, age, renal failure, diabetes, MI at presentation, SYNTAX score >20, hemoglobin <10 g/dl, severe coronary calcification, and lesion length >20 mm. Adjusted odds ratios were calculated with a logistic regression model, and HR with a Cox model. All p values of <0.05 were considered statistically significant. Results were analyzed by intention to treat for primary and secondary endpoints. All statistical analyses were performed with SPSS software (version 24, IBM, Chicago, Illinois).

TABLE 1 Demographic Characteristics and Comorbidities of the Study Population at Baseline

	DES (n = 114)	DCB (n = 118)	p Value
Male	87 (76.9)	83 (70.3)	0.25
Age, yrs	66 (50-82)	64 (48-80)	0.32
Hypertension	76 (67.2)	77 (65.2)	0.74
Diabetes	40 (35.4)	45 (38)	0.65
Insulin-dependent diabetes	15 (13.3)	21 (17.8)	0.66
Smoking	19 (16.7)	23 (19.5)	0.84
Dyslipidemia	63 (55)	72 (61)	0.66
Renal failure	12 (10.6)	4 (3.3)	0.03
Previous MI	34 (30)	45 (38)	0.19
Previous CABG	4 (3.5)	4 (3.3)	0.95
Previous PCI	60 (53)	59 (50)	0.33
LVEF	58 (51-65)	58 (48-68)	0.89
Clinical presentation			
Stable angina	63 (55.7)	64 (54.2)	0.81
Unstable angina	18 (16)	17 (14.4)	0.74
NSTEMI	23 (20.3)	25 (21.1)	0.87
STEMI, late comers	9 (8)	12 (10.3)	0.34

Values are n (%) or median (interquartile range).

CABG = coronary artery bypass grafting; DCB = drug-coated balloons; DES = drug-eluting stent(s); LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

RESULTS

A total of 402 consecutive patients were screened at study centers between May 2015 and May 2018 (**Figure 1**). A total pf 232 patients were finally randomized after the exclusion of 170 patients due to the presence of at least 1 exclusion criterion, or the unwillingness to participate in the study. After randomization, 114 patients were allocated to the DES group, and 118 to the DCB group by intention to treat. **Table 1** describes the baseline characteristics, which were well matched, except for a higher rate of renal failure in the DES group. Overall, 127 patients had stable coronary disease and 105 an acute coronary syndrome at hospital admission.

Table 2 describes baseline angiographic and procedural characteristics. Of note, the percentage of patients with lesion pre-dilatation (84% vs. 69%; p = 0.007), length of device used (21.8 ± 8.2 mm vs. 18.3 ± 6.9 mm; p = 0.04), and mean duration of study device inflation (49 vs. 21 s; p = 0.003) were higher in the DCB group. By contrast, patients in the DES group more often received balloon post-dilatation (59.4% vs. 3.3%; p = 0.001). Interestingly, the rate of bailout stenting in the DCB arm was particularly low (6.8%). As expected, the in-lesion acute gain rate was higher in the EES arm (1.47 ± 0.3 mm vs. 0.99 ± 0.4 mm; p = 0.03), and percent diameter stenosis at the end of PCI was numerically, but not statistically, higher in the DES arm (13 ± 18% vs. 21 ± 22%; p = 0.2). Angiographic and procedural success were not different between the groups. The rate of in-hospital complications related to the intervention was not significantly different as well. However, we observed a not statistically significant increase in periprocedural MI in the DES group (8% vs. 4%; p = 0.07).

After a median of 189 (interquartile range: 160 to 202) days, 105 patients (89%) in the DCB arm, and 104 (90%) in the DES arm underwent the scheduled angiographic control. Of the 23 patients who did not receive control angiography, 18 refused to undergo the planned invasive assessment, and 5 were lost at follow-up.

In-lesion LLL, the primary study endpoint, was significantly lower in the DCB arm (0.04 ± 0.28 mm vs. 0.17 ± 0.39 mm) and showed the hypothesized noninferiority (p = 0.001), but also the superiority (p = 0.03) as compared with DES (Central Illustration). Table 3 describes the angiographic performance of the 2 study groups after the intervention and at angiographic follow-up. Notably, in-lesion binary restenosis (6.5% vs. 6.3%; p = 0.98) and percent diameter stenosis (21.6 ± 13% vs. 25.1 ± 11%; p = 0.37) were similar in both arms.

Twelve-month clinical follow-up (median 348, interquartile range: 292 to 390 days) was obtained in 108 DCB and 106 DES patients (92.2% of the enrolled population). MACE occurred in 7.5% of the DES group and in 5.6% of the DCB group (p = 0.55) (Table 4). There was a numerically, but not significantly, higher incidence of spontaneous MI (4.7% vs. 1.9%; p = 0.23) and vessel thrombosis (1.8% vs. 0%; p = 0.15) in the DES arm. Death, cardiac death, TLR, and target vessel revascularization were not significantly different in the 2 groups. The risk of MACE at 12 months was also not different across the prespecified study groups, and no interaction was found after formal testing (Central Illustration). A Kaplan-Meier analysis of the secondary endpoint MACE is presented in Figure 2.

TABLE 2 Lesion Characteristics and Procedural Aspects

	DES (n = 114)	DCB (n = 118)	p Value
SYNTAX score	17 ± 12	16 ± 11	0.36
Bifurcation lesion	14 (12.3)	15 (12.7)	0.94
Multivessel disease	86 (76)	86 (72.8)	0.5
Target vessel LAD	44 (39)	47 (40)	0.31
Target vessel LCx	35(31)	44 (37.2)	0.12
Target vessel RCA	34 (30.2)	27 (22.8)	0.19
Total contrast use, ml	155 (67–289)	152 (75–301)	0.37
Total fluoroscopy time, min	11 (4 to 67)	13 (5 to 59)	0.22
Pre-dilatation	78 (69)	99 (84)	0.007
Post-dilatation	66 (59.4)	4 (3.3)	0.001
Scoring balloon use for lesion preparation	18 (15.8)	26 (22)	0.13
Number of devices used, mean	1.12	1.03	0.004
Length of device used, mm	18.3 ± 6.9	21.8 ± 8.2	0.006
Inflation pressure, atm	13.7 ± 2.5	11.4 ± 3.3	0.03
Duration of inflation, s	21.4 ± 11.8	49.2 ± 14.5	0.002
Bailout stenting	–	8 (6.7)	–
Angiographic success	113 (99.1)	116 (98.3)	0.88
Procedural success	112 (98.2)	116 (98.3)	0.92
Peak troponin I after the intervention, ng/ml	6.14 ± 5.80	3.6 ± 3.21	0.09

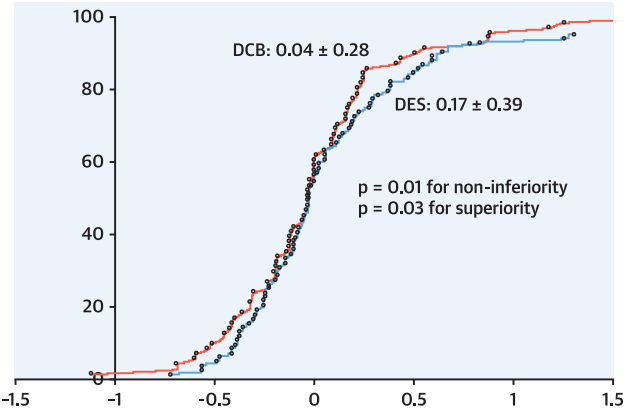
Values are mean ± SD, n (%), or median (interquartile range).
LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; RCA = right coronary artery; other abbreviations as in Table 1.

A specific sensitivity post hoc analysis regarding a comparison between patients with DES implanted after DCB (8 patients, 6.8%) and patients allocated to the control group and the sole-DCB group did not show differences in terms of MACE (respectively, 12.5% vs. 7.5%; p = 0.21, and 12.5% vs. 4.9%; p = 0.08). Likewise, pre-dilatation in the DCB arm did not affect either the angiographic or the clinical outcome (LLL 0.07 ± 0.16 mm in patients without pre-dilatation vs. 0.02 ± 0.31 mm; p = 0.31).

DISCUSSION

SUMMARY OF THE STUDY RESULTS. The PICCOLETO II trial was a multicenter, multinational randomized clinical trial meeting the primary endpoint of non-inferiority and showing the superiority of a new-generation DCB versus a current-generation DES regarding LLL in patients with de novo SVD. Both strategies provide equivalent efficacy in other important surrogate angiographic endpoints including MLD and percent diameter stenosis at follow-up. Although underpowered for clinical events, our study suggests similar mid-term efficacy

CENTRAL ILLUSTRATION **Primary Measure of Outcome, In-Lesion Late Lumen Loss**



Cortese, B. et al. J Am Coll Cardiol Intv. 2020;■(■):■–■.

Primary measure of outcome, in-lesion late lumen loss (LLL), showing both noninferiority and superiority of DCB **(blue)** versus DES **(red)**. DCB = drug-coated balloon; DES = drug-eluting stent(s).

TABLE 3 **Outcomes at 6-Month Angiographic Follow-Up**

	DES (n = 104)	DCB (n = 105)	p Value
Pre-procedure			
RVD, mm	2.18 ± 0.4	2.23 ± 0.4	0.46
MLD, mm	0.83 ± 0.4	0.82 ± 0.5	0.98
Stenosis, % of lumen diameter	76 ± 15	75 ± 17	0.83
Lesion length, mm	14.0 ± 6.9	13.5 ± 7.3	0.75
Post-procedure, in-lesion			
MLD, mm	2.29 ± 0.4	1.89 ± 0.3	0.02
Stenosis, % of lumen diameter	13.1 ± 18	21.4 ± 22	0.20
Acute gain, mm	1.47 ± 0.3	0.99 ± 0.4	0.03
Post-procedure, in-segment			
MLD, mm	1.93 ± 0.3	1.73 ± 0.3	0.04
Stenosis, % of lumen diameter	26.8 ± 12	29.6 ± 16	0.55
Acute gain, mm	1.10 ± 0.2	0.85 ± 0.2	0.05
At follow-up, in-lesion			
MLD, mm	2.12 ± 0.53	1.85 ± 0.49	0.14
Stenosis, % of lumen diameter	21.6 ± 13	25.1 ± 11	0.37
Binary restenosis	7 (6.5)	7 (6.3)	0.98
Late loss, mm	**0.17**	**0.04**	**0.03 for superiority**
At follow-up, in-segment			
MLD, mm	1.79 ± 0.48	1.74 ± 0.46	0.69
Stenosis, % of lumen diameter	32.2 ± 19	36.6 ± 21	0.78
Binary restenosis	10 (9.6)	11 (10.5)	0.94
Late loss, mm	0.14 ± 0.38	0.01 ± 0.25	**0.03 for superiority**
Net luminal gain*	0.96 ± 0.23	0.84 ± 0.19	0.49

Values are mean ± SD or n (%). *Acute gain − late lumen loss. **Bold** indicates a primary endpoint.
MLD = minimal lumen diameter; RVD = reference vessel diameter; other abbreviations as in Table 1.

with both strategies, with a trend suggesting a safer profile of DCB in this challenging anatomic scenario.

NATIVE SVD TREATMENT OPTIONS. We would like to stress the importance of finding an optimal treatment strategy for these lesions accounting for 30% to 50% of all coronary interventions in the Western world, with percentages even higher in some Eastern countries. The general DES strategy in native coronary vessel disease seems weaker here, because the mid-term angiographic performance of DES is reduced and the restenosis rates higher. In the SVD setting, the prospective Spirit SV (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System Small Vessel) study accounts for a target lesion failure rate of 10.8% after 13 months with Xience DES (5). The cumulative data analysis of the SPIRIT and COMPARE (Second-Generation Everolimus-Eluting and Paclitaxel-Eluting Stents in Real-Life Practice) studies shows a 2-fold risk of MACE versus larger vessels (10.4% vs. 5.6%; $p < 0.001$) (13), with a significantly higher risk of MI and TLR. The TWENTE II (DUTCH PEERS [DUrable polymer-based sTent CHallenge of Promus ElemEnt versus ReSolute integrity]) study showed similar data, with a target lesion failure rate of 9.5% versus

TABLE 4 Outcome After 12 Months

	DES (n = 106)	DCB (n = 108)	p Value
MACE	8 (7.5)	6 (5.6)	0.55
Total death	1 (0.9)	0 (0)	0.78
Cardiac death	0 (0)	0 (0)	–
Myocardial infarction,	4 (4.7)	2 (1.9)	0.23
TLR	6 (5.6)	6 (5.6)	0.80
BARC bleeds type 3 or 5	0 (0)	0 (0)	–
Vessel thrombosis	2 (1.9)	0 (0)	0.15

Values are n (%).

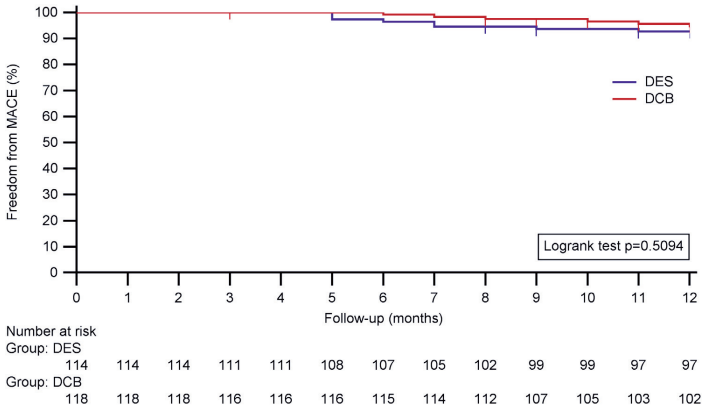
BARC = Bleeding Academic Research Consortium; MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

5.4% in larger vessels after 2 years (HR: 1.60, 95% CI: 1.09 to 2.34), and a significantly higher risk of MI and TLR in the SVD setting (3.1% vs. 1.3%, 4.8% vs. 2.8%. respectively) (7).

The use of DCB may have some potential advantages in this setting (14): it may theoretically overcome the risk of negative vessel remodeling obtained with plain balloon angioplasty, and both the immediate encumbrance and the subsequent neointimal proliferation after stent implantation may be reduced. DCB share dedicated technologies that allow the delivery and persistence of the drug released upon inflation (either paclitaxel or sirolimus are available in the European market). An effective DCB may also exert a positive remodeling effect, which can be perceived to be particularly advantageous in small coronary lumens; this has been already demonstrated with at least 2 different brands of paclitaxel-coated balloons, including the device tested in the PICCOLETO II trial (15,16). Another potential advantage of DCB over stents in native vessel disease is related to the perpetual yearly risk of ≅2% of adverse events with current-generation DES (17), as compared with the theoretical absence of such risk with DCB after the first year in de novo lesions (18,19).

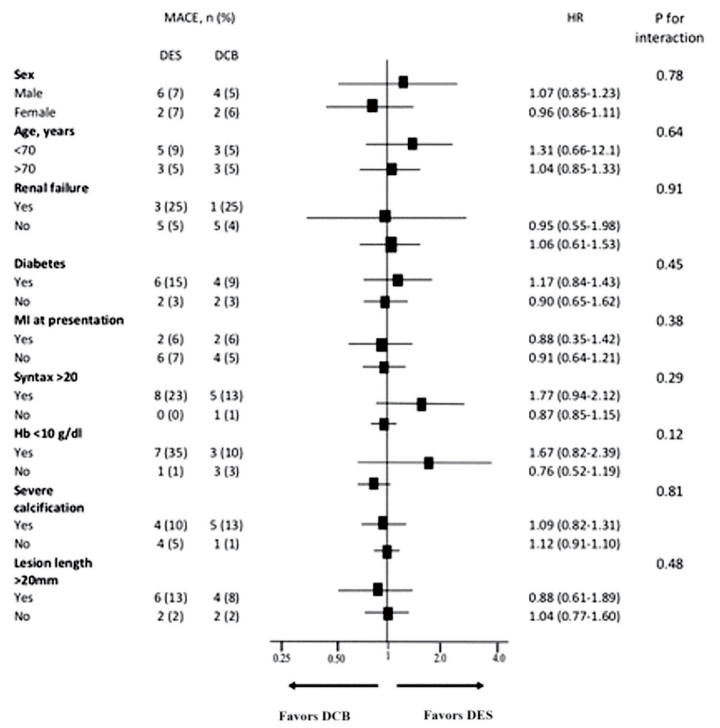
PREVIOUS STUDIES. To date, randomized studies on the use of DCB in small vessels brought variable results. The first-generation Dior DCB (Eurocor, Bonn, Germany) failed to show the angiographic noninferiority versus Taxus DES (Boston Scientific, Marlborough, Massachusetts) in the prematurely interrupted PICCOLETO study, where the rate of MACE after 9 months was higher in the DCB arm (20). The limited effectiveness of this preliminary DCB was blamed for the results (21). On the other hand, newer-generation DCB showed the potential advantages of this technology in native vessel disease. The BELLO study (Balloon Elution and Late Loss Optimization Study) was able to show the angiographic superiority of the In-Pact Falcon DCB (Invatec-Medtronic, Frauenfeld, Switzerland) versus the Taxus

FIGURE 2 Kaplan-Meier Analysis of the Secondary Endpoint MACE at 1 Year



MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

FIGURE 3 Risk of MACE at 12 Months



Risk of MACE at 12 months was not different across the pre-specified study groups, and no interaction was found after formal testing. HR = hazard ratio; other abbreviations as in **Figures 1 and 2**.

stent, and the 3-year data also showed a significant reduction in the rate of MACE (14% vs. 30%; p = 0.015) (18). More recently, the RESTORE SVD (Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease) study compared Restore DCB (Cardionovum, Bonn, Germany) to DES and showed the noninferiority of DCB in terms of percent diameter stenosis during angiographic follow-up (11% vs. 7.5%; p for noninferiority <0.001), with no significant differences in terms of LLL (0.25 ± 0.42 vs. 0.27 ± 0.36; p = 0.41) and 12-month MACE (4.4% vs. 2.6%; p = 0.72) (22). The largest study (powered for clinical endpoints) assessing the role of DCB in a SVD setting (reference vessel diameter <3 mm) after successful lesion pre-dilatation was the BASKET SMALL II (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs. Drug Eluting Stents in Small Vessel Interventions) study. In this study, Sequent Please DCB (B. Braun, Melsungen, Germany) was compared with DES (72% Xience, 28% Taxus). The primary endpoint of MACE at 12 months was 7.3% in the DCB group and 7.5% in the DES group (HR: 0.97, CI: 0.58 to 1.64; p = 0.92) (23).

PRESENT STUDY. The PICCOLETO II study for the first time to our knowledge showed the angiographic superiority, as per the LLL endpoint, of a new-generation DCB versus 1 of the latest-generation DES in a native vessel disease setting, with comparable clinical outcome at 1 year. This finding was

confirmed in all pre-specified subgroups (**Figure 3**). These data seem particularly appealing, taking into consideration the direct correlation between measures of angiographic outcome such as LLL and percent diameter stenosis and late clinical events, and might reflect a favorable effect of paclitaxel delivery by means of DCB leading to late lumen enlargement (15,16). To note, the most important difference between our study and the 2 most recent ones (the BASKET SMALL II and RESTORE SVD trials [22,23]) is that whereas in the latter studies randomization was performed after successful lesion predilatation, in the PICCOLETO II trial, it was performed before lesion preparation, reflecting a real intention-to-treat strategy, of special value for the "real-world" patients seen in routine clinical practice. Despite this, the rate of crossover to stenting from the DCB group or reverse (e.g., a patient assigned to DCB treated instead with DES) was negligible (4.4%). We chose this randomization strategy because the presence of a non–flow-limiting dissection before or after DCB use has not been correlated with worse outcomes in 1 of our previous studies (16).

MORTALITY AFTER DCB USE. A specific mention should be made regarding the hypothetical increase in mortality after paclitaxel application for femoropopliteal interventions (24–26). A recent meta-analysis of randomized controlled trials in the coronary territory showed no increase in mortality after DCB application during PCI as compared with other options including simple angioplasty and bare-metal stent or DES implantation, with a significant reduction in mortality after 3 years with DCB (relative risk: 0.73; 95% CI: 0.53 to 1.00; p = 0.047) (19). The results of the PICCOLETO II trial did not show any safety signal at mid-term follow-up and go in the same direction of the data provided by the latter meta-analysis.

STUDY LIMITATIONS. First of all, due to the open-label nature of the study, some ascertainment bias cannot be completely excluded. However, all clinical data were analyzed by an independent blinded clinical event committee, and an independent core laboratory analyzed the angiographic outcome measures. Second, this study is not powered for hard clinical endpoints. Third, these results have been obtained in centers that had to certify a strong leadership in the use of DCB, therefore it is possible that the results are not reproducible in a different scenario. Finally, the primary endpoint chosen, LLL, could favor the DCB in consideration of the better post-procedural MLD after DES implantation.

CONCLUSIONS

The PICCOLETO II trial for the first time shows the angiographic superiority in terms of LLL, and the equivalence in terms of MLD and percent diameter stenosis, of a novel DCB over 1 of the best-in-class DES for the treatment of de novo coronary lesions in small vessels. This trial also shows the clinical noninferiority of the DCB strategy after 12 months.

AUTHOR RELATIONSHIP WITH INDUSTRY

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Small vessel coronary artery disease still represents a challenging subset for DES.

WHAT IS NEW? This is the first randomized study to show an improved angiographic outcome of "new generation" DCB versus DES in small coronary vessel disease.

WHAT IS NEXT? A larger study adequately powered for hard clinical endpoints is needed in order to confirm these findings.

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KEY WORDS drug-coated balloon, everolimus-eluting stent(s), small coronary vessel disease, native vessel disease

Cardiovascular Revascularization Medicine xxx (xxxx) xxx

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Cardiovascular Revascularization Medicine

Comparison between sirolimus and paclitaxel-coated balloon for revascularization of coronary arteries. The SIRPAC (SIRolimus-PAClitaxel) study

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ABSTRACT

Objective: Our study sought to compare the 12-month clinical outcome of patients treated with paclitaxel-coated balloons (PCB) vs. sirolimus-coated balloons (SCB) during coronary angioplasty.
Background: Drug-coated balloons represent an established therapeutic tool for percutaneous coronary interventions (PCI). A comparison between PCB and SCB is still lacking.
Methods: We performed an indirect comparison between two cohorts of patients previously included into two investigator-driven registries with clinical primary endpoints, 494 treated with the Elutax SV PCB (AR Baltic, Lithuania) from the DCB RISE registry, and 596 treated with the Magic Touch SCB (Concept Medical, India) from the EASTBOURNE registry. The primary endpoint was the rate of major adverse cardiovascular events (MACE) at 12-month clinical follow-up.
Results: After propensity score matching, a total of 580 patients were well matched for baseline clinical and procedural characteristics and were analyzed. At 12 months there was no significant difference between the matched DCB RISE and EASTBOURNE cohorts in terms of the primary endpoint MACE (10.3% DCB RISE vs. 10.7% EASTBOURNE, $p = 0.892$). No significant difference was observed also regarding the rate of TLR (7.9% DCB RISE vs. 8.3% EASTBOURNE; $p = 0.879$, respectively). By multivariate analysis, insulin-dependent diabetes was the only predictor of MACE.
Conclusions: In the SIRPAC study, the first indirect comparison between paclitaxel-coated and sirolimus coated balloons, no significant difference in clinical endpoints were found at 12-month follow-up. Randomized studies are necessary to confirm these findings.

1. Introduction

Despite an increasing use in the last decade and growing scientific evidences provided to date, drug coated balloons (DCB) are still underused by many interventional cardiologists. Their role for the treatment of in-stent restenosis (ISR) [1] is widely acknowledged and current European Revascularization Guidelines recommend their use in either bare metal stent (BMS) or drug eluting stent (DES) restenosis, with a Class I (LoE A) recommendation [2]. Although an official endorsement by clinical guidelines for their use in "de novo" lesions is still lacking, there are several studies suggesting their role in such context, especially in selected clinical and anatomical settings such as small vessel disease [3,4]. In addition, DCB represent an appealing alternative in high-bleeding risk patients, where DES implantation may result in a higher risk of complications [5].

Most of the currently available DCB are coated with paclitaxel (PCB), a highly lipophilic anti-proliferative drug, chemically stable after tissue delivery [6]. However, new debatable findings regarding the long-term safety of paclitaxel-eluting devices (either stents or balloons) for peripheral use have recently raised some concerns in the interventional cardiology field. In fact, a meta-analysis of patients with peripheral artery disease located in the femoro-popliteal vessels suggested a higher risk of mortality after 2 and 4–5 years associated to the use of such

Abbreviations: BMS, Bare-Metal Stent; DES, Drug-Eluting Stent; DCB, Drug-Coated Balloon; ISR, In-Stent Restenosis; MACE, Major Adverse Cardiovascular Event; MI, Myocardial Infarction; PCB, Paclitaxel-Coated Balloon; PCI, Percutaneous Coronary Intervention; SCB, Sirolimus-Coated Balloon; TLR, Target Lesion Revascularization.

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1553-8389/

devices [7]. Thereafter, many interventional cardiologists wondered if PCB could have undesirable long-term effects also in the coronary setting. As a consequence, the perception that other anti-proliferative drugs including -limus analogues could be safer than paclitaxel, led to a substantial boost of the research of newer devices in the field.

In 2016 Magic Touch (Concept Medical, India) was the first sirolimus DCB (SCB) being marketed in Europe and some Asian countries. Thenceforth, some small studies showed the short and mid-term safety and efficacy profile of this device in coronary artery disease [8–11]. Given the absence of any direct comparison between sirolimus and paclitaxel in an "all comer" population, the aim of the SIRPAC study was to compare a new generation paclitaxel-DCB to the Magic Touch SCB.

2. Methods

2.1. Study design

The SIRPAC study was designed to provide a propensity-score matched comparison of clinical outcomes at 12 months between patients enrolled in the DCB RISE and EASTBOURNE registries.

The DCB RISE [12] was an investigator-initiated registry with prospective data-entry of patients treated with Elutax SV (also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) DCB. The aim of this study was to assess the safety and efficacy of Elutax SV at the longest available clinical follow-up. DCB-RISE represented a real-world registry, enrolling 544 all-comer patients at nine Italian centers. A complex, real world population was enrolled, with 32% of diabetics and 51.3% of patients presenting with an acute coronary syndrome. The primary study endpoint was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success and the occurrence of a device-oriented endpoint (DOCE), including cardiac death, target vessel myocardial infarction (MI), stroke, or TLR.

The EASTBOURNE [13] is an ongoing, prospective, multicenter, investigator-initiated, real-world clinical registry with external validation of quality of data input and centralized clinical event assessment, evaluating the performance Magic Touch SCB at 40 European and Asiatic centers. To date, EASTBOURNE represents one of the largest studies in this field, including 2000 consecutive patients with a broad spectrum of lesions, including native vessel disease and in-stent restenosis, and clinical presentations. Similar to DCB RISE, the primary endpoint of the study is TLR at 12 months. Secondary endpoints are: angiographic success, procedural success, MACE at 6, 12, 24 and 36 months. In both studies, patients enrolled underwent a clinical follow up, up to twelve months after the procedure. For the purpose of this analysis we compared the published 12 months clinical outcome of the DCB RISE [12] with the published 12 months "*ad interim*" analysis of the EASTBOURNE [13]. All the events reported in the 2 registries were centrally adjudicated by a dedicated committee. In both registries the manufacturer had no role on the study design, the analysis and interpretation of the data and the publication of the results. Both registries were approved from the Ethical Committee of each center involved.

Inclusion criteria for both studies were symptomatic coronary artery disease (including patients with chronic stable angina, silent ischemia, and acute coronary syndromes) with clinical indication to PCI. Exclusion criteria were the following:

- ☐ Patients with known (and untreatable) hypersensitivity or contraindication to aspirin, heparin, clopidogrel, prasugrel, ticagrelor, sirolimus or a sensitivity to contrast media which cannot be adequately pre-medicated.
- ☐ Patients participating in another clinical evaluation.
- ☐ Target lesion/vessel with any of the following characteristics:
  - o successful pre-dilatation not performed in the target lesion, or not efficacious (residual stenosis >50%);
  - o severe calcification of the target vessel, also proximal to the lesion;
  - o highly tortuous lesions which can impair access of device to treatment site.
- ☐ Visible thrombus at lesion which is not treatable with aspiration.

2.2. Devices description

The Elutax SV is a paclitaxel-coated balloon whose characteristics have been previously described [12]. Briefly, the device consists in a semi-compliant balloon coated with 2.2 μg paclitaxel/mm^2; the top coating is made of 0.7 μg dextran/mm^2, with a maximum amount of 1.89 μg dextran/mm^2, which acts as excipient (drug carrier). After the balloon inflation, the drug is released to the tissue of the vessel wall; the highest uptake of paclitaxel occurs after 1 h and decreases slowly over days and weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time.

Magic Touch is a non-compliant balloon coated with sirolimus through the use of a spray coating on inflated balloon with a technology specifically designed (Nanolutè®); in order to exert its effects, sirolimus is encapsulated in a protective lipophilic package, which allows drug diffusion and transfer into the arterial wall during balloon inflation, overcoming the drug inherent low lipophilia. This package consists of nanospheres of 100–300 nm diameter. The total dosage of the drug corresponds to 1.25 mg/mm^2 of the balloon surface, well within the therapeutic window of the drug. The blood concentration reaches its peak in 30 min, and then disappears within 24 h, while the drug is still detectable within the tissue after 14 days [14].

2.3. Endpoints definition

Primary endpoint of the SIRPAC study was major adverse cardiovascular events (MACE) at 12 months, a composite endpoint including target lesion revascularization (TLR), non-fatal myocardial infarction (MI) and total death. Secondary endpoints were the single components of MACE and a safety endpoint, type 2–4 bleedings according to the BARC classification [15]. TLR was defined as repeated percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the target segment including 5 mm proximal and distal to the previously treated lesion. MI was defined according to the third universal definition of myocardial infarction [16].

2.4. Statistical analysis

Continuous variables are reported as mean ± SD and were compared using ANOVA or Man-Whitney *U* tests. Categorical variables are reported as counts and percentages, and were compared using chi-square or Fisher exact tests. In order to control for confounders between the DCB RISE and EASTBOURNE, a propensity score matching was applied. A propensity (likelihood to undergo major adverse cardiovascular events) score was calculated by means of a multivariate logistic regression model encompassing baseline demographics, clinical, angiographic, and procedural risk factors (age, type 2 diabetes, hypercholesterolemia, smoke, chronic kidney disease, acute coronary syndrome, in-stent restenosis, small target vessel). Patients with similar propensity scores in the two treatment groups were matched using a greedy nearest neighbor matching within specified caliper widths without replacement. Patients without matched observations were excluded. We used C-index and Hosmer Lemeshow goodness of fit test to assess the appropriateness of the model.

All reported *p* values are 2-sided, and p values <0.05 were considered to indicate statistical significance. Univariate analysis was conducted to identify factors associated with MACE at 12 months. Significant factors from univariate analyses were entered into a multivariate logistic regression model. All data were processed using the

Table 1
Patients characteristics and procedural details (before PSM).

	DCB RISE ($n = 494$)	EASTBOURNE ($n = 596$)	p value
Age (mean ± SD)	68 ± 11	65 ± 11	0,001
Male n (%)	349 (71)	479 (80)	<0,001
Hypertension n (%)	340 (69)	441 (74)	0,004
Hypercholesterolemia n (%)	299 (60)	423 (71)	0,008
Smoke n (%)	177 (36)	164 (27)	0,003
Diabetes n (%)	158 (32)	244 (41)	0,012
Family history n (%)	128 (26)	149 (25)	0,203
Previous MI n (%)	181 (37)	263 (44)	0,252
Previous PCI n (%)	324 (66)	408 (68)	0,159
Previous CABG n (%)	61 (12)	76 (13)	0.662
CKD n (%)	54 (11)	61 (10)	0,360
LVEF (%) (mean ± SD)	53 ± 9	52 ± 11	0,322
ACS	243 (49)	267 (45)	0,088
Small vessels (≤ 2,5 mm)	204 (41)	330 (55)	<0,001
In-stent restenosis n (%)	281 (57)	274 (46)	<0,001
Lesion length (mm) (mean ± SD)	17 ± 7	19 ± 9	<0,001
Pre-dilation n (%)	399 (81)	543 (91)	<0,001
DCB diameter (mm) (mean ± SD)	2,8 ± 0,5	2,7 ± 0,6	<0,001
DCB length (mm) (mean ± SD)	20 ± 6	22 ± 7	<0,001
DCB inflation time (*sec*) (mean ± SD)	56 ± 26	60 ± 26	0,007
DCB inflation pressure (atm) (mean ± SD)	11 ± 4	10 ± 4	0,039
Angiographic success n (%)	481 (97)	576 (97)	0,304

PSM = Propensity Score Matching; SD = Standard Deviation; IDDM = insulin–dependent diabetes mellitus; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery By-pass Grafting; CKD = chronic kidney disease; ACS = Acute Coronary Syndrome; DCB=Drug coated balloon.

Table 2
Patients characteristics and procedural details (after PSM).

	DCB RISE ($n = 290$)	EASTBOURNE (n = 290)	p value
Age (mean ± SD)	67 ± 11	66 ± 12	0,507
Male n (%)	219 (75)	224 (77)	0,625
Hypertension n (%)	200 (69)	216 (74)	0,153
Hypercholesterolemia n (%)	177 (61)	194 (67)	0,141
Smoke n (%)	90 (31)	84 (29)	0,587
Diabetes n (%)	103 (35)	131 (45)	0,018
Family history n (%)	86 (30)	86 (30)	0,978
Previous MI n (%)	124 (43)	139 (48)	0,254
Previous PCI n (%)	212 (73)	215 (74)	0,885
Previous CABG n (%)	45 (15)	46 (16)	0,938
CKD n (%)	46 (16)	36 (12)	0,233
LVEF (%) (mean ± SD)	53 ± 9	51 ± 11	0,296
ACS	150 (52)	155 (53)	0,678
Small vessels (≤ 2,5 mm)	117 (40)	134 (46)	0,154
In-stent restenosis n (%)	175 (60)	184 (63)	0,442
Lesion length (mm) (mean ± SD)	16 ± 7	18 ± 9	0,001
Pre-dilation n (%)	263 (91)	261 (90)	0,779
DCB diameter (mm) (mean ± SD)	2,8 ± 0,5	2,8 ± 0,6	0,984
DCB length (mm) (mean ± SD)	19 ± 5	22 ± 7	0,001
DCB inflation time (sec) (mean ± SD)	56 ± 30	58 ± 13	0,188
DCB inflation pressure (atm) (mean ± SD)	11 ± 4	11 ± 4	0,400
Angiographic success n (%)	282 (97)	283 (98)	0,794

PSM = Propensity Score Matching; SD = Standard Deviation; IDDM = insulin–dependent diabetes mellitus; PCI = Percutaneous Coronary Intervention; CABG = Coronary Artery By-pass Grafting; CKD = chronic kidney disease; ACS = Acute Coronary Syndrome.

Statistical Package for Social Sciences, version 23 (SPSS, IBM, Chicago, Illinois).

3. Results

3.1. Characteristics of the broad study population

Briefly, a total of 1090 patients were enrolled in the SIRPAC study, 494 from DCB RISE and 596 from EASTBOURNE. The two groups of patients differed significantly for several clinical and procedural characteristics (Table 1). In particular, diabetes was present in 158 patients (32%) in the DCB RISE, while in the EASTBOURNE it was present in 244 (41%) while the number of smokers was higher in the DCB RISE registry compared to the EASTBOURNE ($n = 177$, 36% vs $n = 164$,27%; p 0.003). Also, lesions located in small vessels were more frequent in the EASTBOURNE ($n = 204$, 41% in DCB RISE vs $n = 330$, 55% in EASTBOURNE; $p < 0.001$) whereas in-stent restenosis was more frequent in the DCB RISE ($n = 281$, 57% vs $n = 274$, 46%; $p < 0.001$). In line with these differences, the mean Propensity Score was significantly lower ($p = 0.007$) in the EASTBOURNE compared to the DCB RISE cohort (Fig. 1).

3.2. Characteristics of patients matched for propensity score

The matched cohort consisted in a total of 580 patients, 290 for each group.

The mean age was 67 ± 11 years and men accounted for 443 (76%) of patients. Diabetes mellitus was present in 234 patients (40%). A total of 305 patients (53%) presented with an ACS, and the culprit lesion occurred in an ISR segment in 359 cases (62%). The mean lesion length was 17.3 ± 8.1 mm. In the matched cohorts there was no significant difference for any covariate, except for diabetes ($n = 103$, 35% vs. $n = 131$, 45%; $p = 0.018$), lesion length and DCB length (Table 2). Accordingly, no significant difference in the mean Propensity Score ($p = 0.98$) was present between the matched cohorts (Fig. 1).

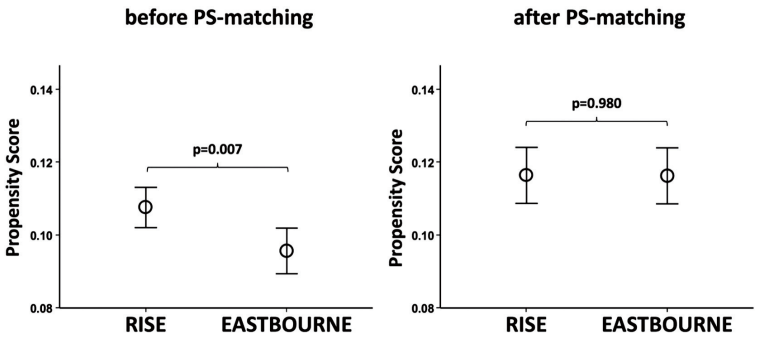

Fig. 1. Propensity score between registries before and after matching.

Table 3
Incidence of clinical endpoints at 12 months (matched cohorts).

	DCB RISE (n = 290)	EASTBOURNE (n = 290)	p value
MACE	30 (10,3)	31 (10,7)	0,892
TLR	23 (7,9)	24 (8,3)	0,879
MI	6 (2,1)	8 (2,7)	0,588
Death	5 (1,7)	4 (1,4)	0,737
Bleeding	2 (0,7)	0	0,157

MACE = Major Cardiovascular Events; TLR = Target Lesion Revascularization; MI = Myocardial Infarction.

3.3. Clinical outcomes of the matched cohorts

At 12 months there was no significant difference between the matched DCB RISE and EASTBOURNE cohorts in terms of the primary endpoint MACE with 30 events (10.3%) in the DCB RISE vs. 31 (10.7%) in the EASTBOURNE (RR = 0.96; 95% CI, 0.60–1.55; $p = 0.892$). No statistical difference was found in the rate of non-fatal acute MI with 6 cases (2.1%) in the DCB RISE vs. 8 (2.7%) in the EASTBOURNE (RR = 0.75; 95% CI, 0.26–2.13; $p = 0.588$) or in the rate of TLR with 23 events (7.9%) in the DCB RISE vs. 24 (8.3%) in the EASTBOURNE (RR = 0.95; 95% CI, 0.55–1.65; $p = 0.879$, respectively). Finally, the rate of BARC 2–4 major bleedings during the follow-up was negligible, without significant differences between the treatment groups (RR = 5.0; 95% CI, 0.24–103.70; $p = 0.157$) (Table 3, Fig. 2). Fig. 3 shows the Kaplan-Meier curves of the primary endpoint and total death rate at 12 months follow-up, again with no significant differences.

3.4. Predictors of adverse clinical outcome

Univariate analysis showed that diabetes, previous MI, ISR and DCB diameter were significant predictors for the occurrence of MACE. At multivariable analysis, diabetes remained the only independent predictor of MACE (Exp B = 2.13; 95% CI, 1.06–4.30; $p = 0.034$) (Table 4).

4. Discussion

SIRPAC is the first study which indirectly compares a SCB with a second-generation PCB in a real-world population of coronary artery disease patients. The main finding of the current study is the absence of significant differences between these 2 devices in terms of clinical endpoints at 1 year. Of note, such findings were confirmed also by the multivariate analysis, where the type of DCB used had no predictive impact on the outcome.

The results of this study are of particular interest, considering the recent warning about a supposed increased risk in late mortality with paclitaxel-eluting devices (DCB or DES) in patients undergoing femoro-popliteal angioplasty, issued after the publication of a meta-analysis by Katsanos et al. [7]; in addition to these unexpected results, last year the U.S. Food and Drug Administration issued a warning on the potential risk of paclitaxel-eluting devices [17]. The lack of biological plausibility for the supposed increased mortality determined by paclitaxel, and the fact that only first-generation devices were investigated with adequate follow up, did not stop the storm against paclitaxel [18–21].

Bittl et al. [22], in a new analysis done applying Bayes factors to the available studies, showed the results by the former meta-analysis to be inconclusive in terms of hard adverse events. Despite these results, such controversial messages led to a decrease in the use of paclitaxel-eluting devices for both peripheral and coronary interventions. Although a signal of late increased mortality cannot be ignored, it is important to point out that:

- Single trials included in the meta-analysis by Katsanos were not powered enough for mortality;
- Paclitaxel systemic exposure after peripheral or coronary interventions is small and self-limited in time, and drug tissue levels are undetectable at 1 year, making it hard to explain how mortality could increase when the drug may not be present anymore [19];
- Much higher dosages of paclitaxel were proven to be safe [23].

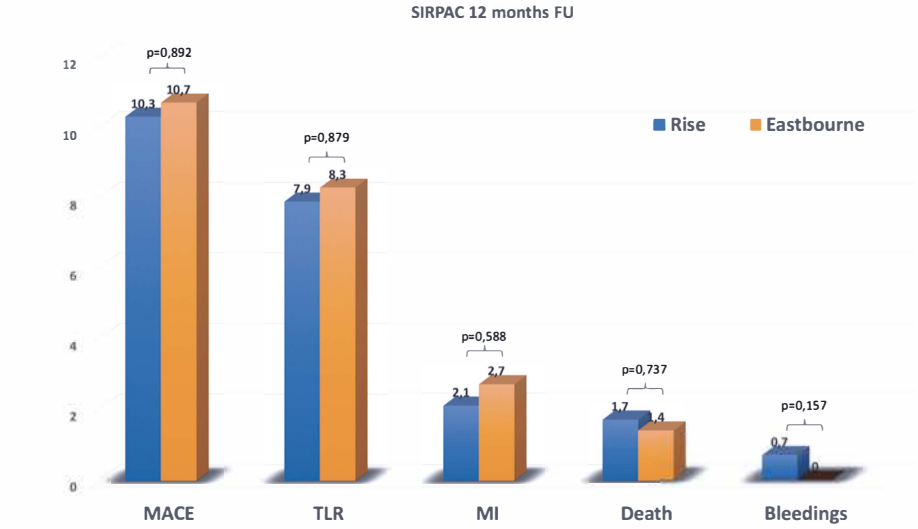

Fig. 2. 12-months clinical outcomes of the SIRPAC study.

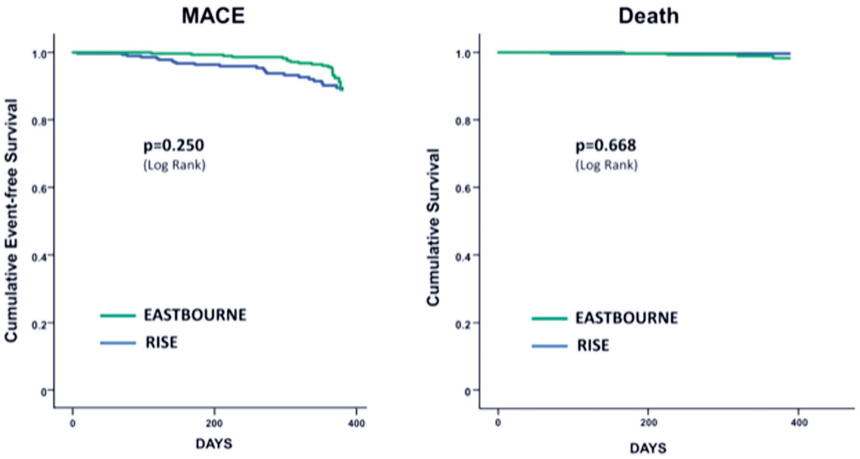

Fig. 3. Kaplan-Meier curves of MACE and total death rate at 12 months follow-up.

Regarding coronary interventions a recently published meta-analysis [24] helped to clear the fog. In this work all available RCTs comparing PCBs with non-PCB devices, for the treatment of both coronary ISR or "de novo" lesions, were included. A clinical follow-up of at least 6 months was required. Interesting, there was no difference in all-cause mortality after 12 months, but a significant reduction after 3 years in DCB-treated patients.

One of the main arguments on this topic is the concept that not all PCBs are equal and there is not a class effect. The meta-analysis of Katsanos takes into consideration only 2 types of the first generation DCB, with devices reporting a high percent of drug loss during manipulation and before reaching the lesion. Afterwards, newer technologies developed drug carriers with higher performances, with the aim of protecting the delivery of the drug to the culprit site, and also a correct distribution during the upcoming weeks in order to exert an effective inhibition of restenosis. This should happen with a limitation of drug loss. It should be noted that we are well aware that the results of SIRPAC do not clarify if the results of the aforementioned meta-analysis should be emphasized or downgraded, taking into consideration the different clinical setting, methodology and the limited follow up duration of our study.

All currently available DES elute a "-limus" drug, which exerts an antiproliferative effect by inhibiting the mTOR chinase. The therapeutic window of this class of drugs is wider than paclitaxel's. The possibility to add sirolimus to a DCB has been extensively studied over the years, with the main difficulties related to the low lipophilia of the drug thence its reduced ability to be retained into the vessel wall upon balloon inflation.

Table 4
Univariate and Multivariate analysis.

	Univariate (p value)	Multivariate Exp B (95% C.I.)	Multivariate (p value)
Diabetes	0,023	2,13 (1,06-4,30)	0,034
Previous myocardial infarction	0,050	1,36 (0,77-2,39)	0,285
ISR	0,010	1,72 (0,85-3,48)	0,128
DCB diameter	0,025	1,33 (0,77-2,31)	0,305

The first DCB eluting sirolimus to be marketed in Europe in 2016 was Magic Touch. A specific protective lipophilic package allows encapsulating the drug into nanospheres, overcoming the low drug lipophilia and allowing a sustained diffusion to the vessel wall. Despite the high expectations on this device, available data in the literature are limited to mid-term follow up. The first experiences and registries showed however promising results [8,9,13,25].

Recently El-Mokdad et al. [11] reported the final result of the Nanolutè study [10], an Indian real world, prospective study, which enrolled 408 patients with ISR or "de novo" lesions and a 24 months follow-up. Magic Touch proved its safety and efficacy in both settings with an overall MACE rate of 4.2%.

Until the results of SIRPAC however, a comparison between DCB eluting sirolimus or paclitaxel was still lacking.

Our analysis contains some limitations that should be acknowledged.

First, this is an indirect comparison between 2 different studies. However we performed an adequate statistical analysis with propensity score matching to overcome such differences, a direct comparison is highly advocated to confirm our results. Data for the SCB have been extracted from the "ad interim" 12 months analysis of the EASTBOURNE registry: the enrollment of this study is expected to finish by Q3 2020. Finally, the follow-up of the current study is limited to 12 months.

5. Conclusions

The SIRPAC study is a non-randomized comparison which shows clinical equivalence between a novel sirolimus-coated balloon and one of the latest generation paclitaxel-coated balloons at 12 months clinical follow up in coronary artery disease patients. Randomized studies are necessary to confirm these findings.

CRediT authorship contribution statement

We state that these were the contributions of each Author to the SIRPAC manuscript:

B. Cortese: conceptualization; data curation; supervision; validation; review & editing.

G. Caiazzo: formal analysis; investigation; methodology; writing.

G. Di Palma: investigation; methodology; data curation; writing.

S. De Rosa: formal analysis, project administration; resources; Bernardo Cortese MD (corresponding author).

Declaration of competing interest

Authors have no competing interest for this manuscript and no relationship with industry.

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Original article

FIC Federazione Italiana di Cardiologia
Italian Federation of Cardiology

Treatment of coronary artery disease with a new-generation drug-coated balloon: final results of the Italian Elutax SV rEgistry-DCB-RISE

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Aims **Drug-coated balloons (DCBs) are a recognized alternative to stents for the treatment of in-stent restenosis (ISR), and there is some initial clinical evidence about their efficacy for the treatment of small coronary vessels. Newer-generation DCBs were developed to overcome the reduced deliverability of the previous generation, also warranting a more effective drug delivery to vessel wall. However, the vast majority of new-generation DCBs still lack of reliability due to paucity of clinical data.**

Methods **Between 2012 and 2015, all patients treated with Elutax SV DCB (Aachen Resonance, Germany) at nine Italian centers were enrolled in this retrospective registry. Primary outcome was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success and occurrence of device-oriented adverse cardiovascular events including cardiac death, target-vessel myocardial infarction, stroke, and TLR. A minimum 6-month clinical follow-up was required.**

Results **We enrolled 544 consecutive patients treated at 583 sites. Fifty-three per cent of the patients had ISR, and the rest native vessel coronary artery disease. Procedural success occurred in 97.5%. At the longest available clinical follow-up (average 13.3 ± 7.4 months), 5.9% of the patients suffered a TLR and 7.1% a device-oriented adverse cardiovascular event. We did not register cases of target-vessel abrupt occlusion. At multivariate analysis, severe calcification at the lesion site was the first determinantfor the occurrence of TLR.**

Conclusion **This registry on the performance of a new-generation DCB shows an adequate profile of safety and efficacy at mid-term clinical follow-up.**

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Keywords: clinical registry, drug-coated balloon, target-lesion revascularization

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Introduction

In recent years, drug-coated balloons (DCBs) have emerged as a therapeutic option in the interventional field.[1,2] Preliminary data showed how DCBs were a valuable treatment strategy in case of in-stent restenosis (ISR), either of bare-metal stent (BMS) or drug-eluting stent (DES).[3–6] Later, DCBs have also been used for the treatment of native coronary vessel disease as an alternative to DES in selected cases.[7] Several paclitaxel-coated balloons were released and obtained the european community mark, with different behavior and outcome, so that a 'class effect' does not exist for this technology. Recent advances, both in terms of device deliverability and effective drug release, and retention led to the creation of the arbitrary names 'second-' or 'latest-generation' DCBs. To this day, the clinical outcome of any of this newer 'generation' of DCBs is not available yet. With the drug-coated balloon- Results of the Italian elutax SV registry (DCB-RISE), we aim to investigate the clinical performance of one of these devices.

Methods

We here report the main results of the DCB-RISE registry, an investigator-initiated, retrospective, all-comer real-world registry of patients who were treated with the Elutax SV (Aachen Resonance, Germany) DCBs. The aim of this registry was to assess the safety and efficacy of Elutax SV at the longest available clinical follow-up. This study was not funded and ethically approved.

Study procedure

All patients underwent percutaneous coronary intervention (PCI) following international guidelines[8,9] and according to local practice. Antithrombotic treatment

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was left at the operator's discretion, with a minimum of 30-day dual antiplatelet therapy (DAPT), that was increased to a minimum of 3 months in case of additional stent implantation, or more based on the clinical indication (e.g. acute coronary syndrome).

Stent implantation after DCB use was discouraged, unless a major dissection (>type B) or vessel recoil was discovered after PCI. In this case, DES use was suggested unless contraindicated. Avoidance of geographical mismatch was also recommended (in case of stenting the prosthesis had to be placed within and not exceeding the area previously treated with DCBs). Finally, in order to avoid acute recoil, we also suggested to wait for at least 10 min after DCB inflation before ending the intervention.[9]

After the procedure patients were clinically followed, according to the local practice.

Device

The device tested in this study is a rapid exchange percutaneous transluminal coronary angioplasty balloon catheter. Once inflated, it delivers the drug it is coated with to the vessel wall. The balloon is coated with an active pharmaceutical agent for preventing restenosis: 2.2 μg paclitaxel mm^{-2} with a tolerance of 1.4–3.00 μg paclitaxel mm^{-2} and has a 0.7 μg dextran mm^{-2} top coating with a maximum amount of 1.89 μg dextran mm^{-2}, which acts as excipient (drug carrier). The functional characteristic of the formulation is to release paclitaxel to the tissue of the vascular wall during inflation and to maintain it during the first days. The uptake of paclitaxel is controlled by the interaction with dextran and the vessel wall. The drug uptake measured in different animal models is highest after 1 h and decreases slowly over days and weeks, with values of around 250 μg ml^{-1} decreasing to around 100 μg ml^{-1} after 1 week to 10 μg ml^{-1} after 4 weeks, allowing a successful inhibition of proliferation and migration of smooth muscle cells over time.

Study endpoints

The primary endpoint was the occurrence of target-lesion revascularization (TLR) at the longest available follow-up. Secondary endpoints were procedural success, defined as angiographic success in the absence of in-hospital complications, and the occurrence of a device-oriented endpoint [device-oriented adverse cardiovascular event (DOCE)], which included cardiac death, target-vessel myocardial infarction (MI), stroke, or TLR.

Angiographic success was defined as Thrombolysis in Myocardial Infarction 3 flow with <50% final stenosis at the end of intervention. MI was defined according to the universal definition[10] and was considered only in case it was spontaneous. TLR was defined as repeat PCI or coronary artery bypass grafting for the target segment or within 5 mm proximally or distally.

Table 1 Baseline patient characteristics

Variable	$n = 544$
Demographic characteristics	
Age years, mean ± SD	67.25 ± 10.7
Male sex	388 (71%)
Cardiovascular risk factors	
Hypertension	413 (76%)
Diabetes	177 (32%)
Smoking history	217 (40%)
Previous myocardial infarction	228 (42%)
Previous bypass surgery	70 (13%)
Clinical characteristics	
LV ejection fraction, mean ± SD	53.3 ± 9.6
Chronic kidney disease (eGFR <30 ml min^{-1})	72 (13%)
Clinical presentation	
UA (troponine negative)	53 (9.7%)
NSTEMI	202 (37%)
STEMI	24 (4.4)
Stable CAD	265 (48.7)

Data are mean ± SD or *n* (%). ACS, acute coronary syndrome; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; LV, left ventricle; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction; UA, unstable angina.

Statistical analysis

Categorical variables are reported as count and percentage, whereas continuous variables as mean and standard deviations or interquartile range (IQR). Gaussian or not Gaussian distribution was evaluated by Kolmogorov–Smirnoff test. The *t* test has been used to assess differences between parametric continuous variables, Mann–Whitney *U* test for nonparametric variables, the chi-square test for categorical variables, and Fisher's exact test for 2×2 tables. Cox multivariate analysis was performed to assess the independent predictors of TLR, including all variables, which differ at univariate analysis or with significant association with TLR.

Proportional hazards assumption was not violated in statistical analysis. A two-sided *P* value less than 0.05 was considered statistically significant; all analyses were performed with SPSS 21.0 (IBM, Armonk, New York, USA).

Results

All consecutive patients treated with Elutax SV at nine Italian centers between December 2012 and December 2015, and with at least 6 months clinical follow-up available, were included in the DCB-RISE registry. In all, 544 patients (age 67 ± 12 years) with 583 lesions were included. One hundred and seventy-seven (32.6%) patients had diabetes mellitus, and 13% had chronic kidney disease with estimated glomerular filtration rate below 30 ml min^{-1}. In 49% of the patients, the clinical indication for PCI was stable coronary artery disease, and 4% of the population had a ST-elevation MI caused by ISR. Table 1 describes the clinical characteristics of the population.

Table 2 Angiographic and procedural characteristics, discharge

Variable (lesions treated with DCB)	583
Target vessel	
Left anterior descending artery	274 (47%)
Left circumflex artery	102 (17%)
Right coronary artery	190 (33%)
Saphenous vein graft	23 (4%)
Arterial graft	5 (0.9%)
Number of diseased vessels	
One-vessel	281 (48%)
Two-vessels	169 (29%)
Three-vessels	124 (21%)
Graft disease	9 (1.5%)
In-stent restenosis	
ISR after BMS	114 (19%)
ISR after DES	189 (32%)
Native vessel disease	280 (48%)
Lesion involving bifurcation with SB >2 m	96 (16.5%)
CTO	20 (3.4%)
Severe calcifications	19 (3.3%)
Moderate calcifications	62 (11%)
QCA analysis	
Lesion length, mm ± SD	16.9 ± 7.2
Long lesions (>24 mm)	88 (15%)
RVD, mm ± SD	2.84 ± 1.18
Preprocedural MLD, mm ± SD	0.43 ± 0.31
Percentage diameter stenosis pre, % ± SD	85.0 ± 11.4
Lesion preparation	
Absence of lesion predilatation	49 (8.4%)
Predilatation with semicompliant balloon	380 (65%)
Predilatation with noncompliant balloon	189 (32%)
Predilatation with scoring balloon	14 (2.4%)
Diameter of predilatation balloon, mm ± SD	2.9 ± 0.67
Number of DCB used/lesion, *n* ± SD	1.3 ± 0.63
DCB diameter, mm ± SD	2.9 ± 0.49
DCB length, mm ± SD	20.5 ± 6.47
DCB inflation, atmospheres ± SD	11.0 ± 3.9
DCB inflation length, s ± SD	55.6 ± 26.4
Stent implantation after DCB PCI	
DES implantation	62 (11%)
BVS implantation	1 (0.2%)
BMS implantation	4 (0.7%)
Final MLD, in segment, mm ± SD	1.57 ± 0.39
Final percentage diameter stenosis, % ± SD	17 ± 11.5
Angiographic success	576 (98.7)
Procedural failure	7 (1.3%)
IVUS/OCT use	60 (10%)
GP IIb/IIIa Inhibitors	21 (3.6%)
Bivalirudin use	2 (0.3%)
Aspirin at discharge	536 (98%)
Clopidogrel at discharge	410 (75%)
Ticagrelor at discharge	39 (7.2%)
Prasugrel at discharge	14 (2.6%)

ACS, acute coronary syndrome; BMS, bare-metal stent(s); BVS, bioresorbable vascular scaffold; CAD, coronary artery disease; DCB, drug-coated balloon; DES, drug-eluting stent(s); FFR, fractional flow reserve; GP, glycoprotein; IVUS, intravascular ultrasound; MLD, minimal lumen diameter; OCT, optical coherence tomography; TIMI, Thrombolysis in Myocardial Infarction.

Drug-coated balloon was used predominantly to treat ISR, either DES (32.4%) or BMS (19.5%) restenosis. On the contrary, treatment of de-novo coronary artery disease occurred in 48.1% of the patients, including 16.5% of patients with bifurcation with greater than 2 mm side branch diameter.

Average lesion length was 16.9 ± 7.2 mm and reference vessel diameter 2.84 ± 1.18 mm. According to study and consensus paper recommendations,[9] only less than 10% of the lesions were directly treated with DCBs, whereas the vast majority was pretreated either with

Table 3 Clinical endpoints at the longest follow-up available

Variable	*n* = 507
Duration of follow-up, months, average (SD)	13.3 (7.4%)
TLR	30 (5.9%)
TLR managed with CABG	4 (0.8%)
TLR managed with PCI	26 (5.1%)
Acute vessel occlusion	0
Target vessel MI	3 (0.6%)
Stroke	2 (0.4%)
All-cause death	12 (2.4%)
Cardiac death	3 (0.6%)
DOCE	36 (7.1%)
TVR (non-TLR)	12 (2.4%)

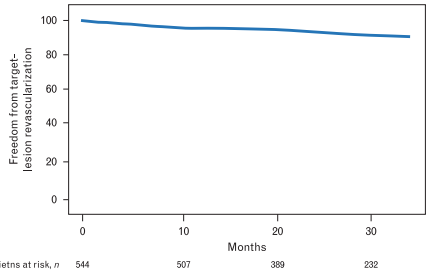
CABG, coronary artery bypass graft; DOCEs, device oriented cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target lesion revascularization; TVR, target vessel revascularization.

semicompliant or noncompliant balloons. The average DCB length was 20.5 ± 6.47 mm, with an average diameter of 2.9 ± 0.49 mm. Stenting after DCB was required in 12.3% of the patients. In seven cases (1.3%), the procedure failed because it was impossible to reach the target lesion with the device, and the procedure was converted to DES-PCI (two cases) or plain-old balloon angioplasty (five cases). Procedural success occurred in 97.5% of the cases.

Dual antiplatelet therapy was prescribed in 452 patients (83.1%) at discharge, and was prolonged for 1 month in 432 of them (79.4%); at final follow-up, only 39 patients (6.4%) were still on DAPT. Table 2 describes the angiographic and procedural characteristics of the population.

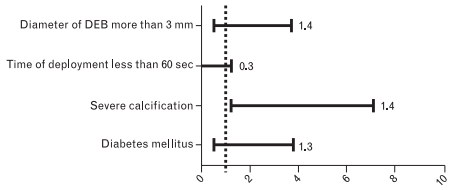
Average clinical follow-up was 13.3 ± 7.4 months and was available for 507 (93.2%) patients. Table 3 describes the main study results. The primary outcome measure, TLR, was observed in 30 (5.9%) patients. TLR was managed with coronary artery bypass graft in four patients (0.8%) and with re-PCI in 26 patients (5.1%) (Fig. 1). DOCE, secondary study endpoint, occurred in 36 (7.1%) patients. Cardiac death or MI occurred in 3 patients (0.6%),

Fig. 1



Kaplan–Meier curve of survival from the primary study endpoint, TLR, at the longest available follow-up. TLR, target-lesion revascularization.

Fig. 2



Multivariate analysis with independent predictors for TLR. TLR, target-lesion revascularization.

whereas all-cause death occurred in 12 patients (2.4%). Cerebrovascular stroke occurred in two patients (0.4%).

Multivariate analysis showed that only severe calcifications at lesion site were an independent predictor of TLR (Figs 2 and 3).

We undertook a subanalysis of the data comparing patients treated for ISR and patients treated for de-novo lesions, and observed a significant difference in the TLR rate that occurred in 9 vs. 2.6% ($P=0.006$), respectively; DOCEs were significantly higher in the ISR group (11 vs. 2.6%; $P=0.001$), whereas no significant statistical difference was observed in terms of cardiac death, target vessel myocardial infarction, and stroke (Table 4). TLR rate was not different between patients with BMS or DES-ISR.

Discussion

The study shows how a PCI performed with one of the latest-generation DCBs is feasible and well tolerated at mid-term follow-up, with a low rate of TLR, also taking into consideration the medium/high-risk profile of the population (half of the patients had ISR as indication for PCI). This endpoint is also similar to the one observed in

Table 4 Clinical endpoints at the longest available follow-up

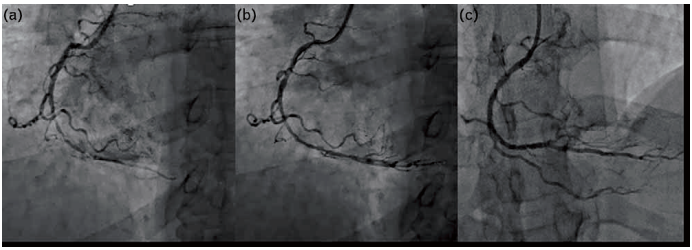
	$n=507$		
	13.3 (7.4)		
Average duration of follow-up, months (SD)	ISR ($n=269$)	*de novo* ($n=238$)	*P*
TLR, *n* (%)	24 (9%)	6 (2.6%)	0.006
TLR managed with CABG, *n* (%)	3 (1%)	1 (0.4%)	0.64
TLR managed with PCI, *n* (%)	21 (7.8%)	5 (2.1%)	0.003
Target-vessel MI, *n* (%)	3 (1.1%)	0	0.14
Stroke, *n* (%)	1 (0.3%)	1 (0.4%)	1
All-cause death	6 (2.2%)	6 (2.5%)	0.36
Cardiac death	3 (1.1%)	0	0.27
DOCE	30 (11%)	6 (2.6%)	0.001

CABG, coronary artery bypass graft; DOCE, device-oriented cardiovascular events; ISR, in-stent restenosis; MI, myocardial infarction; PCI, percutaneous coronary intervention; TLR, target-lesion revascularization.

a registry with one of the most widely used DCB, at a shorter follow-up.[11] In another registry, a different DCB showed similar results in terms of safety and efficacy after 12 months.[12] In the international, multicenter, prospective, all-comers SeQuent Please World Registry,[13] a real-world registry which included both patients treated for ISR and de-novo lesions, the TLR rate was 5.2%, similar to the one observed in our registry; moreover, also analyzing the outcomes in native coronary lesions, TLR rates were comparable in the twio registries (respectively, 2.4 and 2.6%).

The main potential advantages of DCBs are as follows: a quick and homogeneous release of the antiproliferative drug to the vessel wall, which is absorbed and has a prolonged effect, attenuating the process of neointimal hyperplasia; the absence of polymer, which can reduce or eliminate the vascular inflammatory response, which is directly linked to late thrombotic events; the absence of a metal platform; the need for shorter DAPT. The role of DCB has recently gained a precise role in interventional cardiology, being the first choice for the treatment of DES or BMS restenosis in many centers. The DCB role

Fig. 3



(a) Chronic total occlusion of the right coronary artery (RCA). (b) Final angiographic result after angioplasty with a 2.5/30 mm Elutax SV drug-coated balloon, with persisting 30–40% stenosis. (c) Six-month angiographic follow-up, showing good persisting patency of the RCA and visible vessel lumen gain.

for the treatment of native coronary vessels is less recognized and these devices are less widely used in this setting, but some preliminary studies show interesting data in terms of vessel dissection healing and late coronary lumen gain, although prospective studies on the matter are still lacking.[7,14,15] Current patients treated in the cath laboratories of western countries represent a highly complex population with frequent involvement of two or three coronary vessels, diffuse disease, and small vessels. These anatomical settings seem appropriate for a hybrid strategy that can reduce the total stent length, thus may potentially reduce the risk for late adverse events. Our study also confirms how DCBs may constitute a reasonable addendum to DES in diffuse coronary disease, as some preliminary data have previously shown. In this study, 38% of the entire population underwent an all-in-one (21%) or staged (17%) hybrid procedure,[16] and the outcome between hybrid or solo-DCB PCI did not differ.

On the contrary, one potential advantage of a solo-DCB PCI is the possibility to reduce the duration of DAPT. The recently published european society of cardiology 2017 update document on DAPT[17] acknowledges the lack of dedicated clinical trials investigating the optimal duration of DAPT in patients treated with DCBs and recommends a DAPT duration of 6 months (class IIa, B); it must be noted, though, that in the largest randomized trials,[18,19] a 3–12-month DAPT duration was recommended, whereas real-world registries[13] suggest a duration of at least 1 month. In our clinical practice, we follow the recommendations of current consensus documents that suggest 30 days after DCB use for native vessels, and 3–6 months in case of stent implantation.[9] However, the possibility to reduce it further, or even discharge the patient with one single antiplatelet, seems intriguing. In the registry, 17% of the patients did not receive the second antiplatelet at discharge, the main reasons being the need for elective/urgent surgery (6%) or recent bleeding or high risk of bleeding (9%). To note, a subanalysis of the cohort of patients discharged with one single antiplatelet showed clinical results similar to the rest of the population, theoretically suggesting a role for this strategy in a highly selected patient population.

A specific mention should be made on the device used in this study. Preliminary results with the first generation of DCBs showed how these devices are different in terms of efficacy, and underlined the importance of a drug carrier, firstly with the role of targeting paclitaxel to the lesion site (a sort of protection from proximal tortuosities and disease), and then, after balloon inflation, to help the drug to reach the vessel wall and persist there. In the recent years, all new generations of DCBs were developed with dedicated carriers, and both randomized controlled studies and real-world registries showed their good efficacy and no specific safety issue. The Elutax SV DCB tested in this registry has already shown to warrant adequate late lumen loss at 6-month angiographic follow-up.

There are several limitations that need to be acknowledged for the current registry. There was not data monitoring, and clinical event assessment was performed by the single investigators. The absence of a prospective enrollment is another major limitation, for example, it was not possible to know the reasons why operators preferred a DCB over a DES at index procedure, and device selection might have suffered of unknown confounders. Also, there was not a direct comparison with 'old-generation' DCBs. Periprocedural MI was not an endpoint, and only spontaneous MIs were collected.

In conclusion, the DCB-RISE registry shows how the use of the new-generation DCB Elutax SV in an all-comer population is associated with good mid-term clinical outcome, which is comparable with other similar devices present in the market.

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SYSTEMATIC REVIEW AND META-ANALYSIS

Clinical and Angiographic Outcomes With Drug-Coated Balloons for De Novo Coronary Lesions: A Meta-Analysis of Randomized Clinical Trials

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BACKGROUND: The role of drug-coated balloons (DCBs) in the treatment of de novo coronary lesions is not well established.

METHODS AND RESULTS: Electronic databases and major conference proceedings were searched for randomized controlled trials that compared DCBs with stents or angioplasty for de novo coronary lesions. The primary outcome was target lesion revascularization. Summary estimates were conducted using random-effects analysis complemented by several subgroup and sensitivity analyses. A total of 14 randomized controlled trials with 2483 patients were included. At a mean follow up of 12 months, DCBs were associated with no difference in the incidence of target lesion revascularization as compared with alternative strategies (risk ratio [RR], 0.79; 95% CI, 0.35–1.76). There was no difference in treatment effect based on the indication (ie, small-vessel disease, myocardial infarction, bifurcation, or high bleeding risk) ($P_{interaction}$=0.22). DCBs were associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). There was no difference between DCBs and control in terms of major adverse cardiac events, vessel thrombosis, or cardiovascular mortality. However, DCBs were associated with a lower incidence of myocardial infarction (RR, 0.48; 95% CI, 0.25–0.90) and all-cause mortality (RR, 0.45; 95% CI, 0.22–0.94).

CONCLUSIONS: In patients with de novo coronary lesions, use of DCBs was associated with comparable clinical outcomes irrespective of the indication or comparator device. DCBs had a similar rate of target lesion revascularization compared with drug-eluting stents. A randomized trial powered for clinical outcomes and evaluating the role of DCBs for all-comers is warranted.

Key Words: coronary artery disease ■ de novo lesions ■ drug-eluting stent ■ drug-coated balloon ■ meta-analysis ■ mortality ■ small vessels

Drug-eluting stents (DESs), particularly second-generation, remain the cornerstone management during percutaneous coronary intervention.[1] Coronary restenosis as a result of the persistence of the metallic struts within the vessel as well as the need for dual antiplatelet therapy remain major limitations even with the current generation of DESs.[2,3] In this context, drug-coated balloons (DCBs) offer an attractive therapeutic modality because these devices allow for local delivery of the antiproliferative agent directly into the artery wall with a single balloon inflation without the need for the metallic implant.[4] Several randomized trials have established the role of DCBs in treatment of in-stent restenosis of both DESs and bare metal stents (BMSs),[5–8] and the use of DCBs is currently endorsed by the 2018 European Society of Cardiology guidelines for myocardial revascularization as a class I recommendation for this indication.[9]

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CLINICAL PERSPECTIVE

What Is New?

- In patients with de novo coronary lesions, drug-coated balloons were associated with comparable clinical outcomes irrespective of the indication or comparator device.
- Drug-coated balloons had a similar rate of target lesion revascularization compared with drug-eluting stents.

What Are the Clinical Implications?

- These findings suggest the value of drug-coated balloons as an attractive "leave-nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.
- A randomized trial powered for clinical outcomes and evaluating the role of drug-coated balloons for all-comers is warranted.

Nonstandard Abbreviations and Acronyms

BMS	bare metal stent
DCB	drug-coated balloon
DES	drug-eluting stents
MLD	minimum lumen diameter
MI	myocardial infarction
TLR	target lesion revascularization

However, the role of DCBs is not as established for de novo coronary lesions.[4] Recently, several small-to-moderate–sized, randomized trials have evaluated the merits of DCBs for patients with small-vessel disease,[10,11] high risk of bleeding,[12] and myocardial infarction (MI).[13,14] However, most of these individual trials were not powered to assess the differences in clinical outcomes.[10,13,14] Moreover, the trials that were powered for clinical outcomes were noninferiority trials and did not routinely evaluate angiographic outcomes.[11–13] To address this knowledge gap, we performed a comprehensive systematic review and meta-analysis of randomized trials to evaluate the impact of DCBs for de novo coronary lesions on angiographic and clinical outcomes.

METHODS

The authors declare that all supporting data are available within the article (and in the accompanying supplementary material online).

Data Sources and Search Strategy

Electronic databases, including MEDLINE, Embase, and the Cochrane Register of Controlled Trials, as well as major scientific sessions, were searched without language restriction from inception through November 2019 using the search algorithm in Table S1. The bibliography of the retrieved articles was reviewed. The search was independently performed by 2 authors (I.Y.E., F.A.). The protocol for this meta-analysis was prospectively registered at the PROSPERO international prospective register of systematic reviews (CRD42019143329),[15] and was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[16]

Selection Criteria and Data Extraction

Trials that randomized patients with obstructive de novo coronary lesions to DCBs versus any comparator were included (ie, DES, BMS, angioplasty only). We excluded trials that electively performed routine BMS placement after DCBs, but included trials that permitted bailout stent placement after DCBs. Clinical and angiographic data from the longest available reported follow-up time were preferentially used. Observational studies were excluded for inherent risk of bias. Two independent authors (I.Y.E., A.Y.E.) extracted data on study design, sample size, intervention strategies, outcomes, and other study characteristics from the included studies. Discrepancies were resolved by consensus.

Assessment of Quality of Included Studies

The Cochrane Collaboration's tool was used for the assessment of the risk of bias. This consists of 7 points that test for selection, performance, detection, attrition, reporting, and other biases.[17] Performance bias (ie, blinding of participants and physicians) was found to be irrelevant due to the interventional nature in both arms. The overall risk of bias for each trial was classified as low, unclear, or high risk, based on whether level of bias in each domain could have resulted in biases in risk estimation.

Outcomes

The primary clinical outcome was target lesion revascularization (TLR). The secondary clinical outcomes included: major adverse cardiac events, as defined by the individual trials (Table S2); target vessel revascularization; MI; vessel thrombosis; cardiovascular mortality; and all-cause mortality. The following angiographic outcomes were assessed: minimum lumen diameter (MLD); diameter stenosis; late lumen loss; and binary restenosis.

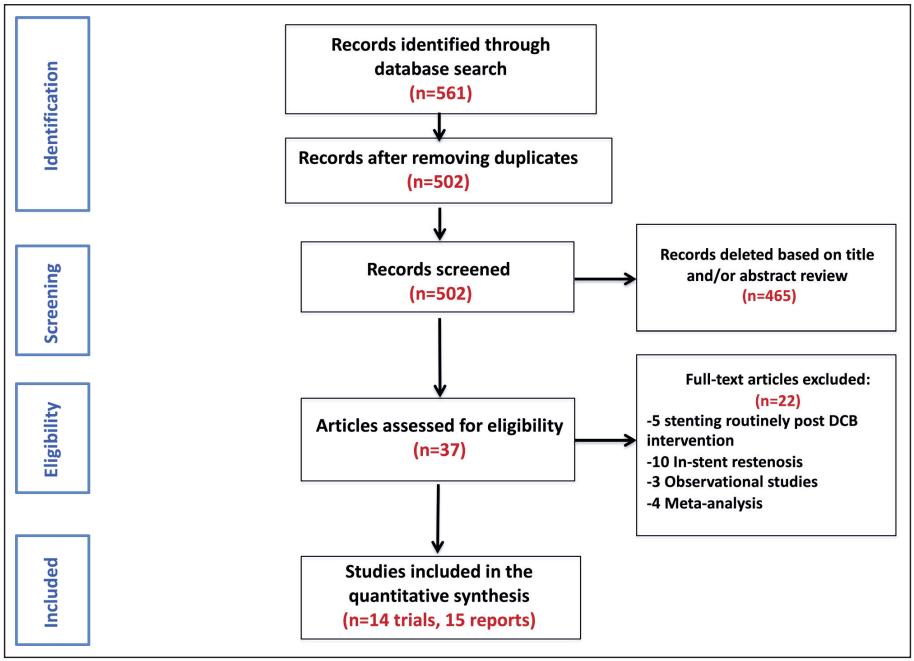

Figure 1. Study search diagram.
Summary of how the systematic search was conducted and eligible studies were identified. DCB indicates drug-coated balloon.

Statistical Analysis

Outcomes were evaluated by an intention-to-treat analysis. Random-effects summary risk ratios were primarily estimated with the DerSimonian and Laird model, because we anticipated a high degree of statistical heterogeneity.[18] Summary odds ratios were also estimated with a Peto model as a secondary analysis due to the low incidence of events.[19] Statistical heterogeneity was assessed using the Cochrane *Q* and I^2 statistics.[20] Egger's method was used to calculate publication bias.[21] Standardized mean differences were used for continuous variables. All *P*-values were 2-tailed, with statistical significance set at 0.05, and CIs were calculated at the 95% level for the overall estimates effect. All analyses were performed using the RStudio software meta package (RStudio, Inc, Boston, MA).

The following prespecified subgroup analyses were performed for the primary outcome (TLR): (1) according to indication; and (2) by comparing DESs versus BMSs. In addition, the following prespecified sensitivity analyses for TLR were also conducted by: (1) excluding trials using the first-generation DCB, which is no longer available[22]; (2) excluding trials using angioplasty alone in the control arm; (3) limiting to trials utilizing second-generation DESs as the control; and (4) excluding trials with high risk of bias. Random-effects meta-regression analyses for the primary outcome were prespecified in relation to baseline reference vessel diameter, diabetes mellitus, and proportion of bailout stent placement in the DCBs arm.[23] Finally, a sensitivity analysis limited to trials using second-generation DESs as the control was performed for the angiographic outcomes, and a sensitivity analysis limited to trials that defined MI as spontaneous (ie, not procedure-related) was also conducted.

RESULTS

Included Studies

The systematic search identified 502 studies after removal of the duplicates, among which 37 were reviewed for eligibility. The final number of records included in this meta-analysis was 14 trials from 15

Table. Characteristics, Interventional Strategies, and Follow-Up of the Included Trials

Trial (Reference No.)	Year	Indication	Drug-Coated Balloon Type	Control Group	Patients (n)	Clinical Follow-Up (months)	Angiographic Follow-Up (months)	Primary Outcome	Reference Vessel Diameter (mm)	Bailout Stenting in DCB Arm (%)
PICCOLETO II[24]	2019	Small-vessel disease	Elutax SV/Emperor	Second-generation DES	118/114	6	6	Late lumen loss	2.2/2.2	6.8
RESTORE CVD[10]	2019	Small-vessel disease	Restore	Second-generation DES	116/114	12	9	Diameter stenosis	2.4/2.4	5.2
BASKET-SMALL 2[11]	2019	Small-vessel disease	SeQuent Please	Second-generation DES	382/376	12	NR	MACE	NR	NR
Funatsu et al[25]	2017	Small-vessel disease	SeQuent Please	POBA	92/41	6	6	TVF	2.0/2.0	2.9
BELLO[26,27]	2012/2015	Small-vessel disease	IN.PACT Falcon	First-generation DES	90/92	36	6	Late lumen loss	2.4/2.4	20.2
PICCOLETO[22]	2010	Small-vessel disease	Dior	First-generation DES	29/31	9	6	Diameter stenosis	2.4/2.4	NR
PEPCAD NSTEMI[13]	2019	Myocardial infarction	SeQuent Please SeQuent Please Neo	BMS/second-generation DES	104/106	9	NR	Target lesion failure	NR	7.3
REVELATION[14]	2019	Myocardial infarction	Pantera Lux	Second-generation DES	60/60	9	9	FFR value	3.3/3.2	18.0
Gobic et al[28]	2017	Myocardial infarction	SeQuent Please	Second-generation DES	41/37	6	6	Late lumen loss	2.6/3.0	7.3
Shin et al[29]	2019	High bleeding risk	SeQuent Please	BMS	20/20	12	9	Late lumen loss	3.0/3.2	NR
DEBUT[12]	2019	High bleeding risk	SeQuent Please	BMS	102/106	9	NR	MACE	NR	2.0
PEPCAD-BIF[30]	2016	Bifurcational lesion	SeQuent Please	POBA	32/32	9	9	Late lumen loss	2.4/2.4	0
BABILON[31]	2014	Bifurcational lesion	SeQuent Please	POBA	52/56	24	9	Late lumen loss	2.3/2.3	7.8
Nishiyama et al[32]	2016	Unspecified	SeQuent Please	Second-generation DES	30/30	8	8	Not specified	2.9/2.7	10.0

Results are presented as drug-coated balloon/control. ACS indicates acute coronary syndrome; BABILON, The Paclitaxel-Coated Balloon in Bifurcated Lesions Trial; BASKET-SMALL 2, The Basel Kosten Effektivitäts Trial–Drug-Coated Balloons versus Drug-eluting Stents in Small Vessel Interventions; BELLO, Balloon Elution and Late Loss Optimization; BMS, bare metal stent; DCB, drug-coated balloon; DEBUT, Drug-Eluting Balloon in Stable and Unstable Angina: A Randomized Controlled Non-Inferiority Trial; DES, drug-eluting stent; FFR, fractional flow reserve; MACE, major adverse cardiac events; NR, not reported; PEPCAD-BIF, Drug eluting balloons as stand alone procedure for coronary bifurcational lesions; PEPCAD NSTEMI, Bare Metal Stent Versus Drug Coated Balloon With Provisional Stenting in Non-ST–Elevation Myocardial Infarction; PICCOLETO, Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels; PICCOLETO II, Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment; POBA, "plain old" balloon angioplasty; RESTORE SVD, Assess the Efficacy and Safety of RESTORE Paclitaxel Eluting Balloon Versus RESOLUTE Zotarolimus Eluting Stent for the Treatment of Small Coronary Vessel Disease; REVELATION, Revascularization With Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stenting in Acute Myocardial Infarction; and TVF, target vessel failure.

reports (Figure 1).[10–14,22,24–32] One trial reported angiographic and clinical outcomes at 6 months[26] and reported an extended follow-up for the clinical outcomes at 36 months.[27] A total of 2483 patients were included: 1268 in the DCBs group and 1215 in the control group. The indication for DCBs was small-vessel disease in 5 trials,[10,11,22,24–27] MI in 3 studies,[13,14,28] high bleeding risk in 2 trials,[12,29] bifurcational lesions in 2 studies,[30,31] and unspecified de novo lesions in 1 study.[32] In the bifurcational lesion trials, 1 trial compared "plain old" balloon angioplasty followed by DCB versus plain old balloon angioplasty alone to the main or side branch,[30] whereas the other trial randomized patients with bifurcational lesions to a strategy of side-branch dilation with DCB versus plain old balloon angioplasty.[31] The SeQuent Please paclitaxel-coated balloon was used by most of the included studies (9 of 14). Only 1 trial tested the Dior paclitaxel-coated balloon, which is no longer available.[22] The control group was exclusively second-generation DES in 6 trials,[10,11,14,24,28,32] first-generation DESs in 2 trials,[22,26] BMSs in 2 trials,[12,29] and plain old balloon angioplasty alone in 3 trials.[25,30,31] In 1 trial, the control was second-generation DESs or BMSs, and a subgroup analysis was reported for the outcomes based on the stent type.[13] The weighted mean reference vessel diameter was 2.5 mm. Table shows the baseline trial characteristics, follow-up duration, and interventional strategies. Table S3 summarizes the pertinent patient demographics and trial information. Performance bias was unclear in all the trials. One trial was at high risk for detection bias and unclear for allocation bias,[32] otherwise the remainder of the trials were considered to be of high quality (Table S4).

Angiographic Outcomes

Routine angiographic follow-up was performed at a weighted mean of 7 (range, 6–9) months. There was no difference between DCBs and control in terms of MLD (1.9 mm versus 2.0 mm; standardized mean difference, −0.13; 95% CI, −0.32 to 0.06; P=0.17), diameter stenosis (28.0% versus 28.1%; standardized mean difference, 0.22, 95% CI, −6.92 to 7.36; P=0.95), and binary restenosis (13.9% versus 16.3%; RR, 0.83; 95% CI, 0.40–1.71; P=0.61). However, DCBs were associated with lower late lumen loss (0.08 mm versus 0.24 mm; standardized mean difference, −0.17; 95% CI, −0.24 to −0.10; P<0.0001) (Figure 2). There was a significant degree of statistical heterogeneity observed for the angiographic outcomes (I^2 ranged from 60% to 94%), which was explained on the sensitivity analysis limited to trials comparing DCBs with second-generation DESs (I^2=0% for all the outcomes, except for diameter stenosis where I^2=56%). The findings of the sensitivity analysis were consistent with the main analysis for all angiographic outcomes except for a lower MLD with DCBs (Figure S1).

Target Lesion Revascularization

The weighted mean follow up for the clinical outcomes was 12 (range, 6–36) months. There was

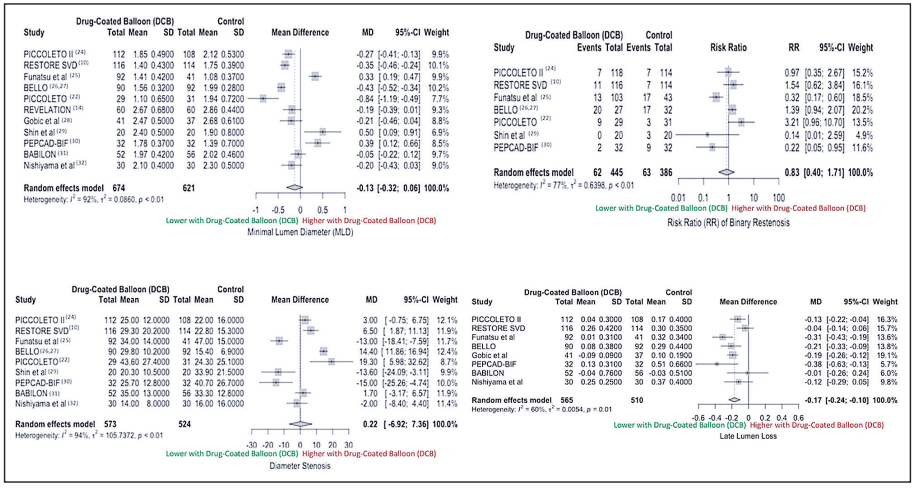

Figure 2. Summary plots for the angiographic outcomes.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; MD, mean difference; MLD, minimal lumen diameter; and RR, risk ratio.

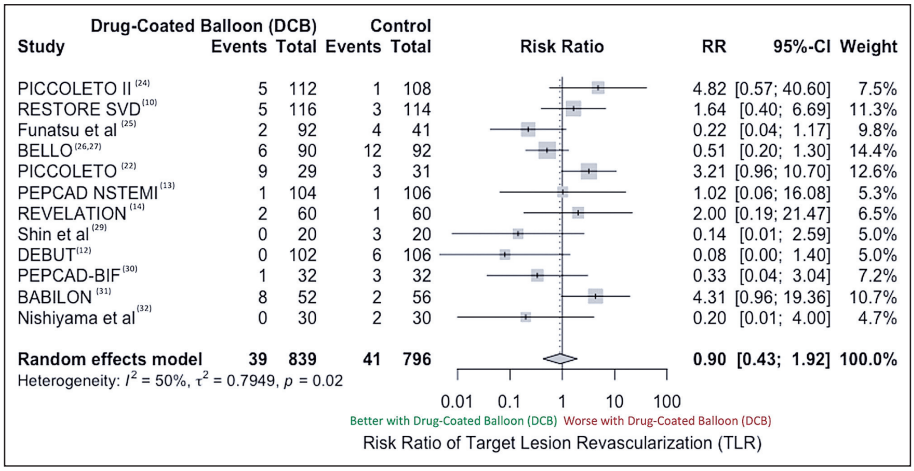

Figure 3. Summary plot for target lesion revascularization.
The relative size of the data markers indicates weight of sample size from each study. DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

no difference in the incidence of TLR with DCBs compared with control (random effects: 4.6% versus 5.1%; RR, 0.79; 95% CI, 0.35–1.76; P=0.56; fixed effects: OR, 0.91; 95% CI, 0.58–1.44; P=0.69) (Figure 3). There was no evidence of publication bias using Egger's test (P=0.45). The outcome was characterized by moderate heterogeneity (I^2=50%; χ^2=22.1; $P_{heterogeneity}$=0.02). DCBs showed similar TLR compared with control, irrespective of the indication ($P_{interaction}$=0.22) (Figure 4). The incidence of TLR was similar when DCBs compared with DESs (RR, 1.37; 95% CI, 0.62–3.05; I^2=34%), but DCBs were associated with a lower incidence of TLR compared with BMSs (RR, 0.19; 95% CI, 0.04–1.00; I^2=0%) ($P_{interaction}$=0.03) (Figure 5). The findings of the prespecified sensitivity analyses for TLR were consistent with the overall analysis: (1) excluding trials that utilized the older generation DCBs (RR, 0.76; 95% CI, 0.35–1.65; I^2=43%; χ^2=17.6; $P_{heterogeneity}$=0.06) (Figure S2); (2) excluding trials using angioplasty alone in the control arm (RR, 0.97; 95% CI, 0.42–2.27; I^2=45%; χ^2=14.5; $P_{heterogeneity}$=0.07) (Figure S3); (3) limited to trials utilizing second-generation DESs as control (RR, 1.65; 95% CI, 0.65–4.34; I^2=0%; χ^2=2.9; $P_{heterogeneity}$=0.57) (Figure S4); and (4) excluding the trial with high risk of bias (RR, 0.97; 95% CI, 0.45–2.12; I^2=52%; χ^2=21.0; $P_{heterogeneity}$=0.02) (Figure S5). Meta-regression analysis did not identify a difference in the treatment effect based on baseline reference vessel diameter (P=0.81), diabetes mellitus (P=0.37), and proportion of bailout stent placement (P=0.63).

Secondary Clinical Outcomes

Compared with control, DCBs were associated with no difference in the incidence of target vessel revascularization (6.0% versus 5.3%; RR, 1.21; 95% CI, 0.60–2.44; P=0.59; I^2=52%; χ^2=8.3; $P_{heterogeneity}$=0.08), major adverse cardiac events (6.9% versus 9.1%; RR, 0.83; 95% CI, 0.50–1.36; P=0.46; I^2=53%; χ^2=23.3; $P_{heterogeneity}$=0.02), vessel thrombosis (0.3% versus 1.1%; RR, 0.38; 95% CI, 0.13–1.13; P=0.08; I^2=0%; χ^2=0.5; $P_{heterogeneity}$=0.91), and cardiovascular mortality (1.5% versus 1.5%; RR, 0.90; 95% CI, 0.27–3.00; P=0.86; I^2=56%; χ^2=6.8; $P_{heterogeneity}$=0.08). Importantly, DCBs were associated with a lower incidence of all-cause mortality (1.2% versus 2.9%; RR, 0.45; 95% CI, 0.22–0.94; P=0.03; I^2=0%; χ^2=0.78; $P_{heterogeneity}$=0.85), and MI (1.1% versus 2.9%; RR, 0.48; 95% CI, 0.25–0.90; P=0.02; I^2=0%; χ^2=6.2; $P_{heterogeneity}$=0.62) (Figures 6 and S6 through S11). In the sensitivity analysis limited to trials that defined MI as spontaneous MI, DCBs were associated with lower incidence of spontaneous MI (RR, 0.49; 95% CI, 0.25–0.96; P=0.04; I^2=0%) (Figure S12). There was no evidence of publication bias for any of the secondary clinical outcomes using Egger's test (all P>0.05).

DISCUSSION

In this meta-analysis of 14 randomized trials including 2483 patients with de novo coronary lesions undergoing percutaneous coronary intervention irrespective of

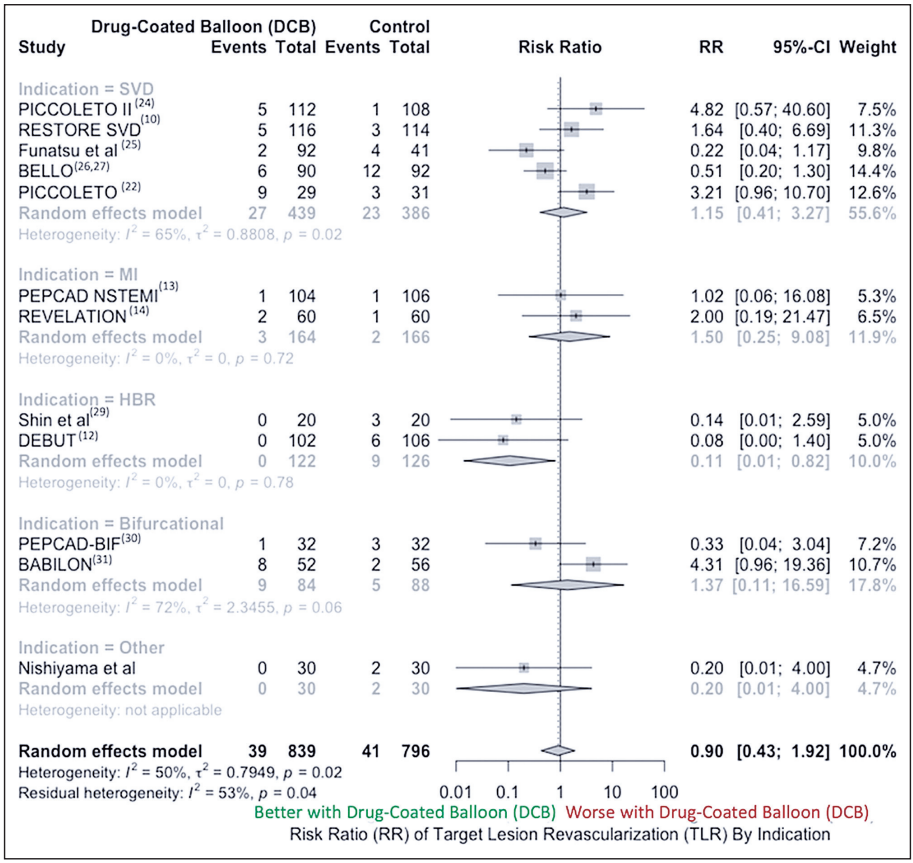

Figure 4. Subgroup analysis for target lesion revascularization according to indication.
The relative size of the data markers indicates weight of sample size from each study. There was no difference in treatment effect according to the different indications ($P_{interaction}$=0.22). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

indication, we documented that DCBs were associated with similar MLD, diameter stenosis, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up at a mean of 7 months. These findings were similar when DCBs were only compared with second-generation DESs (except that DCBs were associated with lower MLD). At a mean of 12 months, DCBs were associated with no difference in the incidence of TLR compared with control. This effect was consistent, regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and on multiple sensitivity analyses, including comparing DCBs with second-generation DESs. DCBs were associated with lower risk of TLR compared with BMS. There was a moderate degree of statistical heterogeneity for TLR, which was partly explained by our subgroup analysis comparing DCBs with DESs versus BMSs, and on the sensitivity analysis limited to second-generation DESs. DCBs were also associated with no difference in the incidence of target vessel revascularization, major adverse cardiac events, vessel thrombosis, and cardiovascular mortality. Importantly, the incidence of all-cause mortality and MI (even when spontaneous MI was analyzed separately)

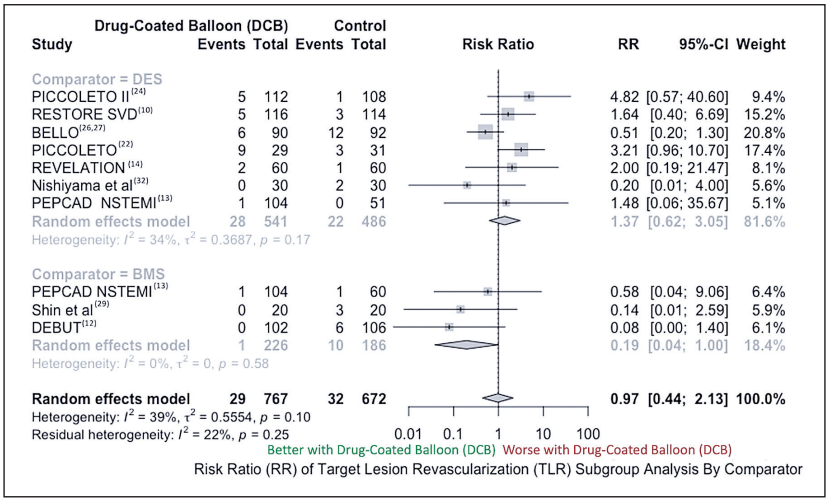

Figure 5. Subgroup analysis for target lesion revascularization comparing bare metal and drug-eluting stents.
The relative size of the data markers indicates the weight of the sample size from each study. Drug-coated balloon use was associated with lower target lesion revascularization compared with bare metal stents and similar target lesion revascularization compared with drug-eluting stents ($P_{interaction}$=0.03). DCB indicates drug-coated balloon; and TLR, target lesion revascularization.

was lower with DCBs. However, these findings were based on a small number of trials and the number of events was low, and therefore should be only considered as hypothesis-generating. Altogether, our findings strongly suggest the value of DCBs as an attractive "leave–nothing-behind strategy" for selected patients with de novo coronary lesions provided a satisfactory result is obtained after lesion predilation.

DCBs offer the advantage of locally delivering the antiproliferative drug without the need for

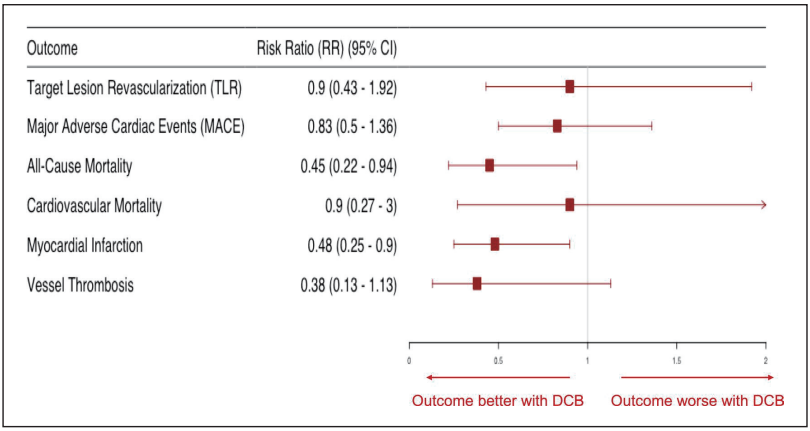

Figure 6. Forest plots for the clinical outcomes evaluated in this meta-analysis.
For each comparison, boxes and horizontal lines correspond to the respective point estimate and accompanying 95% CI. DCB indicates drug-coated balloon; MACE, major adverse cardiac events; and TLR, target lesion revascularization.

metal struts, thus directly inhibiting the process of neointimal hyperplasia and negative remodeling.[4] Although use of DCBs in patients with in-stent restenosis has been extensively investigated,[9] trials evaluating DCBs for de novo lesions have been small and evaluated specific indications. Our meta-analysis, including the most recent trials, has demonstrated that DCBs were associated with favorable clinical outcomes irrespective of the indication, even when compared with second-generation DESs. Although most patients undergoing percutaneous coronary intervention are treated with a second-generation DES,[1] BMSs are still used in a minority of patients, such as those with a high risk of bleeding to minimize the duration of antiplatelet therapy. Our meta-analysis showed that DCBs represent a reasonable therapeutic strategy for this subset of patients.

Second-generation DESs may not offer an effective therapeutic strategy in small vessels due to the late lumen loss resulting in late in-stent restenosis.[34] In this challenging setting, several randomized trials have shown that DCBs are noninferior to DESs for major adverse cardiac events.[10,11] By significantly increasing the sample size, the current meta-analysis has extended our knowledge by showing that DCBs are associated with similar TLR compared with any control, including second-generation DESs. Moreover, our meta-regression analysis has shown that there was no difference in treatment effect based on the reference vessel diameter.

One meta-analysis of randomized trials has raised some concerns about late mortality with DCBs for patients with peripheral artery disease.[35] That meta-analysis was subject to several limitations,[36] and the late mortality finding was not replicated in several large observational studies and patient-level meta-analysis.[37,38] Our meta-analysis provides some support for the use of DCBs for coronary lesions. However, the lower mortality seen with DCBs in our meta-analysis should be interpreted with caution given the limited number of studies that evaluated all-cause mortality and the low number of events.

Previous meta-analyses addressed use of DCBs for a specific indication, such as small-vessel disease or bifurcational lesions.[39–41] In addition, those meta-analyses included observational studies, which are prone to ascertainment and selection biases.[39–41] Furthermore, those works did not include the results of several recently published and presented trials.[10,13,14,24] The present meta-analysis only included randomized trials and has provided a comprehensive overview of the angiographic and clinical outcomes of DCBs irrespective of indication. In addition, we performed several subgroup and sensitivity analyses to explore the statistical heterogeneity.

Our meta-analysis has several limitations. First, although all the included studies used a paclitaxel-coated balloon, there are several pharmacokinetic differences between the devices. For example, one trial used the first-generation Drior paclitaxel-coated balloon, which was shown to be inferior in terms of deliverability and is no longer available. Thus, we performed a sensitivity analysis excluding this trial for the primary clinical outcome. Second, there were differences in the core laboratory assessment of the angiographic outcomes across the trials, which could be a source of the significant heterogeneity noted with these outcomes. However, we observed no heterogeneity for most of the angiographic outcomes on the sensitivity analysis comparing DCBs with second-generation DESs. Third, we noted a moderate degree of statistical heterogeneity for the primary clinical outcome (ie, TLR). We attempted to mitigate this by using a random-effects model. In addition, we performed multiple subgroup, sensitivity, and meta-regression analyses to explore the heterogeneity; however, the number of studies included in some of these subgroup and sensitivity analyses was small, so the findings can only be considered as hypothesis-generating. Fourth, one of the included trials was at high risk for bias,[32] so we performed a sensitivity analysis excluding that trial for TLR. Fifth, despite the extensive subgroup, sensitivity, and meta-regression analyses conducted, there may be some considerations about clinical and methodologic heterogeneity, because the meta-analysis included different comparators and the indication for DCBs were variable. Finally, the lack of patient-level data precluded a careful evaluation for the patient and lesion characteristics that would benefit most from DCBs.

CONCLUSIONS

In this meta-analysis of 14 randomized trials comprising 2483 patients with de novo coronary lesions, DCBs were associated with similar MLD, diameter stenosis, acute lumen gain, binary restenosis, and lower late lumen loss compared with control on routine angiographic follow up. There was no difference in the incidence of TLR between DCBs compared with control. This effect was observed regardless of indication (ie, small-vessel disease, high bleeding risk, MI, or bifurcational lesions), and was maintained when compared with second-generation DES alone. Finally, DCBs were associated with lower risk of MI and all-cause mortality, albeit with a low number of events, so our work should be only considered hypothesis-generating. Our findings support the need for a randomized trial powered for clinical outcomes evaluating the role of the DCBs in all-comers.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S4
Figures S1–12
References 10–14, 22, 24–27, 29, and 31

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Effect of Drug-Coated Balloons in Native Coronary Artery Disease Left With a Dissection

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ABSTRACT

OBJECTIVES The authors sought to understand the clinical and angiographic outcomes of dissections left after drug-coated balloon (DCB) angioplasty.

BACKGROUND Second-generation DCB may be an alternative to stents in selected populations for the treatment of native coronary lesions. However, the use of these devices may be hampered by a certain risk of acute vessel recoil or residual coronary dissection. Moreover, stenting after DCB has shown limited efficacy. Little is known about when a non-flow-limiting dissection is left after DCB angioplasty.

METHODS This was a prospective observational study whose aim was to investigate the outcome of a consecutive series of patients with native coronary artery disease treated with second-generation DCB and residual coronary dissection at 2 Italian centers. We evaluated patient clinical conditions at 1 and 9 months, and angiographic follow up was undertaken at 6 months.

RESULTS Between July 2012 and July 2014, 156 patients were treated with DCB for native coronary artery disease. Fifty-two patients had a final dissection, 4 of which underwent prosthesis implantation and 48 were left untreated and underwent angiographic follow-up after 201 days (interquartile range: 161 to 250 days). The dissections were all type A to C, and none determined an impaired distal flow. Complete vessel healing at angiography was observed in 45 patients (93.8%), whereas 3 patients had persistent but uncomplicated dissections, and 3 had binary restenosis (6.2%). Late lumen loss was 0.14 mm (−0.14 to 0.42). Major adverse cardiovascular events occurred in 11 patients in the entire cohort and in 4 of the dissection cohort (7.2% vs. 8.1%; p = 0.48). We observed 8 and 3 target lesion revascularizations, respectively (5.3% vs. 6.2%; p = 0.37).

CONCLUSIONS In this cohort of consecutive patients treated with new-generation DCB and left with a final dissection, this strategy of revascularization seemed associated with the sealing of most of dissections and without significant neointimal hyperplasia. (J Am Coll Cardiol Intv 2015;8:2003–9) © 2015 by the American College of Cardiology Foundation.

Drug-coated balloons (DCB) were developed to overcome neointimal hyperplasia and have been widely tested for the treatment of in-stent restenosis, in which setting they have shown an efficacy comparable to drug-eluting stents (DES) in terms of target lesion revascularization (TLR) (1–4). For this indication, DCB gained a Class I, Level of Evidence: A in the latest European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for myocardial revascularization (5).

However, from the mechanical point of view, DCB behave just like simple balloons, thus they share some of the main limitations of these devices after angioplasty, namely coronary dissection and acute recoil.

Very preliminary observations seem to show how new-generation DCB could be associated with a faster spontaneous healing of an arterial dissection left after balloon angioplasty, especially in case of angioplasties of the femoropopliteal region and for the treatment of in-stent restenosis (6,7). The aim of this study was to test this hypothesis in a consecutive series of patients with native coronary vessel disease.

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ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon(s)

DES = drug-eluting stent(s)

LLL = late lumen loss

MACE = major adverse cardiac event(s)

MLD = minimal lumen diameter

PCI = percutaneous coronary intervention

RVD = reference vessel diameter

TLR = target lesion revascularization

METHODS

This is an observational study conducted at 2 centers expert in DCB angioplasty. The aim of the study was to investigate the outcome of consecutive coronary dissections left after DCB angioplasty in native vessels.

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Inclusion criterion was any percutaneous coronary intervention (PCI) performed with DCB in native coronary vessels. Exclusion criteria were any use of DCB for reasons different from the aforementioned (e.g., for in-stent restenosis); ST-segment elevation myocardial infarction that occurred in the previous 48 h; or life expectancy <1 year. Other clinical indications for PCI, unstable hemodynamics at presentation, and the presence of renal insufficiency were not exclusion criteria. We had a restrictive use of DCB in case of big vessel size (e.g., >3 mm in diameter) or in case of very calcific vessels, especially when we feared possible vessel recoil.

In the current study, the following devices were used: Restore (Cardionovum, Milano, Italy) and Elutax SV (Aachen Resonance, Lainate, Italy) DCB. These 2 devices, both eluting paclitaxel, may be considered a second-generation DCB because of a more efficient delivery of paclitaxel to the vessel wall, which results in a longer persistence of the drug. Restore DCB has a concentration of paclitaxel of 3.0 μg/mm^2 of balloon surface, and shellac is used as a carrier. Elutax SV DCB has a concentration of paclitaxel of 2.2 μg/mm^2 of balloon surface, and is embedded in a 3-layer matrix. Available measures for both devices used in this study included diameters of 2.0, 2.5, and 3.0 mm, and lengths of 15, 20, 25, and 30 mm.

The intervention was performed according to international guidelines and the recent Italian position paper on DCB PCI (8). Specifically, pre-dilation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after pre-dilation, we recommended considering conversion to a stent PCI without using a DCB. The DCB was inflated for 30 to 45 s at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 min, in order to catch early vessel recoil. In this event, bailout stent implantation was considered. The type of stent or scaffold was left to the operator's discretion.

Patients with any residual coronary dissection after DCB use entered the current analysis. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute [NHBLI] classification system for intimal tears, developed by the Coronary Angioplasty Registry) with Thrombolysis In Myocardial Infarction (TIMI) flow grade 3. In case of coronary dissections of type D or higher and/or impaired distal flow, it is our habit to implant a stent.

After sheath insertion, all patients were administered unfractionated heparin (single bolus of 5,000 IU, then adjunctive boluses following activated clotting time) or bivalirudin (bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure). A bailout glycoprotein IIb/IIIa receptor inhibitor strategy was allowed in case of high thrombus burden. All patients received aspirin (either 100 mg/day for at least 3 days before PCI or with a pre-PCI 300-mg intravenous bolus), and clopidogrel (300 or 600 mg as a loading dose, followed by 75 mg daily) or prasugrel (60 mg as a loading dose, followed by 10 mg daily) or ticagrelor (180 mg as a loading dose, followed by 90 mg twice a day) following clinical indication. The duration of prescribed dual antiplatelet treatment was 1 month, or 6 months in case of stent implantation; after this time, patients were prescribed only aspirin.

Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI flow

TABLE 1 Patients' Clinical Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Age, yrs	61 (54–67)	59 (51–64)	60 (54–66)	0.18
Female	50 (32.0)	31 (29.8)	19 (36.5)	0.31
Hypertension	91 (58.3)	59 (56.7)	32 (63.5)	0.21
Hypercholesterolemia	95 (60.9)	65 (62.5)	30 (57.7)	0.32
Diabetes	55 (35.2)	37 (35.6)	18 (34.6)	0.86
Prior MI	14 (9.3)	10 (9.6)	4 (8.4)	0.48
Prior revascularization	17 (10.9)	9 (8.7)	8 (13.5)	0.16
Multivessel coronary disease	78 (50)	52 (50)	26 (50)	0.91
Stable angina	82 (52.6)	55 (52.9)	27 (51.9)	0.84
Unstable angina	31 (19.9)	19 (18.3)	12 (23.0)	0.33
Non–ST-segment elevation MI	43 (27.6)	30 (28.8)	13 (25)	0.75
Culprit vessel				
Left anterior descending artery	88 (56.4)	52 (50)	35 (67.0)	**0.02**
Left circumflex artery	13 (8.3)	10 (9.6)	3 (5.8)	0.06
Right coronary artery	55 (35.2)	42 (40.4)	14 (26.9)	0.842

Values are median (interquartile range) or n (%). p Value in **bold** have reached statistical significance.

DCB = drug-coated balloon; MI = myocardial infarction.

grade 3. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE) (defined as any occurrence of ST-segment elevation acute myocardial infarction, target vessel revascularization, TLR, or death). Periprocedural myocardial infarction was defined as a post-procedural increase in cardiac troponin T >5 × 99th percentile of the upper reference limit.

All patients underwent clinical follow-up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow-up with quantitative coronary assessment after 6 months, in order to assess the degree of coronary dissection healing. All measurements were performed on cineangiograms recorded after 200 mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging, Maastricht, the Netherlands). The following parameters were analyzed: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL) (defined as the difference between MLD after index PCI and MLD at angiographic follow up), lesion length, binary restenosis, and persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow-up.

Primary endpoint of this study was the percentage of dissection healing detected at angiographic follow-up. Secondary endpoints included TLR, binary restenosis, LLL, and the occurrence of MACE.

Data are presented as mean ± SD or median (interquartile range) as appropriate for continuous variables, and as proportions (%) for dichotomous variables. The differences between groups were assessed by chi-square test or Fisher exact test for categorical data, and paired Student *t* test for continuous data. The relative risk and its 95% confidence interval were calculated for each study endpoint. A 2-sided p value <0.05 was considered statistically significant.

RESULTS

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with second-generation DCB for native coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database. Thirty-five percent of patients had diabetes, and clinical indication was stable angina in 82, unstable angina in 31, and non-ST-segment elevation myocardial infarction in 43 patients. Procedural success was achieved in all patients.

TABLE 2 Procedural Characteristics

	All DCB Population, Native Vessels (N = 156)	No Dissection Cohort (n = 104)	Dissection Cohort (n = 52)	p Value
Radial approach	144 (92.3)	96 (92.3)	48 (92.3)	0.95
Total occlusion	18 (11.5)	9 (8.7)	9 (17.3)	0.47
Reference vessel diameter, mm	2.83 (2.12–3.01)	2.87 (2.15–3.0)	2.80 (2.07–2.97)	0.21
Minimal lumen diameter, mm	0.4 (0.0–0.73)	0.37 (0.03–0.65)	0.41 (0.00–0.79)	0.11
Stenosis severity, %	83 (72–100)	82 (71–100)	84 (70–100)	0.18
Lesion length, mm	21 (10–33)	19 (10–28)	22 (12–33)	0.10
Severe-moderate calcification (visual estimation)	100 (64.1)	60 (57.7)	40 (76.9)	**0.01**
Pre-dilation balloon diameter, mm	2.45 (2.0–3.0)	2.35 (2.0–3.0)	2.5 (2.0–3.0)	**0.04**
DCB diameter, mm	2.55 (2.0–3.0)	2.50 (2.0–3.0)	2.60 (2.0–3.0)	**0.035**
DCB length, mm	25 (15–30)	24 (15–30)	25 (15–30)	0.37
Max pressure during DCB angioplasty, atm	12 (8–14)	11 (9–14)	12 (8–15)	0.49
DCB inflation duration, s	35 (30–45)	37 (32–45)	34 (30–42)	0.33
OCT/IVUS guidance	15 (9.6)	11 (10.6)	4 (7.7)	0.13
Minimal lumen diameter after PCI, mm	2.21 (1.75–2.67)	2.17 (1.75–2.58)	2.24 (1.84–2.67)	0.22
Procedural success	156 (100)	104 (100)	52 (100)	0.87
Periprocedural myocardial infarction	21 (13.5)	13 (12.5)	8 (15.4)	0.42
Bivalirudin	15 (9.6)	9 (8.7)	6 (11.5)	0.23
Dual antiplatelet therapy				
ASA + clopidogrel	130 (83.3)	85 (81.7)	45 (86.5)	0.24
ASA + ticagrelor/prasugrel	26 (16.7)	19 (18.3)	7 (13.5)	0.36

Values are n (%) or median (interquartile range). Values in **bold** have reached statistical significance.

ASA = acetylsalicylic acid; DCB = drug-coated balloon; IVUS = intravascular ultrasound; OCT = optical coherence tomography; PCI = percutaneous coronary intervention.

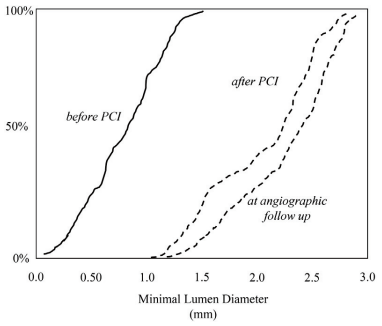
TABLE 3 Angiographic Follow-Up of Patients With Dissection After DCB PCI

	Dissection Cohort (n = 48)
Reference vessel diameter, mm	2.87 (2.11 to 2.98)
Minimal lumen diameter, mm	2.42 (2.22 to 2.66)
Diameter stenosis, %	12 (8 to 20)
LLL, mm	0.14 (−0.14 to 0.42)
Complete vessel healing	45 (93.8)
Binary restenosis	3 (6.2)

Values are median (interquartile range) or n (%). Follow-up was at 201 days (interquartile range 161 to 250 days).

LLL = late lumen loss; other abbreviations as in Table 2.

FIGURE 1 MLD Before DCB PCI, After DCB PCI, and at Angiographic Follow-Up in Patients Left With a Dissection



Notably, there was a diffuse lumen enlargement at angiographic control. DCB = drug-coated balloon; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention.

For the purpose of this analysis, we studied the 52 patients that had an angiographically detectable dissection after DCB angioplasty. All patients of this cohort underwent programmed coronary angiography after 6 to 9 months. Baseline clinical characteristics and clinical indication to PCI of the entire population and of the 2 cohorts are shown in **Table 1**. The dissection study group did not differ significantly from the entire DCB group, if we exclude a higher incidence of left anterior descending artery as the culprit vessel, the degree of calcification of the culprit lesion, the size of balloon used for predilation, and the size of the DCB (**Table 2**). Baseline angiographic characteristics are shown in **Table 2**. Of note, the vessel diameter was 2.83 mm in the entire population, and 2.80 mm in the dissection population.

Of the 52 patients with residual dissection after DCB PCI, 4 had a prosthesis implanted (2 a bare-metal stent, 1 a DES, and 1 a biovascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in 1.

All patients with a final dissection underwent scheduled angiographic follow-up with quantitative coronary assessment, that was undertaken after 201 days (interquartile range 161 to 250 days). Angiographic outcome is presented in **Table 3**. Of note, LLL was as low as 0.14 ± 0.28 mm in this group. We also observed a late lumen enlargement in the treated segments (**Figure 1**).

Complete vessel healing at angiography was observed in 45 of 48 patients (93.8%) (**Figure 2**). The 3 patients that had an unhealed dissection had, respectively, a type A, type B, and type C coronary dissection after the index PCI. TLR occurred in 3 patients (6.2%) in the dissection cohort and in 8 patients (5.3%) in the entire DCB population ($p = 0.49$) (**Figure 3**). Of the 3 patients that underwent TLR in the dissection cohort, the first 2 had recurrence of angina after 4 and 6 months, respectively; angiography showed subocclusive coronary stenoses (of 85% and 90%, respectively) at the site of the previous PCI that were successfully treated with DES implantation. The third patient was asymptomatic but had a persisting, chronic coronary dissection discovered at angiographic follow-up that was sealed with DES implantation.

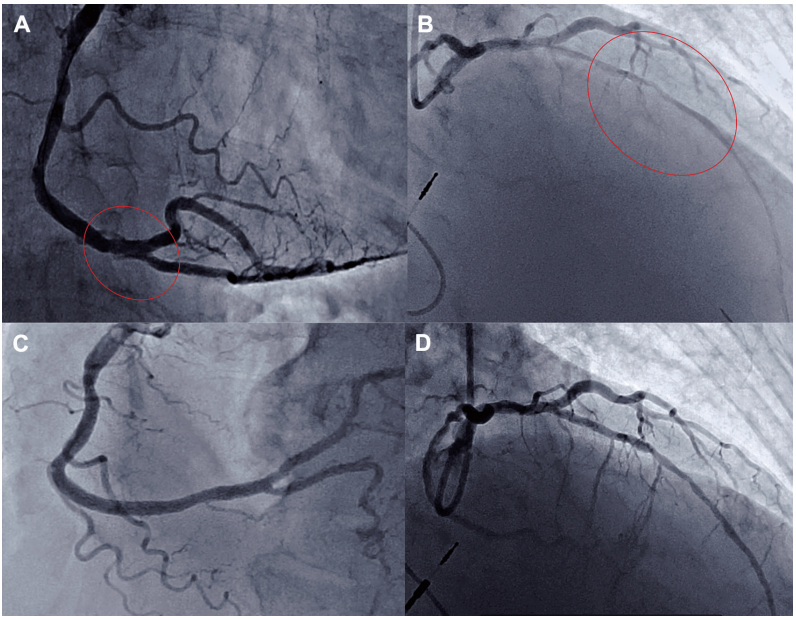
The other clinical endpoints showed no significant differences between the whole group and the groups with and without dissection (**Figure 3**). Interestingly, we did not observe cases of target vessel myocardial infarction during the entire clinical follow-up (average length 9 ± 3 months). Finally, there were no significant differences between the 2 devices tested in terms of clinical and angiographic endpoints.

DISCUSSION

This prospective observational study describes the first consecutive series of patients treated with DCB for native coronary artery disease and with final dissection left "unsealed" with prosthesis. Our results confirm that leaving a non-flow-limiting dissection untreated after DCB PCI is safe and not associated with an increase in myocardial infarction and TLR, despite the short-term (1 month) dual antiplatelet treatment. Notably, we did not observe a correlation between the type of dissection at baseline (type A, B, or C) and the propensity to healing (**Figure 4**).

DCB were developed to overcome neointimal hyperplasia and have been first tested in the in-stent restenosis setting with good results maintained for years (3,9). However, the use of DCB for the treatment of native vessels seems particularly encouraging, especially in the case of small vessels and distal lesions, where the encumbrance of a stent may limit its potential and is associated with increased rates of restenosis and stent thrombosis. However, the application of this technology as standalone procedure in de novo lesions has resulted in conflicting results. After some early mistakes, such as the ones depicted in the PICCOLETO (Paclitaxel-Eluting Balloon Versus Paclitaxel-Eluting Stent in Small

FIGURE 2 Angiographic Outcome of Dissections Left After DCB Angioplasty



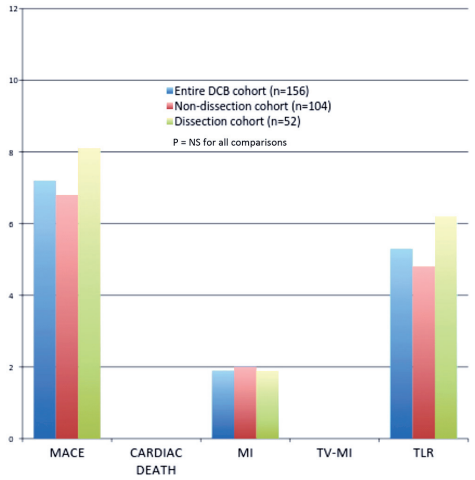
A and B show the final dissections (respectively, a type C and a long type A dissection, **red circles**); after 6 months, both dissections were healed **(C and D).** DCB = drug-coated balloon.

Coronary Artery Diseases) study (10,11), a newer generation of DCB has been tested in the BELLO (Balloon Elution and Late Loss Optimization) study for the treatment of native coronary vessels. Here, DCB overcame Taxus DES for the treatment of small vessel disease in terms of the primary endpoint of LLL (0.08 ± 0.38 mm vs. 0.29 ± 0.44 mm; 95% confidence interval: −0.34 to −0.09; p = 0.001) (12). Recently, the 2-year follow up of the BELLO study, that showed persisting good results of DCB in terms of clinical endpoints, has been published. (13) Similar encouraging results for this technology in native coronary vessels were shown in large registries with different, new-generation DCB (14,15).

This study was performed with 2 devices of the latest available technology, that provides optimal paclitaxel delivery to the vessel wall and contemporarily allows its longer persistence.

The central point of our findings is the safety of leaving a dissection after DCB angioplasty. Early experiences have shown how leaving a dissection after plain old balloon angioplasty was associated with increased rates of thrombotic events, early reocclusion, and recurrence of restenosis, and this was one of the main indications for the use of stents in an earlier era (16). The widespread use of more potent antiplatelet regimens (e.g., the association of aspirin with a $P2Y_{12}$ receptor inhibitor) has undoubtedly improved the early outcome of this type of patient. In the early stent era, a previous series of patients treated consecutively with plain angioplasty and with a final dissection, despite a very low occurrence of thrombotic events and an acceptable rate of restenosis (12%), 36.7% of dissections left were still visible at 6-month angiographic follow-up (17). With this current study, we have opened the hypothesis that the effect of paclitaxel, when correctly delivered to the vessel wall, may have a role in facilitating the healing of coronary vessels.

FIGURE 3 Clinical Follow-Up After 9 Months in the Entire Population and in the Dissection and No-Dissection Cohorts



p Values are not significant for all comparisons. DCB = drug-coated balloon; MACE = major cardiovascular event(s); MI = myocardial infarction; TLR = target lesion revascularization; TV = target vessel.

FIGURE 4 The Fate of Dissections After DCB Angioplasty

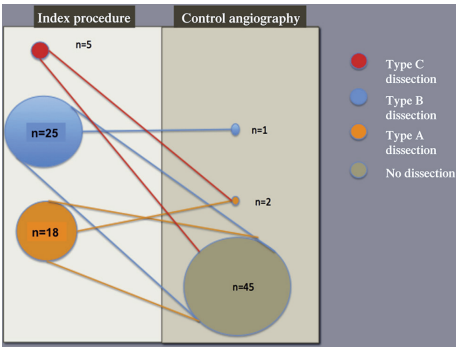


Figure shows what happened to dissections at 6-month angiography: 45 were healed and 3 were chronic. There was not an apparent correlation between the type of initial dissection left after DCB angioplasty and its fate. We followed the NHLBI classification for coronary dissections. DCB = drug-coated balloon; NHLBI = National Heart, Lung, and Blood Institute.

This effect was already described in a post-hoc analysis of the THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries) study (6), where patients with femoropopliteal disease were randomized to simple angioplasty or DCB. In this analysis, patients treated with DCB resulting in final dissection of any grade had significantly lower LLL than patients with dissection after simple angioplasty (0.4 vs. 1.9 mm; p = 0.001), especially if the dissection grade was severe (type C to E) (0.4 vs 2.4 mm; p = 0.05). This result was maintained for all the duration of the 2-year follow-up, with a TLR of 10% versus 56% respectively (p = 0.002) (6). In another study, Agostoni et al. (18) have found how leaving small dissections after DCB angioplasty for in-stent restenosis resulted in complete dissection healing at optical coherence tomography after 6 months. In addition to this information, we also found that our patients, who did not have a "caged" coronary artery because they did not have in-stent restenosis, also had an improved late lumen gain, as already described in another series of patients treated with DCB for native coronary vessel disease (19). This late lumen enlargement (**Figure 1**) is another interesting effect of DCB that needs further, dedicated analysis.

In this study, we decided to limit the degree of dissections left to a low-medium grade (type A to C) because of ethical reasons (the eventual vessel occlusion would result in myocardial infarction). Now with our results, if the dissection is of low-medium grade, it seems safe to leave it untreated. In fact, data from the literature show how any stent strategy associated with DCB use is unsafe or yields unsatisfactory results (20,21). There are some initial data on the use of DES after DCB, but such data are limited in number and are without angiographic follow-up (22), thus the contemporary use of 2 different antirestenotic drugs with stent metal layers needs to be better understood before recommending this strategy. Moreover, in this case, the advantages of using a DCB are immediately lost (23).

STUDY LIMITATIONS. First, the population is limited and derives from 2 centers expert in this type of PCI, thus it may not be reproducible everywhere without an adequate learning curve. Moreover, we have to disclose an initial bias at the time of decision of leaving the dissection untreated. So far, these results are not easily reproducible in all settings. Our findings, although a confirmation of other previous studies, are the first assessment of this property of new-generation DCB in native coronary lesions, and need to be validated in other ad hoc clinical studies.

CONCLUSIONS

In a consecutive series of patients treated with new-generation DCB for native coronary artery disease and with a final non-flow-limiting dissection, these lesions tended to heal despite their initial severity. After DCB angioplasty, a strategy of bailout stenting should be reserved to more severe, flow-limiting dissections.

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PERSPECTIVES

WHAT IS KNOWN? DCB are a useful tool for the treatment of small coronary arteries. However, little is known regarding the fate of dissections left unsealed after DCB PCI.

WHAT IS NEW? With this study, for the first time in the coronary tree, we showed a pro-healing effect of DCB when a final dissection was left at the end of PCI.

WHAT IS NEXT? We now need an adequately powered study (e.g., a randomized controlled study) to test this preliminary report in a broader population of coronary artery disease patients.

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KEY WORDS angiographic follow-up, coronary dissection, dissection healing, drug-coated balloon

Effect of drug-coated balloons in native coronary artery disease left with a dissection.

Subanalysis and comparison between Restore and Elutax SV drug-coated balloons

This prospective observational study invesigated the outcome of native coronary artery disease treated with second-generation DCB and residual coronary dissections with angiographic follow up after 6 months.

The current sub-analysis of the study investigated the performance of Restore DCB vs. Elutax SV DCB in the study population (see main publication: B. Cortese et al., JACC Interventions, Dec. 2015).

The intervention was performed according to international guidelines and the recent Italian Position Paper on DCB-PCI.(8) Specifically, predilatation with an undersized semicompliant balloon was mandatory (the recommended size was 0.9:1 of DCB). In case of flow-limiting dissection after predilatation, we recommended to consider conversion to a stent-PCI without using a DCB. DCB was inflated for 30-45 seconds at nominal pressure, according to the morphological characteristics of the lesion (e.g., degree of calcification, length, tortuosity). After DCB use, final assessment was undertaken after at least 5 minutes, in order to catch early vessel recoil. In this evenience, bailout stent implantation was considered. The type of stent or scaffold was left at operator's discretion. It is our habit not to stent coronary dissections of type A to C (National Heart, Lung, and Blood Institute (NHBLI) classification system for intimal tears, developed by the Coronary Angioplasty Registry) with TIMI 3 flow grade. In case of coronary dissections of type D or higher and/or impaired distal flow it is our habit to implant a stent.
Angiographic success was defined as a final residual stenosis <50% by visual estimate, with TIMI 3 flow. Procedural success was defined as angiographic success without the occurrence of in-hospital major adverse cardiac events (MACE: any occurrence of ST-elevation acute myocardial infarction, target vessel revascularisation, TLR, or death).

All patients underwent clinical follow up after 1 and 9 months; all patients in the dissection cohort underwent angiographic follow up with quantitative coronary assessment (QCA) after 6 months, in order to assess the degree of coronary dissection healing. All measurements were

performed on cineangiograms recorded after 200mg of intracoronary nitroglycerin administration. Identical projections were used for each comparison. Quantitative analysis of angiographic data were initially assessed by a single experienced investigator, and afterwards validated by an internal committee of experts, using the CAAS II research system (Pie Medical Imaging). The following parameters were analyzied: reference vessel diameter (RVD), minimal lumen diameter (MLD), percent diameter stenosis (the difference between RVD and MLD divided by RVD), late lumen loss (LLL, the difference between MLD after index-PCI and MLD at angiographic follow up) lesion length, binary restenosis, persistence of dissection (NHBLI classification). Measurements included the whole segment treated plus 5 mm proximally and distally. Binary restenosis was defined as stenosis of at least 50% of the luminal diameter at angiographic follow up.

Primary endpoint of the study was the percentage of dissection healing detected at angiographic follow up. Secondary endpoints included TLR, binary restenosis, LLL and the occurrence of MACE.

The study population consisted of 156 consecutive patients treated between July 2012 and July 2014 at 2 centers with II generation DCB for native coronary artery disease (87 with Restore and 69 with Elutax SV), that were prospectively entered in the database.

For the purpose of this analysis, we studied the 52 patients that had an angiographically-detectable dissection after DCB-angioplasty. All patients of this cohort underwent programmed coronary angiography after 6-9 months. Of the 52 patients with residual dissection after DCB-PCI, 4 had a prosthesis implanted (2 a bare-metal stent, one a DES and one a bio-vascular scaffold). The reason for implanting a stent/scaffold was impairment of distal flow in 3 patients, and the presence of a spiral, type D dissection in one.

All patients with a final dissection underwent scheduled angiographic follow up with QCA, that was undertaken after 201 days (I.Q. range: 161-250 days). The main results of this sub-analysis are shown in the Table below.

	Restore	***Elutax SV***	***p***
Late lumen loss, mm	0.20 (0.07 to 0.42)	0.08 (-0.14 to 0.28)	0.073
Vessel healing, %	89	98	NS
Binary restenosis, %	9.4	3	0.05
Target lesion revascularization, %	9.5	3	0.049
Cardiac death, %	0	0	NS

In conclusion, in a consecutive series of patients treated with new generation DCB for native coronary artery disease and with a final not flow-limiting dissection, these lesions tended to heal despite their initial severity. In this limited patient population, Elutax SV seems to achieve an improved angiographic outcome.

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Letter to the Editor

Drug-coated balloon angioplasty: An intriguing alternative for the treatment of coronary chronic total occlusions

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Dual antiPlatelet therapy (DAPT)
Drug-eluting stent (DES)

Dear Editor,

The treatment of coronary chronic total occlusions (CTOs) is one of the most exciting and, at the same time, delicate challenges for the interventional cardiologist. In the last few years specific devices have been implemented in order to increase the rate for a successful CTO recanalization. Current treatment options are drug-eluting stents, surgery or medical treatment. We here present an emblematic case of a new approach to this disorder.

An 80-year-old male was admitted at our department for worsening effort angina. In his medical history he had an anterior myocardial infarction managed with PCI and DES implantation of the left anterior descending artery (2008), and thereafter he underwent successful simple angioplasty of the ostium of 2nd obtuse marginal (OM2) due to subocclusive stenosis (Fig. 1A–B, Movie 1). Subsequently he developed a HCV-related hepatitis with episodes of gut and upper airway bleeding.

Coronary angiography showed a chronic total occlusion (CTO) of the ostial OM2 (Fig. 1C, Movie 2) for which we attempted antegrade recanalization. The lesion was not easily wired by a 12-g CTO guidewire supported by a 1.5 mm balloon. We thus performed further predilatations with 2.0 and 2.5 mm balloons obtaining adequate angiographic result. Given the high bleeding risk of the patient, we delivered a 2.5/30 mm drug-coated balloon (DCB), obtaining a good angiographic result with TIMI 3 grade flow and without visible dissection (Fig. 1D, Movie 3). The patient was discharged on dual antiplatelet treatment (DAPT) and after 30 days withdrew clopidogrel. Six-month scheduled coronarography showed persisting good angiographic result with improved lumen gain (Fig. 2A–B, Movie 4). One year later, the patient was still angina-free and had no ischemic or bleeding adverse events.

The use of DCB for the management of coronary artery disease is increasing for several clinical indications/anatomical settings. Specifically, we believe that this device could represent a new intriguing alternative to stents for the treatment of CTO as well [1]. To the best of our knowledge, this is a unique case in which a coronary CTO was managed with a DCB-only strategy. DCB delivers paclitaxel with a single shot and determines a homogeneous distribution of the drug on the vessel wall, resulting in a high concentration during the first days, when the restenotic process is developing [2]. Another advantage is that no permanent prosthesis is delivered, thus reducing the risk of late thrombotic events and the need for prolonged DAPT [3]. More so, the increased risk of late thrombotic events of newer generation DES may be explained by a delayed struts coverage if delivered for a CTO instead of other coronary lesions, thus requiring longer DAPT [4]. Conversely, a DCB-only strategy allows DAPT withdrawal after 2–4 weeks only, especially in patients at higher bleeding risk [5].

We believe that DCB may be a reasonable alternative to stents for the management of CTO. A dedicated study of DCB-only angioplasty seems a provocative idea and is eagerly awaited, especially for those patients that cannot undergo prolonged DAPT.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ijcard.2015.03.223.

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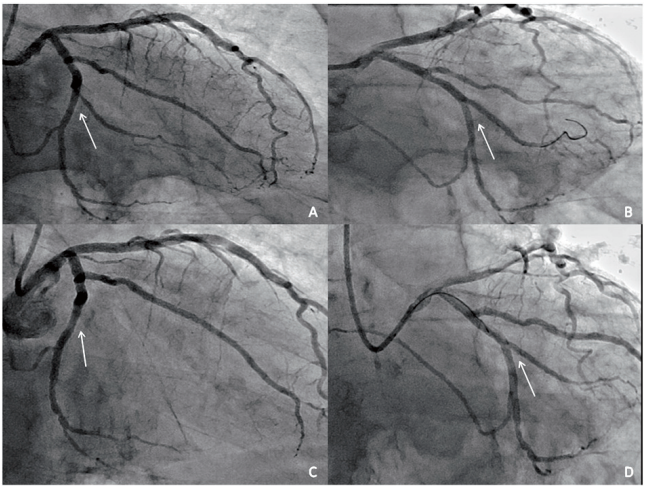

Fig. 1. A: subocclusive stenosis of the ostium of 2nd obtuse marginal branch (OM2). 1B and Movie 1: final angiographic result after simple balloon angioplasty. 1C and Movie 2: chronic total occlusion of the ostium of OM2. 1D and Movie 3: final angiographic result after drug-coated balloon angioplasty.

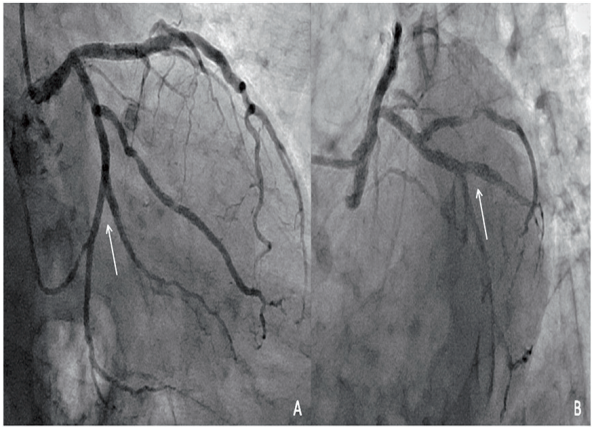

Fig. 2. A–B and Movie 4: six-month angiographic follow-up showing good patency of index lesion and increased vessel diameter.

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Cardiovascular Revascularization Medicine

First experience of drug-coated balloons for treatment of bioresorbable vascular scaffold restenosis☆

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ABSTRACT

Objectives: The aim of this study is to evaluate the role of drug-coated balloons (DCB) for the management of bioresorbable vascular scaffold (BVS) restenosis.
Methods and results: In a series of 25 BVS restenosis discovered during systematic angiographic follow up of 246 consecutive BVS implantations at our institution, DCB was used as a primary therapeutic tool in 9 patients and 3 different types of DCB were used. Follow-up coronary angiography at 12 months after DCB treatment was performed to all the patients. Among the 9 patients treated with DCB, angiographic follow up revealed failure in two patients that experienced type III restenosis (both of them treated with the same type of DCB). Both patients were treated with drug eluting stent implantation.
Conclusions: In this case series of consecutive patients with BVS restenosis, the use of certain types of DCB is safe and effective in order to maintain vessel patency at mid-term follow up. Despite the small sample size and the study limitations, DCB can provide therefore an alternative treatment option in this setting, avoiding the implantation of further metallic stents in a patient where a different strategy was initially planned.

1. Introduction

The use of drug-coated balloons (DCB) is one of the treatments of choice for both bare metal stent and drug-eluting stent (DES) restenosis [1]. Bioresorbable vascular scaffolds (BVS) are one of the most recent revolutionary steps in interventional cardiology. Studies are ongoing to evaluate the long-term efficacy of these biodegradable devices in a real world setting. There are limited data regarding the clinical outcome following target lesion revascularization (TLR) for BVS failure, with the optimal management currently unclear [2]. Several treatments are commonly used in this setting, including DES, re-BVS and DCB use. Currently, only few data are addressing the safety and the efficacy of DCB in the management of BVS restenosis.

The aim of this study, in the form of case series of consecutive patients, is indeed to evaluate the role of DCB in the management of BVS restenosis.

2. Methods

Out of 246 consecutive BVS implantations (Abbott Vascular, Santa Clara, CA, USA) between January 2013 and December 2015 performed at our institution, 210 underwent scheduled angiographic follow up after institutional review board approval and patient's informed consent. At a mean of 12 months, coronary angiography revealed 26 in-scaffold restenosis, defined as >50% restenosis at treatment site: 4 of them were left untreated due to the absence of evident signs of myocardial ischemia, 9 underwent DES implantation, 3 underwent further BVS implantation due to edge-restenosis, 1 underwent coronary artery bypass grafting and 9 patients received revascularization with DCB. At 12 months, a second coronary angiography was scheduled for the patients treated with DCB. Quantitative coronary angiography (QCA) performed by one single expert operator was used for the assessment of all procedures. Optical coherence tomography (OCT) (Ilumien, St. Jude Medical, MN, USA) was used for the assessment of the scaffold failure. Angiographic pattern of scaffold restenosis was classified according to Mehran's classification [3]. Data are presented as mean ± SD. Categorical variables are expressed as count and percentages.

3. Results

From the analysis of our data emerges a complex population. Table 1 describes the clinical characteristics of the patient and baseline procedural data, whereas Table 2 describes the procedural characteristics of

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Table 1
Clinical characteristics and procedural details at the initial procedure (time of BVS implantation).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Clinical characteristics	Age	56	42	57	70	55	76	81	58	79
	Sex	Female	Male	Male	Male	Male	Male	Male	Male	Male
	DM	No	No	Yes	No	Yes	No	No	Yes	No
Initial Procedure (BVS implantation)	Vessel	LCX-OM1	D2	Distal LAD	Prox. RCA	Proximal LCX	RI	Distal. RCA	LCX-OM1	Prox. LAD
	Lesion length (mm)	25	18	25	25	15	25	25	24	15
	RVD (mm)	2.75	2.5	2.5	3.5	2.5	2.5	3	2.5	3
	MLD (mm)	0.75	0.1	0.75	0.4	0.5	0.3	0.1	0	0.3
	% Stenosis	70	99	70	90	80	90	99	100	90
	Lesion type	B1	B1	B1	B1	B1	Type II ISR	Type II ISR	C	B1
	Degree of calcification	No	No	Mild	No	Mild	No	No	Mild	No
	Pre-dilatation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Scaffold length (mm)	28	18	28	28	18	28	28	28	18
	Scaffold diameter (mm) Mean= 2.66 ± 0.35 mm	2.5	2.5	2.5	3.5	2.5	2.5	2.5	2.5	3
	Post-dilatation	yes	yes	yes	yes	yes	yes	yes	yes	yes
	MLD	2.5	2.5	2.5	3.5	2	2.5	3	2.5	3
	Residual stenosis post-procedure(%)	0	0	0	0	20	0	0	0	0
	Acute again (mm)	2	2.4	1.75	3.1	16	2.2	2.9	2.5	2.7

the DCB procedure. At baseline, 6 patients had type B1 lesions, 1 type C lesion and 2 had type II ISR. Mean BVS diameter was 2.7 ± 0.35 mm and mean scaffold length was 24.7 ± 5 mm. The average time from the index procedure to scaffold failure was 12 ± 3 months. At index procedure, all the lesions were predilated by semi-compliant balloons in order to reach a <30% lesion stenosis. The mean diameter of the DCB was 2.6 ± 0.33 mm while the mean DCB length was 24.3 ± 7.8 mm (Table 2) and 3 different types of DCB were used.

Angiographic follow-up after the use of DCB was available for all the patients at a mean of 12 ± 2.6 months (Table 3). We observed two cases of DCB failure, both of them treated with Restore DCB (Cardionovum, Germany). For demonstrative purposes, 3 lesions were represented in Figs. 1–3. In particular, the first lesion was treated by 2.5 × 28 mm BVS at the LCX–OM1 bifurcation. The patient had unstable angina and coronary angiography revealed BVS failure with an 80% stenosis. This lesion was managed as mentioned by the use of 2.5 × 25 mm Restore DCB. At the scheduled angiographic follow-up we observed a recurrent 80% type III ISR, which was treated by the implantation of DES.

The other case of DCB failure the patient had received a 2.5 × 18 BVS in the proximal LCX. After 14 months angiographic follow-up performed for myocardial ischemia at stress test showed BVS failure with a 99% stenosis, and was managed by the use of one 2.5 × 20 Restore DCB. At the 6 months scheduled angiographic follow-up, the patient had type III restenosis that was managed by the implantation of 1 DES (Fig. 1).

During angiographic follow up, late lumen loss observed with DCB was 0.68 ± 0.7 mm. Clinical follow up revealed no hard clinical events.

4. Discussion

The BVS, heralded as the "fourth revolution in interventional cardiology [4], offers the possibility of transient scaffolding of the vessel to prevent acute vessel closure and recoil while eluting an antiproliferative drug to counteract the constrictive remodeling and the neointimal hyperplasia.

Absorb-BVS is the first drug-eluting BVS available for human use and is composed of PLLA and PDLLA. The bioresorbable polymer poly (L-lactide) (PLLA) scaffold is coated with a blend of the antiproliferative drug everolimus and bioresorbable polymer poly (D, L-lactide) (PDLLA) and pre-mounted on a rapid exchange (RX) scaffold delivery system. The scaffold is comprised of a series of circumferentially oriented sinusoidal rings that open during expansion. Two platinum markers are embedded at each end to enable fluoroscopic visualization, as the scaffold material is not radiopaque [5]. The first-generation of BVS was tested in the ABSORB Cohort A study, which showed late lumen enlargement, feasibility of non-invasive imaging with computed tomography (CT) scanning, and restoration of vasomotor and endothelial function at 2 years [6]. The second-generation of the device, tested in the ABSORB Cohort B, demonstrated a MACE rate of 9.0% (3 non-Q-wave MI, 6 ischemia-driven TLR, and no cardiac death) during the 2-year follow-up, with no alarming safety issues [7].

Later, Absorb II trial aimed at assessing the efficacy and safety of BVS in a broader patient population, and BVS was directly compared to Xience DES (Abbott Vascular, USA) [8]. The 3-year follow up of the trial, recently published, revealed a higher rate of target lesion failure

Table 2
Procedural details of the index procedure (Time of DCB use).

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Procedural Characteristics of the index procedure (DCB use)	Time from BVS implantation Mean= 12 ± 3 months	17	7	11	11	14	11	12	13	11
	MLD	0.5	0	0.75	1	0.3	0.75	1.09	0	0.9
	% stenosis	80	100	70	70	99	70	60	100	70
	DCB type	Restore	Elutax SV	Elutax SV	In.Pact Falcon	Restore	In.Pact Falcon	In.Pact Falcon	Elutax SV	Elutax SV
	DCB length Mean= 24.3 ± 7.8 mm	25	30	20	20	20	14	20	40	30
	DCB diameter Mean= 2.61 ± 0.33 mm	2.5	2	2.5	3	2.5	2.5	3	2.5	3
	Final MLD	2.5	2	2.5	3	2	2.5	3	2.5	3
	Final % stenosis	0	0	0	0	20	0	0	0	0

Table 3
Angiographic and clinical follow up after DCB use.

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Follow up after DCB	Time from DCB PCI (months)	7	8	8	12	6	6	15	6	11
	MLD (mm)	0.5	2	2.5	3.5	0.5	1.75	1.8	1.5	2.7
	% Stenosis	80	0	0	0	80	30	28	40	10
	Late lumen loss Mean= 0.68 ± 0.7 mm	2.25	0	0	0	2	0.75	1.2	1	0.3
	Death	No	No	No	No	No	No	No	No	No
	MI	No	No	No	No	No	No	No	No	No
	TLR	Yes	No	No	No	Yes	No	No	No	No

in the BVS group (7 vs. 3%, p = 0.07). In this trial, BVS failure was either caused by scaffold thrombosis (including 6 very late definite cases) and restenosis (11 cases at 3 years).

In terms of restenosis, many mechanisms were suggested to explain BVS failure, such as: neointimal hyperplasia, neoatherosclerosis, BVS collapse, fracture, edge phenomenon and late dismantling. In our experience, BVS failure is most likely caused by neointimal proliferation if it occurs during the first months. After the device has lost its integrity (usually after 6–12 months), contrary to metallic stents BVS failure can be also caused by scaffold recoil, although limited data are available in the literature on this topic [9]. Based on the assumption that BVS and metallic stents both share the same pathogenesis for restenosis, accordingly DCB appears to be an appealing option in this subset of patients. In our study, immediate and late angiographic success was achieved in 7 patients, all treated with latest-generation DCB. We can only speculate on the pathogenesis of BVS failure in this case series; however, the use of intravascular imaging seems to us an important tool in order to understand its etiology.

Historically, failure of re-PCI after ISR occurs in 30–70% of the cases regardless of the technique used [10,11]. In our study, DCB failure occurred in 2 patients who were both treated with Restore DCB. Nowadays, it is quite clear how all DCB were not created equal, probably because of the complex mechanisms under this technology that firstly aim at protecting paclitaxel while reaching the target lesion, and later should allow its diffusion and persistence in the vessel wall [11,12].

This case series has several limitations that need to be accounted. First, despite the complete angiographic follow up, sample size is small. Second, although clinical and angiographic outcomes are promising, the nature of this case series does not allow a comparison of different types of DCB. Larger studies, prospectively designed, with a larger population and a comparison with DES seem the best way to deeply understand if DCB may have a role for the treatment of BVS restenosis.

5. Conclusions

Management of BVS restenosis requires a deep understanding of its pathogenesis. In this case series of consecutive patients treated with DCB we suggest that this strategy is a safe and effective option to maintain the vessel patency at mid-term. Larger studies to address the etiology of BVS failure and to assess the role of DCB in such lesions are needed.

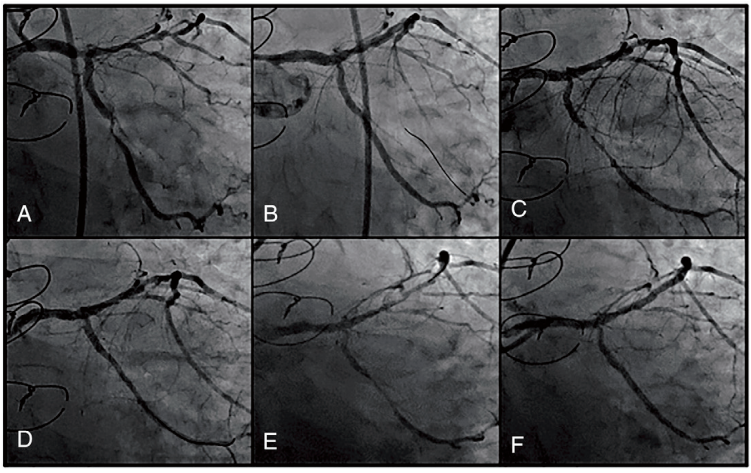

Fig. 1. A: significant stenosis at mid LCX at the initial procedure, B: result after BVS implantation. C: BVS restenosis, D: immediate angiographic result after DCB use, E: OCT revealing well apposition of the BVS, F: angiographic follow up showing DCB failure, F: OCT showing scaffold failure secondary to neointimal hyperplasia, G: angiographic result after DES implantation (Patient 1).

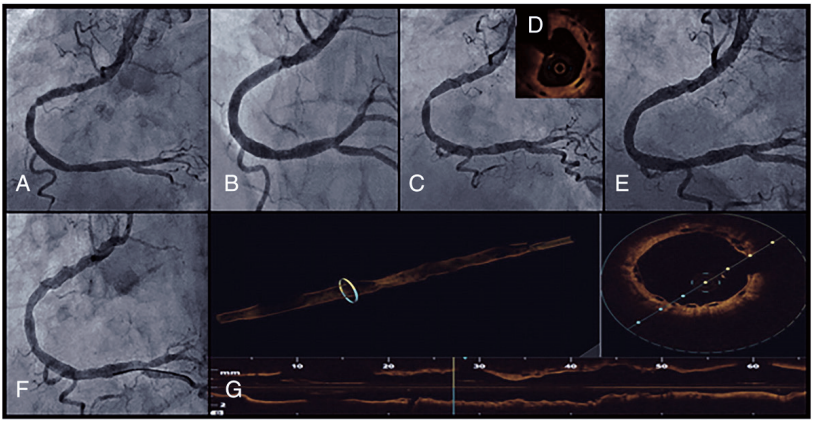

Fig. 2. A: significant stenosis at mid RCA during the initial procedure, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 11 months, D: OCT analysis, showing neointimal hyperplasia within the BVS with preserved integrity of the scaffold, E: angiographic result immediately after DCB, F: angiographic follow up after 12 months, G: OCT run showing sustained good result at 12-months angiographic follow-up after DCB use (Patient 4).

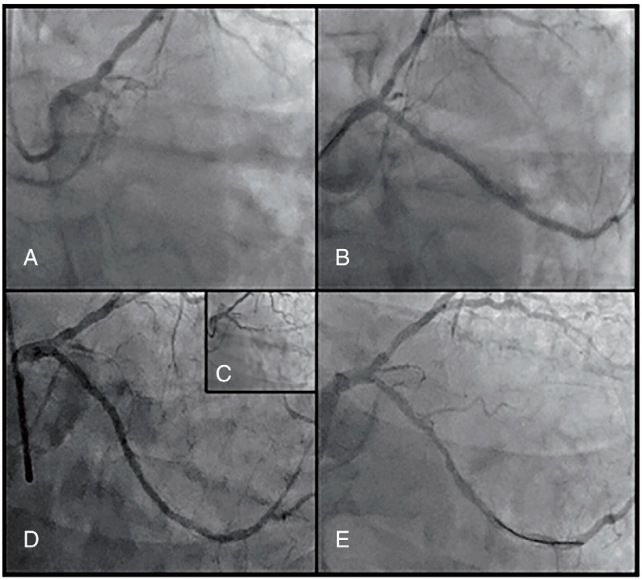

Fig. 3. A: total occlusion at the proximal LCX, B: angiographic result after BVS implantation, C: BVS restenosis occurred at 13 months, D: angiographic result after DCB use, E: angiographic follow up showing mild restenosis (Patient 8).

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PICCOLETO II: More Support for DCB Safety and Efficacy in Small Coronaries

In-lesion late lumen loss was similar for a gel-based balloon versus an EES, but a trend was seen for more thrombosis with the stents.

By L.A. McKeown October 04, 2019

SAN FRANCISCO, CA—A new gel-based paclitaxel drug-coated balloon (DCB) outperformed an everolimus-eluting stent (EES) in terms of late lumen loss and resulted in comparable diameter stenosis, binary restenosis, and short-term clinical outcome in patients with small-vessel CAD, results from PICCOLETO II suggest.

Presenting here at TCT 2019, Bernardo Cortese, MD (Clinica San Carlo, Milan, Italy), said that although the study is small and not powered for hard endpoints, it adds to existing data hinting that drug delivery via a balloon may optimize outcomes better in small vessels than a stent.

"The best-in-class drug-eluting stents show a rate of target lesion failure

the superiority of DCB in terms of angiographic outcome," he told TCTMD.

PICCOLETO II is the latest trial to show DCB as a potential alternative to DES in patients with small-diameter lesions. At EuroPCR 2019, investigators from the BASKET-SMALL 2 trial presented new angiographic data showing similar late lumen loss with both treatments out to 1 year. Surprisingly, the angiographic data also showed eight cases of stent thrombosis in the DES group versus no complete thrombotic vessel occlusions in the DCB group. The PICCOLETO II data line up with those results.

"Similarly, we found a 1.8% rate of stent thrombosis in the EES arm, and no thrombosis in the DCB arm," Cortese told TCTMD. "We thus confirm the findings of BASKET-SMALL 2. The opportunity not to leave a stent in small vessels may protect from thrombotic events."

Gel May Improve Drug Delivery

PICCOLETO II is a follow up to the PICCOLETO study, in which patients with stable or unstable angina undergoing PCI of small coronary vessels (≤ 2.75 mm) were randomized to the Dior DCB (Eurocor) or Taxus DES (Boston Scientific).

As Cortese explained to TCTMD, the first study used a balloon that had paclitaxel sprayed onto the surface. The drug was lost during transit and manipulation, which the researchers believed prevented it from having the desired effect. For PICCOLETO II, they instead used the Elutax SV (Aachen Resonance), "a new-generation DCB with a gel which protects and mostly helps [paclitaxel] to be delivered to the vessel wall, and persist there for 4 to 6 weeks in order to obtain its effect," Cortese noted. The gel is hydrophilic, which is intended to help the drug stay on the balloon longer and prolong the absorption time. The paclitaxel dose on the balloon is 2.2 µg/мм^2 .

For the multicenter, open-label trial, 118 patients similar to those in the earlier PICCOLETO trial were randomized to the DCB and 114 to the Xience EES (Abbott Vascular). Predilatation was strongly recommended for both strategies, with at least a 30- to 60-second dilatation of the balloon but no specific advice for the EES.

Aside from a higher percentage of renal failure patients in the EES group, there were no significant baseline differences between the two arms. More than half of patients in each group had stable angina and about 20%

Predilatation was performed in 69% of the EES group and 84% of the DCB group, while postdilatation was performed in nearly 60% of the EES group and only 3% of the DCB group ($P = 0.001$). The number of devices used in the DCB group was lower than in the EES arm, but length of devices was a bit longer (8.2 mm vs 6.9 mm; $P = 0.04$).

At 6 months, in-lesion late lumen loss, the primary endpoint, was 0.17 ± 0.39 mm in the EES group and 0.04 ± 0.28 mm in the DCB group, meeting noninferiority criteria for the balloon ($P = 0.03$). There were no significant differences in clinical outcomes, although a trend was seen toward higher TLR in the DCB group ($P = 0.23$).

Minimum lumen diameter, a secondary endpoint, increased more in the DES group (from 0.83 mm before the procedure to 2.29 mm after the procedure) than in the DCB group (0.82 mm to 1.89 mm). Percent diameter stenosis changes, however, were similar in both arms. Other secondary endpoints of percent diameter stenosis and binary restenosis were similar between the treatment arms at 6 months (both in-stent and in-segment).

Smaller Lesions, Bigger Payoff With DCBs?

According to Cortese, the PICCOLETO II outcomes with regard to late lumen loss are among the best so far in small-vessel disease, a setting that includes studies such as PEPCAD SVD, BELLO, RESTORE SVD, and FASICO NATIVES.

Discussant Fernando Alfonso, MD, PhD (Hospital Universitario La Princesa. Madrid, Spain), said he was “nicely surprised” by the results of PICCOLETO II.

In theory, as you go smaller and smaller, the benefits of non-scaffold-based therapy might be even greater," added discussant Robert M. Bersin, MD (Swedish Heart & Vascular, Kirkland, WA). “Have you broken this down to the very small [lesion] subsets, like 2.22 mm and smaller to see whether or not you get a signal of superiority with DCB? Overall you have equivalence here, but you may even be superior the smaller you go.”

Cortese responded that the study is a proof-of-concept, and while that possibility does exist, it remains to be shown in future trials.

Given that the drug on the balloon is paclitaxel and that a meta-analysis recently turned the endovascular community on its head with suggestion that this drug may increase mortality when used to treat PAD, Cortese told TCTMD that long-term follow up of patients will be conducted “even if all the studies performed in the coronary arena till now never gave

Sources

Cortese B. Drug-coated balloon vs drug eluting stent for small coronary vessel disease: 6-mo primary outcome of the PICCOLETO II randomized clinical trial. Presented at: TCT 2019. September 27, 2019. San Francisco, CA.

Disclosures

Cortese reports consulting for Abbott Vascular, Astra Zeneca, Kardia, Innova, Stentys, Daiichi Sankyo, Philips-Spectranetics, Reva, Bayer, and Cardinal; honorarium from Amgen, Stentys, Sanofi, B. Braun, Servier, and Alvimedica; and institutional research/grant support from AB Medica, St Jude, and Abbott.

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Balloon dilatation of pulmonary vein stenosis using PACLITAXEL eluting balloon: midterm result in an infant

A. Koch, M. Glöckler, C. Breuer, O. Toka, S. Dittrich

Introduction:

Pulmonary vein stenosis has an unfavorable outcome because neither surgical nor interventional therapy prevents restenosis.

According to promising results in pre-clinical studies, single infants with pulmonary vein stenosis have been treated by balloon dilatation using balloons coated with PACLITAXEL, an antimitotic agent from cancer therapy [1]. First results were encouraging, however, follow-up was cut off early in the two patients published so far, because both died within a few weeks [1,2].

Case Report:

A girl with univentricular heart, increased pulmonary perfusion, and mesocardia was treated by pulmonary banding at 3 weeks. Within the next weeks an increasing stenosis of the left sided pulmonary veins was suspected by echocardiography and confirmed by cardiac catheterization. Subsequently a Damus-Kaye-Stansel anastomosis, an aortopulmonary shunt, and a sutureless repair of the left sided pulmonary venous obstruction were performed at the age of 4 months.

At the age of 6 months, stenosis of the aortopulmonary shunt caused implantation of a 4mm coronary stent. Concurrently severe restenosis of the left pulmonary veins was diagnosed (fig.1) and treated by balloon dilatation.

6 weeks later, re-evaluation in the cath lab revealed severe restenosis, and again dilatation of the left pulmonary veins was performed now using PACLITAXEL coated balloons (5 and 6mm diameter).

This procedure was repeated at the age of 10, 13, and 16 months. 2 weeks after the last intervention (fig.2), surgical treatment with right sided Glenn anastomosis and left sided aortopulmonary shunt (5mm) was performed. 8 days after surgery the girl went home.

Out-patient follow-up after 6 weeks revealed the girl in a proper clinical condition with accelerated left-sided pulmonary venous return (Doppler Vmax 2.3m/s).

At the age of 22 months the girl was transferred to the cath lab for re-evaluation because of mildly increasing cyanosis. The left sided pulmonary vein showed moderate obstruction, and again re-dilatation was performed using a 6mm PACLITAXEL coated balloon (fig.3).

The right sided Glenn anastomosis was without obstruction, but there was a big anomalous venovenous connection between the superior vena cava and a paravertebral venous plexus draining to the inferior vena cava. The collateral was closed using an Amplatzer duct occluder (fig.4).

Conclusion:

Repeated balloon dilatation of pulmonary venous obstruction using paclitaxel eluting balloons may be useful in the interventional treatment of this frequently fatal condition. Although restenosis occurred also in our patient after the use of paclitaxel eluting balloons, the diameter of the treated vessel showed a reasonable increase, and the patient was able to undergo the next surgical step.

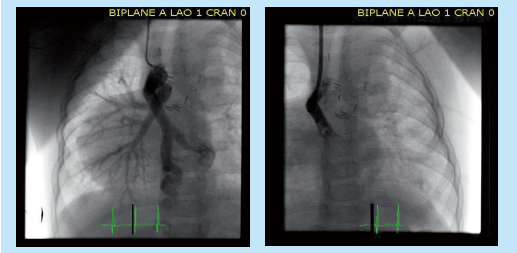

Fig. 4: Venovenous collateral (a), occlusion by Amplatzer duct occluder (b).

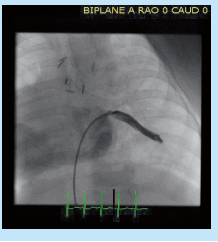

Fig.1: Pulmonary vein stenosis at the age of 6 months

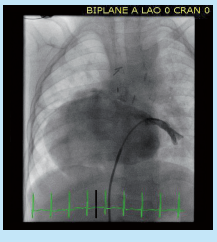

Fig.2: Pulmonary vein at the age of 16 months before surgery

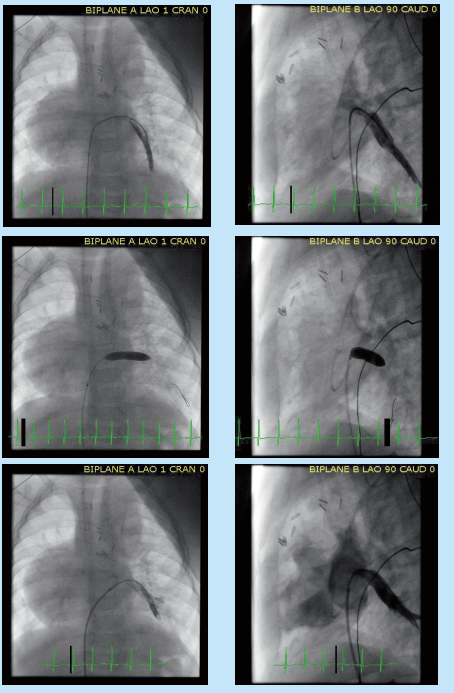

Fig. 3: Left pulmonary vein at the age of 22 months before (a,b), and after (e,f) redilatation using a 6mm PACLITAXEL coated balloon (c,d).

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Paclitaxel-Coated Balloon Angioplasty for Symptomatic Central Vein Restenosis in Patients With Hemodialysis Fistulas

Alexander Massmann, MD[1], Peter Fries, MD[1], Kerstin Obst-Gleditsch, MD[1], Peter Minko, MD[1], Roushanak Shayesteh-Kheslat, MD[2], and Arno Buecker, MD[1]

Abstract

Purpose: To report a retrospective observational analysis of standard balloon angioplasty (BA) vs. paclitaxel-coated balloon angioplasty (PCBA) for symptomatic central vein restenoses in patients with impaired native hemodialysis fistulas. **Methods:** A retrospective review was conducted of 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90) with 32 central vein stenoses (CVS; 6 axillary, 11 subclavian, 12 brachiocephalic, and/or 3 superior caval veins) treated successfully using BA. Freedom from reintervention after BA of de novo lesions was 7.4±7.9 months (range 1–24). Twenty-five (92.6%) patients developed symptomatic restenoses and were treated one or more times by BA (n=32) or PCBA (n=20) using custom-made paclitaxel-coated balloons (diameter 6–14 mm). **Results:** Technical (<30% residual stenosis) and clinical (functional fistula) success rates for the initial and secondary angioplasty procedures were 100%. No minor/major procedure-associated complications occurred. Mean follow-up was 18.4±17.5 months. Kaplan-Meier analysis for freedom from target lesion revascularization (TLR) found PCBA superior to BA (p=0.029). Median freedom from TLR after BA was 5 months; after PCBA, >50% of patients were event-free during the observation period (mean freedom from TLR 10 months). Restenosis intervals were prolonged by PCBA (median 9 months) vs. BA (median 4 months; p=0.023). **Conclusion:** Paclitaxel-coated balloon angioplasty of central vein restenosis in patients with hemodialysis shunts yields a statistically significant longer freedom from TLR compared to standard balloon angioplasty.

Keywords

endovascular intervention, vein, central venous stenosis, drug-eluting balloon, restenosis, hemodialysis, arteriovenous fistula, target lesion revascularization

Introduction

Symptomatic central vein stenosis (CVS) is a clinically relevant complication in hemodialysis patients. Stenoses of central veins typically result in dysfunctional dialysis shunts, venous collaterals, edema, ipsilateral extremity tenderness, pain, and cellulitis.[1,2] Further complications include shunt vein thrombosis and excessive bleeding after puncture for dialysis. CVS is commonly associated with central vein catheterization with an incidence of 25% to 50%[3,4] or insertion of pacemaker wires in up to 27%.[5–7] The incidence of CVS without previous central vein catheterization is about 1% to 10%.[8,9] A typical mechanism for the development of CVS is intravasal trauma to the venous endothelium, which results in inflammation of the vessel wall. Microthrombus, intimal hyperplasia, and fibrotic alteration finally lead to CVS.[10,11] The pathophysiological mechanism of CVS in dialysis shunts without a history of central vein catheterization is unclear. A higher venous blood flow and increased pressure after creation of a dialysis fistula are considered the cause.[8,9]

Endovascular treatment with balloon angioplasty is generally accepted as the primary treatment for CVS.[3,12] However, restenosis is frequent. Restenotic lesions are characterized by a significant increase in fibroplastic proliferation within the venous neointima and media as compared to primary stenotic lesions.[13] Several experimental[14,15] and clinical[16–18] studies confirmed the hypothesis of vascular

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remodeling owing to adventitial angiogenesis and scar development. This is the theoretical background for application of antiproliferative therapy at the time of balloon angioplasty within the venous system, as drug-coated balloon angioplasty has been shown to lead to a significant reduction in restenosis in peripheral artery disease.[19,20] Venous smooth muscle cells (SMCs) are more sensitive to the effects of antiproliferative agents as compared with arterial SMCs.[21] Paclitaxel in the perivascular area of hemodialysis grafts resulted in an effective inhibition of neointimal hyperplasia and prevention of restenosis in several animal models.[22,23] A recent randomized controlled clinical trial favored paclitaxel-coated balloon angioplasty (PCBA) for stenoses of hemodialysis access.[24]

Based on these in vitro and clinical results, the purpose of this study was to retrospectively evaluate standard balloon angioplasty (BA) vs. PCBA for the treatment of recurrent symptomatic CVS in patients with hemodialysis fistulas.

Methods

Study Design and Patient Cohort

Between 2008 and 2014, 27 consecutive patients (15 men; mean age 66±13.8 years, range 39–90), all with diabetic end-stage renal disease, presented with considerable edematous arm swelling and severely impaired native lower or upper arm hemodialysis fistulas inappropriate for dialysis. Catheter-directed venography depicted 32 de novo nonmalignant CVS (Figure 1) in the axillary (n=6), subclavian (n=11), brachiocephalic (n=12), and/or superior caval vein (n=3). Three patients had 2 venous stenoses and 1 patient had 3. Complete chronic occlusions were not detected. The interval between creation of the hemodialysis fistulas and development of the initial CVS was 39±49 months (range 1–216).

After institutional review board approval and patient informed consent, all 27 patients underwent initial balloon angioplasty. Overall, 52 reinterventions were necessary in 25 (92.6%) of the 27 patients due to clinically symptomatic restenosis and impaired hemodialysis fistula. Fifteen patients underwent 32 reinterventions using standard BA and 10 patients underwent 20 reinterventions using PCBA (Table 1). Selection of patients for BA or PCBA was at the operator's discretion.

Standard Balloon Angioplasty

Angiography was performed after needle (22-G) puncture of the brachial artery to exclude relevant stenoses in the hemodialysis fistula, arteriovenous anastomosis, and draining shunt veins. CVS was verified by direct phlebography via the shunt vein, into which a standard 0.035-inch hydrophilic guidewire and 7-F sheath (10- or 25-cm long) were inserted. Five thousand units of unfractionated heparin were given through the sheath. Intraluminal crossing of the CVS was always achieved with the 0.035-inch guidewire and 4-F catheter.

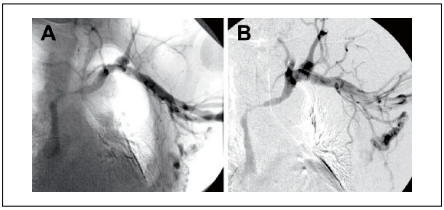

Figure 1. (A) Unsubtracted and (B) digital subtraction phlebography via an antecubital vein reveals typical extensive venous collaterals along the chest wall because of high-grade stenosis of the left brachiocephalic vein.

Balloon size was determined according to the diameter of the adjacent normal vein and the length of the stenosis. In most cases, the balloon catheters were typically 40-mm long with diameters ranging from 6 to 12 mm. Inflation pressure was 14 atmospheres for 60 seconds. Additional dilation with larger balloons was performed if recoil with relevant residual stenosis occurred; inflation pressure was also 14 atmospheres for 60 seconds. Pretreatment with 6-mm diameter cutting balloons (Boston Scientific, Natick, MA, USA) and posttreatment high-pressure balloon angioplasty (24 atm for 60 seconds) was also used as necessary for severe recalcitrant recoil. The diameter of the high-pressure balloon was identical to the largest size of the primary balloon. Technical success was defined as residual stenosis <30%. Heparin therapy was maintained for 48 hours. Clinical success was defined as the ability to successfully use the fistula for dialysis after angioplasty.

Paclitaxel-Coated Balloon Angioplasty Treatment

As drug-coated balloon catheters of appropriate size (diameter >7 to 14 mm) for central veins were not commercially available, all paclitaxel-coated balloons were custom-made using standard over-the-wire balloon catheters (Figure 2) coated with polymer-free microcrystalline paclitaxel at a concentration of 2 µg/mm^2 (Elutax-SV; Aachen Resonance, Aachen, Germany).

The PCBA followed the same BA protocol for vascular access, heparin use, sizing of the paclitaxel-coated balloons, and adjuvant procedures for pretreatment and recoil. Balloon catheter length was 40 mm for the 6- to 10-mm diameter balloons and 20 mm for the 10-, 12-, and 14-mm diameter balloons. Inflation pressure was 14 atmospheres for 60 seconds, similar to the BA group.

Table 1. Characteristics of Patients Treated for Central Vein Restenosis.[a]

	Standard Balloon Angioplasty	Paclitaxel-Coated Balloon Angioplasty
Patients	15	10
Age, y	66.8±15.0 (39–90)	64.5±11.2 (50–85)
Men	9 (56)	6 (60)
Diabetes mellitus	15	10
Native arteriovenous fistula	15	10
Dialysis access age, mo	26.9±22.9 (1–67)	50.9±62.8 (1–216)
Location left arm	10	7

[a]Continuous data are presented as the means ± standard deviations (range); categorical data are given as the counts (percentage).

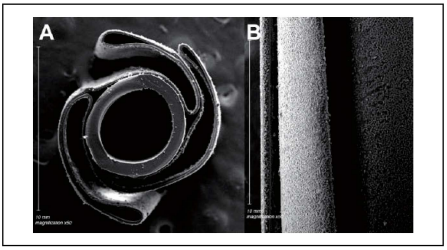

Figure 2. Scanning electron microscopy cross-sectional image illustrating (A) special balloon folding and (B) the paclitaxel-coated surface of Elutax SV completely covering the balloon. The drug itself is protected within the folds of the balloon.

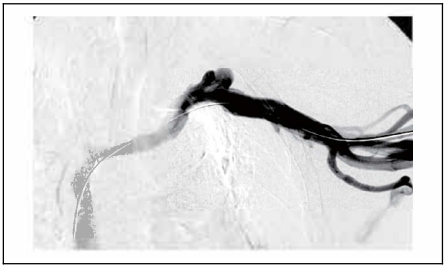

Figure 3. Postinterventional venography after dilation with a 10×40-mm paclitaxel-coated balloon depicts a successful reduction in the central venous stenosis. Consequently, there is an obvious improvement in venous inflow and a considerable reduction of venous collaterals.

Statistical Analysis

Continuous data are presented as the means ± standard deviations; categorical data are given as the counts. The differences between groups were evaluated using the unpaired *t* test; differences achieving $p<0.05$ were considered to be statistically significant. Freedom from target lesion revascularization (TLR) was estimated using the Kaplan-Meier method; differences between groups were examined with the log-rank test. Statistical analysis was performed using the Prism software for MacOSX (version 6.0.4, Graphpad, La Jolla, CA, USA).

Results

Primary technical success (residual stenosis <30%) in the BA and PCBA groups was 100% (Figure 3). Additional dilation with larger balloons was performed in 10 BA patients and 8 PCBA cases because of recoil with relevant residual stenosis. The mean diameters were 8±2 mm for the standard balloons and 10±2 mm (range 6–14) for the coated balloons. Pretreatment with cutting balloons and posttreatment high-pressure balloon angioplasty were necessary in 2 patients in each group. No minor or major procedure-associated complications were observed. There was no relevant bleeding, hematoma, superior vena cava thrombosis, or worsening of hemodialysis fistula function after BA or PCBA. Stent placement was avoided in all patients. Function of the hemodialysis shunts normalized after intervention, which allowed appropriate use for dialysis.

Four patients in the BA group experienced very early restenosis. One patient had 11 reinterventions within 2.7±1.3 months, another patient had 4 reinterventions over 7.8±2.2 months, and 2 patients had recurrences after 1 and 2 months. Although PCBA was under evaluation, the superior results in the PCBA group finally led to crossover of these 4 patients to PCBA for ethical reasons. After crossover to PCBA, the intervention-free time interval markedly increased up to 21 months. One patient died after 6 months without the need for reintervention.

Over a mean follow-up of 18.4±17.5 months, 9 (33%) patients died after 7.2±5.9 months (median survival 6 months, range 1–19); no death was related to the procedure. Failing hemodialysis fistula due to shunt occlusion after BA occurred in 4 patients after 4.0±3.1 months (range 1–9) and after PCBA in 1 patient after 3 months.

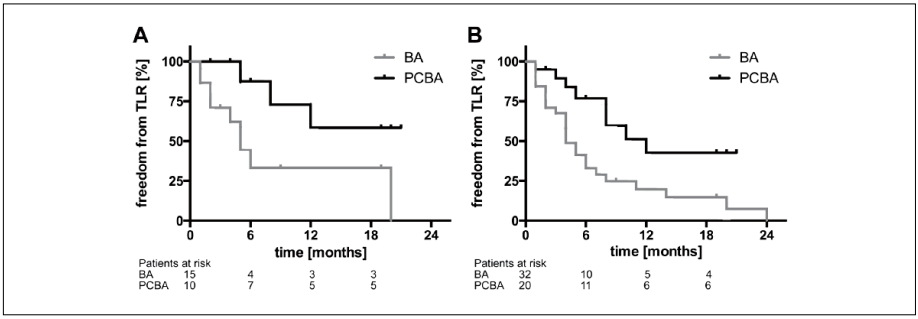

Figure 4. Kaplan-Meier plots demonstrate freedom from target lesion revascularization (TLR) after standard balloon angioplasty (BA) and paclitaxel-coated balloon angioplasty (PCBA) of central venous restenosis: (A) initial treatment and (B) pooled data in a crossover design of lesions treated.

Comparative Analysis

Kaplan-Meier analysis of freedom from TLR after first reinterventions revealed PCBA significantly superior to BA (p=0.025; Fig. 4A). The median freedom from TLR after BA was 5 months. For PCBA, 66.7% of patients were event-free during the observation period, resulting in a mean freedom from TLR of 10 months.

A crossover-design analysis in which each patient serves as his or her own control was completed to integrate additional data from recurrent restenosis. Additional statistical analysis of pooled data respecting all consecutive treatments showed a median freedom from TLR after PCBA of 12 months vs. 4 months after BA (p=0.006; Fig. 4B). Time to recurrent restenosis was also significantly prolonged by PCBA (mean 9.5±1.9 months in 4 patients) vs. BA (mean 5±4.9 months in 5 patients, 1 early death). The median time interval to restenosis after PCBA was 9 months vs. 4 months after BA (p=0.021).

Discussion

Preservation of hemodialysis fistula function in patients with central vein occlusive disease is a relatively common problem. Unfortunately, all available interventional treatment options result in poor midterm patency. As a consequence, several reinterventions are often mandatory. Standard BA is so far the common first-line treatment of choice in CVS. Compared with standard balloons, paclitaxel-coated balloons in endovascular treatment of peripheral artery disease have demonstrated lower restenosis rates and superior clinical outcomes with prolonged time to reintervention. However, due to a limited number of patients and variable designs of existing studies, definitive recommendations for optimal treatment of CVS are lacking. Furthermore, the pathophysiology of atherosclerotic disease is different from the development of CVS. Nonetheless, looking at the histopathology, CVS has similarities to arterial stenosis. In both, hyperproliferation of fibroblasts have been identified as part of the problem.[10,12,13,21,22,24] Neointimal hyperplasia is a local inflammatory process. Local wall delivery of the antiproliferative agent paclitaxel reduces neointimal hyperplasia by inhibition of SMC proliferation and migration. Paclitaxel stabilizes the arrangement of microtubules by binding β-tubulin dimers, inhibiting their depolymerization. The long-lasting disruption of normal microtubule function interferes with a number of cell properties, including division, motility, and shape. Low doses of paclitaxel cause cell-cycle arrest in the G1 phase without causing cellular apoptosis. The resulting cytostatic response with inhibition of SMC proliferation and migration represent the key processes for reduction of neointimal hyperplasia.[25–27] Other studies demonstrated a varying technical success rate for standard balloon dilation of CVS between 70% and 90%. Unsatisfactory initial results and short-term restenosis are often observed.[28] Primary patency rates range from 23% to 55% and 12% to 50% at 6 and 12 months, respectively. A high technical failure rate of 10% to 30% necessitates close surveillance with the need for multiple reinterventions.[29–32]

Bare metal or covered stents have been evaluated with differing results. While bare stents have high primary technical success rates of 82% to 100%, midterm results are as disappointing as they are with BA. Primary patency of self-expanding bare stents range from 42% to 89% at 6 months and 14% to 73% at 12 months.[32–34] Intimal hyperplasia, stent fracture, and migration due to (respiratory) motion and compression lead to early restenosis. Furthermore, bare stents may complicate further endovascular or surgical treatment.[32–34]

The use of covered stents should combine the advantages of mechanical stability and lower in-stent restenosis caused by intima hyperplasia. The primary technical success rate was 100%, but primary patency was only 32% to 67% at 12 months, which makes stenting questionable in vessel segments exposed to high biomechanical stress.[35–37]

Recently, drug-coated balloon angioplasty was used for venous anastomotic stenosis of dialysis fistulas and synthetic grafts. The use of the IN.PACT Amphirion paclitaxel-coated balloon showed a statistically significant improvement in primary patency (70%) compared to BA (25%) after 6 months ($p<0.001$).[24] In failing dialysis fistulas caused by de novo or recurrent juxta-anastomotic stenoses, PCBA achieved a primary patency rate of 92% after 9 months.[38]

In our study, patients with symptomatic CVS initially underwent the well-accepted treatment of choice with BA. As mentioned above, the restenosis rate was high and the intervention-free time interval was relatively short. Even though BA of CVS is a fast and low-risk procedure, patients have to be hospitalized recurrently, and balloon angioplasty itself is uncomfortable and painful. To avoid the disadvantages and complications related to stent implantation, we evaluated the use of PCBA in patients with symptomatic CVS. A technical prerequisite for successful treatment of CVS using PCBA is an appropriate sizing of the drug-coated balloon catheters. Central veins are usually larger in diameter than coronary or peripheral arteries, for which several balloons of different sizes (diameter ≤7 mm) are commercially available. In most of our cases, the diameter of the central veins was too large for commercially available balloon catheters. Consequently, all the PCBA catheters needed to be especially produced, but there was no balloon rupture or disintegration of coating before application. Notably, the treatment with a "double dose" of paclitaxel in 8 patients did not result in any vascular damage, for example, but the patients are too few for subgroup analysis.

Short-term results of a randomized controlled trial of PCBA in the peripheral venous system showed PCBA superior to BA for the treatment of hemodialysis access stenoses.[24] Similar to these results and those of drug-coated balloons in coronary and peripheral artery disease, our patients experienced significantly fewer restenoses of the central veins after PCBA. Furthermore, vessel patency was improved, which resulted in a prolonged freedom from TLR.

Limitations

The study was limited by its small cohort and single-center observational retrospective design. Furthermore, the fact that all patients were diabetics may mean that our results are not reproducible in non-diabetic patients. However, the improved outcome supports the use of PCBA in the management on CVS, at least after inadequate primary BA of de novo lesions.

Conclusion

Paclitaxel-coated balloon angioplasty of central vein restenosis yields a statistically significant longer freedom from TLR in patients with hemodialysis shunts. A randomized controlled trial for the use of PCBA as first-line strategy is justified.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Prof Dr med Arno Buecker was a co-founder of Aachen Resonance.

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CIRSE

Drug-Eluting Balloon Angioplasty for Juxta-Anastomotic Stenoses in Distal Radiocephalic Hemodialysis Fistulas: Long-Term Patency Results

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Abstract
Purpose To evaluate long-term primary and secondary patency results of drug-eluting balloon angioplasty for the treatment of juxta-anastomotic stenoses in distal radiocephalic arteriovenous fistulas.
Materials and Methods Thirty-eight patients with juxta-anastomotic stenotic distal radiocephalic arteriovenous fistulas who underwent endovascular treatment with drug-eluting balloons between January 2014 and August 2016 in our interventional radiology department were included in this retrospective study. Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure. Kaplan–Meier analysis was used to estimate primary and secondary patency rates.
Results Totally, 42 angioplasty with drug-eluting balloons was performed in 38 patients (20 men and 18 women; mean age 66.42 ± 12.01). Technical and clinical success rate was 100% (42/42). The mean follow-up period was 27.71 months ± 12.98 (range, 1–54 months). The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%). The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%).
Conclusion Drug-eluting balloon angioplasty is a useful, effective technique in dysfunctional radiocephalic fistulas due to juxta-anastomotic stenoses. We demonstrated remarkably high primary patency rates at 6, 12, 24, and 48 months.

Keywords Drug-eluting balloon · Percutaneous transluminal angioplasty · Juxta-anastomotic stenosis

Introduction

End-stage renal disease (ESRD) is the final stage of chronic kidney disease. It is predicted that the prevalence of ESRD and the need for hemodialysis will grow in the future as the average lifespan increases [1]. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines advise autologous arteriovenous fistula (AVF) for vascular access [2]. Distal radiocephalic AVFs are the first option due to its technical simplicity, lower complication, and higher patency rates [3]. However, in spite of being superior to other accesses, fistulas also have a limited time for appropriate usage. Stenosis, which usually occurs in 3 cm before and after the anastomosis, is the main reason for

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dysfunctional AVFs [4–6]. These types of stenoses are regarded as juxta-anastomotic stenoses (JASs) [7].

Endovascular treatment in AVFs is recommended in K/DOQI guidelines. Several reports have revealed the efficacy of endovascular treatment in AVFs [6, 8–10], but most of the studies have included all types of fistulas such as radiocephalic, radioulnar, or brachial-basilic. Moreover, long-term patency results after percutaneous transluminal angioplasty (PTA) in the most preferred fistula type, radiocephalic fistulas [3], are lacking. Over the past few years, drug-eluting balloons (DEBs) have evolved and taken part in stenotic AVF treatment by inhibiting neointimal hyperplasia [11]. However, it is still needed to be demonstrated how effective is the DEB angioplasty, which has been proven as the primary treatment method [12], in distal radiocephalic fistulas.

The aim of our study was to assess long-term patency results of DEB angioplasty for the treatment of JASs in distal radiocephalic AVFs.

Materials and Methods

Patients

Local ethics committee approval was obtained for this retrospective study. Patients who underwent fistulography and endovascular treatment in our department between January 2014 and August 2016 were reviewed. Since we wanted to elucidate long-term outcomes, patients with a minimum follow-up of 2 years were selected for the present study. The interventions performed before the year 2014 were not scanned for the lack of acceptable demographic and clinical data. The inclusion criteria were as follows: autologous distal radiocephalic fistulas with JASs. Arteriovenous grafts, patients without follow-up information, and fistulas that had treated formerly in different hospitals were the exclusion criteria. JASs were described as stenoses occurred in 3 cm before and after the anastomosis. After all, a total of 38 patients (20 men and 18 women; mean age 66.42 $\pm$ 12.01) with sufficient demographic, clinical, and radiologic follow-up data were incorporated in the study.

Pretreatment Evaluation

Patients in the study were directed to our department with AVF problems from dialysis units. The decrease of the blood flow greater than 20% per month, observing total access blood flow less than 300 mL/min were the conditions that displayed AVF dysfunction. One operator with 15 years of experience performed all the color Doppler examinations and operated all the endovascular treatments (A.G.). Color Doppler examination was used to localize the abnormality, estimate the degree of stenosis, evaluate the outflow vein, figure out the treatment method, and determine the access site. Along with clinical problems, narrowing greater than 50%, peak systolic velocity (PSV) ratio greater than 2:1 compared to the 2-cm proximal from the lesion, and PSV of $\geq$ 500 cm/sec were considered abnormal [13]. Further evaluation with fistulography was performed in these patients.

Endovascular Treatment

A digital subtraction angiography device (Allura Xper FD10, Philips Healthcare, the Netherlands) was used for fistulography and endovascular procedures. Retrograde outflow vein puncture was performed by ultrasound guidance to minimize hematoma in all procedures. Inflow, fistula, and outflow segments were assessed carefully before the procedure. Blood pressure cuff was used to observe arterial anastomosis better. Initially, we performed a fistulography via 18G cannula. Fistulography images were evaluated, and treatment decision was made by the same experienced interventional radiologist who had performed patients' initial color Doppler examination.

A standard technique was used for the treatment of JASs [14]. If we decided to do angioplasty after fistulography, we placed the sheath using 0.035-inch guidewire through the 18G cannula under local anesthesia. Heparin (5000 IU) was administered intravenously after vascular sheath placement in all cases. Juxta-anastomotic target lesion was passed by manipulation of a 0.035-inch hydrophilic guidewire and a 4F multipurpose vertebral catheter. After advancing the catheter to the arterial side, hand injection was performed for the final decision of balloon size. Then, 0.035- or 0.018-inch guidewire was advanced, and the catheter was removed. After predilatation with plain balloons, DEBs were advanced via guidewire to the lesion. Types of DEBs we used were Elutax SV OTW, ab medica, Dusseldorf, Germany (in 12 procedures), and IN.PACT Admiral Drug-coated balloon, Medtronic, California, USA (in 30 procedures). After the termination of the stenosis, the balloon was held on inflated for 2 min to prevent the elastic recoiling. For refractory lesions, cutting balloons were used. When successful appearance was gained, the procedure was terminated with control of central veins. After sheath removal, hemostasis was gained by manual compression.

Clinical Outcome and Follow-Up

Technical success, clinical success, primary patency, secondary patency, and minor and major complication rates were considered during clinical outcome analysis.

Technical success was described as the increase in the "thrill" and residual stenosis lower than 30% in both angiographic images and color Doppler examination. The operator performed color Doppler examination and thrill assessment before and after the procedure. During the procedure, the operator evaluated the angiographic images. However, all angiographic images were reviewed retrospectively by 6-year (O.S.) and 5-year (A.P.) experienced radiologists. The radiologists were unaware of the patients' diagnosis and operation findings. The two radiologists assessed the pre- and post-dilatation images and recorded the residual stenoses of $\geq$ 30% if any. Clinical success was defined as the access of the fistula without any problem during dialysis. Total access blood flow of $>$ 300 mL/min was a supportive criterion of the clinical success. Clinical success was evaluated by dialysis unit nephrologists. In the first dialysis session after the procedure, feedback was received via phone call.

Primary patency and secondary patency rates were evaluated based on the instructions of Society of Interventional Radiology Technology Assessment Committee [15]. Primary patency was defined as the time between the first intervention until access thrombosis and repeated endovascular treatment. The interval after the first intervention until the fistula is surgically revised or abandoned was regarded as secondary patency.

Color Doppler examination for follow-up was performed 15 days, 6 months, 12 months, 18 months, 24 months, 36 months, and 48 months after the procedure by an 8-year experienced radiologist (O.A). If a problem was detected by nephrologist, or dialysis unit nurse, patients were directly referred without waiting for the follow-up date. Color Doppler examinations, repeated angiography images, and records of dialysis units were inspected for follow-up data. Follow-up ended in August 2018. Complications were graded according to the CIRSE classification [16].

Statistical Analysis

Statistical analysis was performed by using the Statistical Package for the Social Sciences (SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA). Kaplan–Meier survival analysis was used to estimate primary and secondary patency rates after intervention. Stated patency rate intervals in this study were 95% confidence intervals (CIs). Renal transplantation, exitus because of an independent cause from renal disease with functional AVF, and loss to follow-up were regarded as censored data.

Results

Characteristics of AVFs and patients' demographic data are demonstrated in Table 1. Forty-two PTA with DEBs was performed in 38 patients. The mean size of the balloons was 5.55 mm $\pm$ 0.67. Cutting balloon was used in one procedure due to refractory stenosis after DEB.

Our technical and clinical success rate was 100% (42/42). Grade 1 complications were experienced in 4 cases. Hematomas at the puncture site that did not affect blood flow were reported after two interventions (2/42, %4.76). Contrast extravasation was observed in two procedures and was managed with balloon inflation (2/42, %4.76).

The mean follow-up period in this study was 27.71 months $\pm$ 12.98 (range, 1–54 months). Eight patients died of an unrelated cause from renal disease with functional fistula during the follow-up period.

At the sixth month, one patient underwent surgical creation of a new fistula; one patient needed reintervention due to stenosis of the same location; one patient died with functional fistula. Thirty-five patients had successfully working AVF at the end of 6 months.

Between the 6th and 12th months, 4 fistulas were thrombosed and abandoned. Repeated endovascular treatment to the same region was performed in one patient.

After 18 months, 4 patients died with functional fistula. 3 fistulas were surgically revised. One patient had recurrent JAS and reintervention was done.

At 24-month follow-up, 3 patients could not continue dialysis with their fistulas and underwent surgical revision.

Table 1 Demographic features of the patients and characteristics of the AVFs

Number of patients	38
Age (years)	66.42 $\pm$ 12.01
Female to male ratio	18/20
Hypertension	21/38 (55.3%)
Hyperlipidemia	17/38 (44.7%)
Diabetes mellitus	
Type 1	1/38 (2.6%)
Type 2	20/38 (52.6%)
Type of AVF	
Radiocephalic	38/38 (100%)
Side of AVF	
Right	13/38 (34.2%)
Left	25/38 (65.8%)
Age of AVF at the first intervention (months)	15.2 $\pm$ 18.3
Stenosis location	
Juxta-anastomotic	38/38 (100%)

AVF arteriovenous fistula

One patient died with functional fistula. At the end of 2 years, there were 18 patients remaining with no necessity for additional intervention.

Between the 24th and 36th months, 2 patients died of heart problems with functional fistula. No endovascular intervention or surgery was performed during this period.

At 48th month, two fistulas were occluded, and surgery was performed to revise. By the end of 48 months, 14 patients did not need any intervention and underwent dialysis successfully. At the end of the follow-up interval, 17 patients (%44.7) had functional AVFs.

At the follow-up, three patients were needed reintervention. At 5 months, one patient had stenosis and the patient was treated by angioplasty with DEB. Two months later, restenosis was detected and the same procedure was performed; 11 months later, restenosis was detected again at the same region and treated with DEB again. No further intervention was needed, and fistula is still patent. The second patient had stenosis at the same site after the intervention, and the patient was treated by angioplasty with DEB. No further stenosis was detected during the follow-up period. The other patient also had recurrent stenosis at 14 months of follow-up; he was treated by angioplasty with DEB. No more stenosis occurred during the follow-up period.

The estimated primary patency rates at 6 months were 94.7% (95% CI, 80.9%–99.0%), at 12 months were 81.2% (95% CI, 64.6%–91.4%), at 18 months were 70.3%, (95% CI, 53.1%–83.4%), at 24 months were 60.7% (95% CI, 43.6%–75.7%), at 36 months were 60.7% (95% CI, 43.6%–75.7%), and at 48 months were 53.1% (95% CI, 36.5%–69.1%).

The estimated secondary patency rates at 6 months were 97.3% (95% CI, 84.5%–99.8%), at 12 months were 86.5% (95% CI, 70.7%–94.8%), at 18 months were 78.4%, (95% CI, 61.6%–89.4%), at 24 months were 69.0% (95% CI, 51.8%–82.4%), at 36 months were 69.0% (95% CI, 51.8%–82.4%), and at 48 months were 61.7% (95% CI, 44.6%–76.5%). Figure 1 summarizes the patency results.

Discussion

Our study demonstrated that endovascular treatment of JASs in radiocephalic hemodialysis fistulas with DEBs is an effective method. We recorded pretty high primary patency rates even at 48 months with DEBs in this study. Secondary patency rates were greater than primary patency rates as expected.

PTA is an established procedure and is the first option for the management of JASs with its minimally invasive nature [7, 17, 18]. Although surgical creation of a new fistula has lower rates of recurrence [19], secondary patency rates are comparable with surgery and PTA [20]. Despite high recurrence rates, endovascular treatment allows immediate usage of AVF after the procedure and prevents waiting for maturation after the new surgery.

Many studies compared the DEBs and plain balloons in the treatment of stenotic AVFs [12, 21, 22]. All these studies demonstrated that DEBs provide significantly higher primary patency rates and lower recurrence rates. Animal trials displayed the efficacy of paclitaxel on preventing neointimal hyperplasia and reported that local therapy is more useful [23, 24].

Although miscellaneous reports assessed the efficacy of DEBs in AVFs, the sample in these studies included radiocephalic and brachiocephalic fistulas or grafts, juxta-anastomotic, or outflow venous stenoses [6, 8, 9, 25, 26]. As far as we know, minimal number of studies assessed the long-term patency rates after DEB angioplasty in a uniform sample such as autologous radiocephalic AVFs with JASs [7].

We demonstrated better primary patency rates at 6 (94.7%) and 12 (81.2%) months compared to other studies [6, 9, 27, 28]. These results illustrate the efficacy of DEB angioplasty in JAS. Patanè D et al. [7] achieved similar results. The treatment of JASs with DEBs reduces the rate of restenosis and therefore makes the primary patency rates higher. With less repeated interventions, patient comfort and cost-effectiveness get better [22]. After the intervention, two restenoses occurred, and reintervention was performed within 1 year in our study. This number was much better than most of the other studies, except one study had the same number [7].

Patanè D et al. [7] showed a significant decrease in the primary patency rates from the 12th month to the 24th month. Similarly, there was a decline in our study from the 18th (70.3%) month to the 24th (60.7%) month. This decrease may be the consequence of repetitious punctures and vascular damage. However, the results remained the same at the 36th (60.7%) month. These rates are significantly higher than all studies that assessed the management of JASs in radiocephalic fistulas [7, 17, 27, 28].

Manninen et al. [17] assessed the effectiveness of the brachial arterial approach to the failing radiocephalic fistulas. Their primary patency rate was 32.0% at 36 months. This significant lower result compared to our study may be due to the heterogeneous target lesion (JASs or other segments) selection. Moreover, not only DEB angioplasty but also other treatment options such as thromboaspiration or stent deployment were performed in their study. Mortamais et al. [28] evaluated long-term results after endovascular treatment in JASs. They included only radiocephalic AVFs with JASs in their research and reported primary patency rates of 25.5% at 36 and 48 months. We demonstrated significantly greater rates at

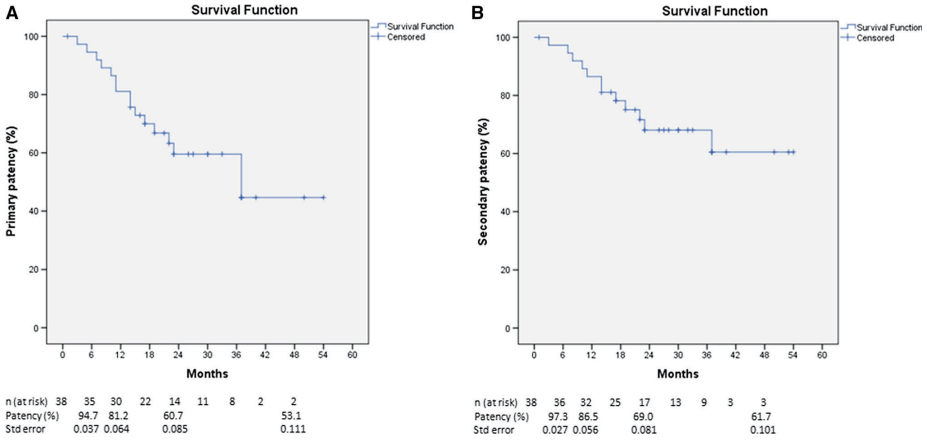

Fig. 1 Kaplan–Meier survival curves of estimated primary (**A**) and secondary (**B**) patency

48 months (53.1%). These encouraging rates at 6, 12, 18, 24, 36, and 48 months may be the result of DEB selection for the particular lesions in radiocephalic AVFs.

During our follow-up period, recurrent stenosis in the juxta-anastomotic region occurred in only three patients. This promising result may be due to the relatively small sample group. Mortamais et al. [28] reported that residual stenosis after the intervention, stenosis length, and time before the first restenosis significantly increase repeated interventions. On the other hand, Rajan et al. [8] demonstrated that no clinical or anatomic variable affects patency outcome.

The study had some limitations. The retrospective study design was the major limitation of the present study. Second significant limitation was the lack of a control group who were treated by plain balloons. Another limitation was the relatively small sample size of the patient group.

In conclusion, DEB angioplasty is a safe, effective treatment method with high primary patency rates even at long terms. The results we gained in this study demonstrate that JASs in distal radiocephalic AVFs can be effectively treated with DEBs and AVFs can be used safely for years after DEB angioplasty.

Acknowledgements This study was carried out in Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval For this type of study, formal consent is not required. Ethics committee approval was received for this study from the local ethics committee.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Consent for Publication Consent for publication was obtained for every individual person's data included in the study.

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The Mid-Term Clinical Follow-Up Using Drug-Eluting Balloons on Tibial Artery "De Novo" Lesions in Patients With Critical Limb Ischemia: A Cohort Study

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Abstract

Rationale: Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). The purpose of this study was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions. **Methods:** A retrospective analysis was performed and included all consecutive patients who underwent endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial artery stenosis and (2) Rutherford class >4. Lesions were further divided by TransAtlantic Inter-Societal Consensus (TASC) classification into groups A, B, C, and D. **Results:** Between January 2010 and March 2013, a total of 138 patients underwent simple PTA or DEB for CLI, and the groups were clinically and demographically homogenous. We decided to use DEBs in 70 cases. An improvement in the Rutherford Scale in cumulative and single TASC lesions classification was better in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. In the DEB group, the increase in ankle–brachial index was significantly higher than in the PTA group ($P = .039$). **Conclusions:** Our experience in addition to the existing literature supports the use of DEB in patients with CLI Rutherford class >3.

Keywords
intimal hyperplasia, drug-eluting balloon, restenosis

Introduction

Restenosis due to intimal hyperplasia (IH) is a major clinical issue that affects the success of lower limb endovascular surgery. After 1 year, restenosis occurs in 40% to 60% of the treated vessels. The possibility to reduce IH using local antiproliferative drugs, such as taxols, has been the rationale for the clinical applications of drug-eluting stents and drug-eluting balloons (DEBs). TransAtlantic Inter-Societal Consensus (TASC) II classification has been recently updated.[1] The intent of this new revision is to provide a complete anatomic lower limb TASC lesion classification, including the infrapopliteal segment, and an updated literature review of new endovascular techniques and practice patterns employed by vascular specialists today.[4] The new infrapopliteal lesion classification incorporates several features that attempt to address the multivessel nature of possible infrapopliteal anatomies.[6,7,12] Occlusive disease in a single tibial artery rarely leads to clinical signs or symptoms. Thus, a clinically significant reduction in distal arterial perfusion requires multivessel disease that can occur from multiple anatomic patterns of arterial occlusions. According to the new TASC II classification,[1] the purpose of this study

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Table 1. Demographic and Clinical Data.

Variables Data	DEB	PTA	*P* Value
Patients (138)	70	68	
Age, years	65.4 ± 9.0	66.1 ± 9.6	.125
Male	37 (75.5%)	35 (71.4%)	.234
CAD	18 (36.7%)	20 (40.8%)	.389
Smoking	36 (73.4%)	38 (77.5%)	.202
Diabetes	12 (24.4%)	11 (22.4%)	.371
Hyperlipidemia	18 (36.7.7%)	16 (32.6%)	.442
Obesity	4 (8.1%)	6 (12.2%)	.312
Reactive C-protein, mg/dL, >9.8 mg/dL	8 (16.3%)	7 (14.2%)	.256
Plasmatic homocysteine >15 μmol/L	11 (22.4%)	12 (24.4%)	.371
Ankle–brachial index (ABI)	0.35 ± 0.18	0.36 ± 0.21	.231
Rutherford classification			Cumulative
4	45	43	.291
5	17	14	
6	8	11	
TASC classification			Cumulative
A	2	2	.451
B	13	14	
C	26	22	
D	8	11	

Abbreviations: CAD, coronary artery disease; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

was to evaluate the clinical and instrumental efficacy of DEBs versus simple percutaneous transluminal angioplasty (PTA) in patients affected by chronic limb ischemia (CLI) with tibial artery "de novo" lesions.

Methods

Patients

A retrospective analysis was performed, including all consecutive patients who underwent an endovascular treatment for CLI in our centers between January 2011 and March 2013. Inclusion criteria were (1) "de novo" tibial arteries stenosis and (2) Rutherford class >4. Exclusion criteria were as follows: (1) recurrent stenosis; (2) inability to undergo aortography before the procedure; and (3) inability to give informed consent. Lesions were further divided by TASC II classification[1,2] into groups A, B, C, and D. A comparison was made between patients who were treated with paclitaxel DEB and simple balloon angioplasty (PTA). Patient selection was reviewed retrospectively to select patients with similar clinical and demographic data, but with different types of treatment (DEB or PTA), to reduce the bias of a nonrandomized cohort study (Table 1). All patients underwent aortography before the procedure to exclude iliac and femoral "in-flow" lesions and to study all of the tibial and plantar vessels. A written consent was obtained before the intervention for all patients. All bailout stenting and technical failures were considered a bias and were excluded from the analysis.[3] Study medication regimens and schedules were according to local clinical practice with aspirin (100-325 mg/d indefinitely) and clopidogrel or prasugrel loading dose (75 or 300 mg) with maintenance for 1 month. Clinical follow-up and instrumental follow-up were performed 24 months after the procedure.

Table 2. Type of Device.

Device	DEB	PTA
Elutax Aachen resonance	32	
Lutonix Bard	25	
Armada Abbott		38
FoxPlus Abbott		28
ClearPac Clearstream		36

Abbreviations: DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty.

Techniques and Devices

An antegrade approach was used in the majority of the interventions. Procedures were performed with a portable imaging fluoroscopic C-arm (OEC 9900 elite; GE Medical Siemens, Milwaukee, Wisconsin) or in a hybrid operating room using an Artis Zeego system (Artis Zeego; Siemens AG, Forchheim, Germany). Iodinated or gadolinium contrast was used, respectively, in patients with normal creatinine or with creatinine level >1.5 mg/dL. Intraoperative anticoagulation was achieved using 100 U/kg heparin, and the activating clotting time was maintained above 250 seconds. A 4F (for Elutax Aachen, FoxPlus Abbott, ClearPAc Clearstream) or 6F (for Lutonix Bard, Armada Abbott) introducer sheath was used with a 0.14-inch guidewire. Catheters for PTA or DEB were selected from a dedicated vascular shelf (Table 2). Predilatation was performed in 100% of the DEB cases. A 1-mm oversizing, after PTA, was considered for DEB diameter. Hence, all patients were primarily treated with PTA after, according to the operator's choice, they did or did not undergo DEB. The interventionist's decision was based on clinical and angiogram findings, his or her experience, cost-effectiveness of the procedure, and final results after POBA.

End Points

All patients were clinically and instrumentally evaluated 24 months after the procedure in a dedicated outpatient study. The primary end point of our study was a significant improvement in Rutherford Scale (IRS). Secondary end points were ankle–brachial index (ABI), the rate of restenosis (RR) measured by color-duplex scanning, mortality, and amputation rate. Finally, we considered the single endovascular tool in terms of clinical and instrumental efficacy. The RR was defined as a peak systolic velocity >2.4 m/s and a circumferential IH with a lumen loss more than 70% detected on ultrasound.[8]

Table 3. Type of Lesions and IRS.

IRS	DEB	PTA	*P* Value
Cumulative	74%	51%	.024
TASC II A lesions	76%	69%	.047
TASC II B lesions	86%	59%	.012
TASC II C lesions	65%	41%	.042
TASC II D lesions	55%	31%	.044

Abbreviations: DEB, drug-eluting balloon; IRS, Rutherford Scale; PTA, percutaneous transluminal angioplasty; TASC, TransAtlantic Inter-Societal Consensus.

Statistical Analysis

Data were collected in a dedicated Office Xcel (Microsoft, Redmond, Washington) file and analyzed using SPSS 21.0 software (IBM, Armonk, New York). Continuous variables with a normal distribution are expressed as the mean ± standard deviation, and categorical variables as frequency and percentage. The study required at least 110 patients to provide ≥80% power to detect an improvement in the Rutherford classification, expressed as the change in the class number between baseline and the 24-month control (calculated for individual patients). Significance between the treatment groups was tested by Cochran-Mantel-Haenszel statistics. Categorical variables (given as number and percentage) were compared by the use of Fisher exact test. Survival and amputation are presented as Kaplan-Meier analysis with Mantel-Cox log-rank test. Differences were considered statistically significant at $P < .05$.

Results

Between January 2010 and March 2013, we treated 138 patients with CLI using simple PTA or DEB; the groups were clinically and demographically homogenous. We decided to perform DEB in 70 cases. Preoperative Rutherford classification showed an equal distribution for both the groups, and the same results were obtained when considering the anatomy of the lesions with TASC II classification[1] (lesion types A, B, C, and D). An antegrade and retrograde approach was used in 83.3% (110 cases) and 16.7% (28 cases), respectively.

Primary End Point

Rutherford Scale in cumulative and single TASC lesion classification was superior in the DEB group (74% vs 51%; $P = .024$) at 24 months than in the PTA group. The TASC II B lesions showed further superior results with a significant improvement in IRS with respect to the PTA group (Table 3). When matching the IRS in both groups, a longer lesion was associated with worst long-term results, even if the DEB group had a superior significant improvement in IRS. Irrespective of the type of treatment, TASC II type C and D lesions showed the worst results when compared to types A and B.

Table 4. ABI and RR in the Two Groups.

	DEB	PTA	*P* Value
ABI cumulative	0.64 ± 0.35	0.52 ± 0.22	.039
ABI TASC II A	0.65 ± 0.19	0.58 ± 0.15	.078
ABI TASC II B	0.71 ± 0.23	0.48 ± 0.12	.025
ABI TASC II C	0.49 ± 0.15	0.43 ± 0.21	.041
ABI TASC II D	0.40 ± 0.15	0.39 ± 0.21	.044
RR cumulative (psv >2.4 m/s + stenosis >70%)	19%	32%	.028
RR TASC II A	16%	19%	.068
RR TASC II B	15%	24%	.043
RR TASC II C	21%	38%	.034
RR TASC II D	38%	62%	.012

Abbreviations: ABI, ankle–brachial index; DEB, drug-eluting balloon; PTA, percutaneous transluminal angioplasty; RR, rate of restenosis; TASC, TransAtlantic Inter-Societal Consensus; psv, peak of systolic velocity.

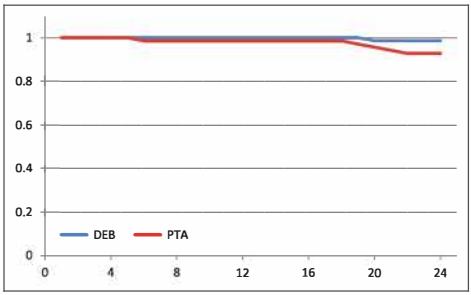

Figure 1. Cumulative Survival Rate.

Secondary End Point

In the DEB group, the increase in ABI was significantly higher than in the PTA group ($P = .039$; Table 4). For patients with TASC B lesions, DEB was most beneficial, resulting in a significant ABI increase and a lower RR (TASC B with DEB: from 0.35 ± 018 to 0.71 ± 0.23; TASC B with PTA: from 0.36 ± 0.21 to 0.48 ± 0.12; $P = .025$). In patients with TASC C and D lesions, the ABI improved less and the RRs were higher compared to the patients with TASC A and B lesions. Both the cumulative survival rate and the amputation rate showed significantly superior results for the DEB group (Figures 1 and 2). Major amputations were only performed in patients who were IRS 5 and 6. All analyzed variables were similar between the PTA and the DEB groups.

Discussion

In practical terms, although the level of evidence is low, the initial revascularization strategy for femoropopliteal disease is commonly an endovascular approach.[5,12,15] This is supported by a recent meta-analysis of the published literature regarding

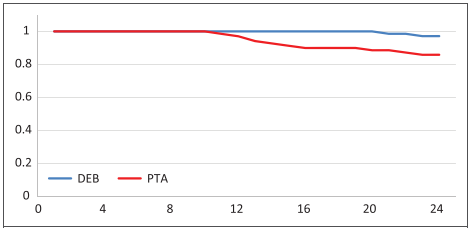

Figure 2. Amputation Rate.

endovascular versus surgical revascularization for femoropopliteal disease.[9] We investigated the long-term clinical results in patients with critical limb ischemia treated with PTA or DEB. Demographic data (Table 1) showed a homogenous distribution of the patients in the 2 groups, which reduced the bias resulting from a lack of randomization. Chronic limb ischemia remains a remarkable risk factor for cardiovascular events and amputation 1 year after the onset of symptoms. This aggressive pathology has been deeply investigated,[2,10] and there is a common agreement that CLI requires urgent and complete treatment. As reported by the TASC II and American Heart Association guidelines, endovascular therapy is the preferred treatment for type A and B lesions, whereas surgery is the preferred treatment for low-risk patients with type C and D lesions.[2,10] The patient's comorbidities, fully informed patient preference, and the local operator's long-term success rate must be considered when making treatment recommendations for type C and D lesions. According to this recommendation, we treated 98 patients with "de novo" lesions for CLI. Type C and D lesions were considered for endovascular therapy according to our endovascular experience, and all patients in the type C and D group were successfully treated with angioplasty. There has been an evolution of newer technologies, specifically patency-enhancing drug coating for balloons and stents. There is growing evidence from randomized trials that supports the use of DEB.[11,13,16,17] These trials underline the long-term benefit of lowering restenosis both for quality of life[18,19] and for life expentancy.[20] In our experience, we focused on clinical improvement using the IRS. Restoring an effective blood flow in the pedal and tibial vessels permits lesions to heal, relieves pain, and reduces the release of inflammatory cytokines.[21-23] The efficacy of endovascular therapy is correlated with vessel outflow, meaning there is a strict correlation between the number of patent vessels and the final outcome.[24] In our experience, we have used Lutonix Bard and Elutax Aachen as DEB. Lutonix has been supported by clinical trials,[10] and a second trial of Levant 2 is still ongoing to validate this DEB. No randomized trial has been considered for Elutax, and the literature lacks data[25] concerning the use of this DEB for tibial vessels. Nonetheless, we decided to use this device based on the good results in other experiences.[1,25] The 6-month results of Elutax SV showed this DEB to be comparable to and as effective as other DEBs that have undergone clinical trials. Our preliminary experiences reported that the ABI improved from 0.49 to 0.89, and the Rutherford stage decreased from 3 to 1. Another "pro" for the use of this DEB is the low-profile catheter, which always permits the use of a 4F introducer sheath with all of the diameters in peripheral vessels. Patients with reduced tibial outflow (3-vessel runoff) showed a significantly reduced patency relative to patients with 3-vessel runoff.[17,24] In our experience, we noted that reduced tibial outflow, such as in C type lesions, might be a causative factor in the reduced primary patency of percutaneous interventions; it is also possible that it is simply a marker for increased disease severity. Those with more severe or extensive disease might be more likely to represent with recurrent symptoms, thus leading to more frequent documentation of failure in this group relative to those with type A and B lesions. Drug-eluting balloons were shown to be more effective in controlling the worsening of IRS with significant cumulative results. Restenosis was significantly controlled in the DEB group, and an increased ABI was noted. The ABI provides key information on long-term prognosis, with an ABI $\leq$0.90 associated with a 3- to 6-fold increased risk of cardiovascular mortality. The benefits of a long-term improvement in ABI are evidenced by the better results in the free-from-amputation and survival rates as shown by Kaplan-Meier analysis (Figures 1 and 2).[7,14,15] The rationale of DEB has been already described,[11,13,18] but it is important to underline that the coated balloon releases most of the drug immediately during the first inflation when there is short contact with the vessel wall for 60 seconds. The duration of inhibition of cell proliferation exceeds the time that cells are actually exposed to the drug. In some studies,[11,18] only approximately 6.4% $\pm$ 2.9% of the original paclitaxel dose was found to be extractable from the surface of the balloons used in our trial. Although animal studies indicate that as much as 70% to 80% of the drug dose might be lost in the bloodstream,[25] the remaining dose and duration of drug exposure seem to be sufficient to prevent neointimal proliferation.

Conclusion

Although this study has a limitation due to the lack of randomization, we observed superior results with DEB. The cumulative free-from-amputation rate shows the benefit of using DEB. All patients who required an amputation belonged to Rutherford class 5 and 6. We showed that the DEB group obtained a better IRS, leading to a lower risk of amputation for these patients. Further research is needed before we can consider the DEB as the gold standard therapy for CLI. However, our experience, in addition to the existing literature, supports the use of DEB in patients with CLI Rutherford class >4. With the reduced need for a stent and considering the statement "leaving nothing behind", DEB can be considered a safe treatment of choice in CLI.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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CIRSE

Drug-Coated Balloon Angioplasty of Infrapopliteal Lesions in Patients with Critical Limb Ischaemia: 1-Year Results of the APOLLO Trial

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Abstract

Purpose This study intended to assess effectiveness and safety of the drug-coated balloon (DCB) angioplasty of infrapopliteal atherosclerotic lesions in patients with critical limb ischaemia (CLI) in a real-world setting.

Methods Consecutive patients with critical limb ischaemia who underwent infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB were enrolled into the prospective, multicentre, single-arm observational registry. Primary outcome was clinical improvement at 6 and 12 months. Secondary outcomes were change in quality of life, primary patency, freedom from repeat revascularisation, and amputation-free survival at 6 and 12 months.

Results A total of 164 patients (74.7 ± 9.2 years) with CLI were included at nine German sites between November 2015 and September 2017. The majority (79.9%) of patients had diabetes mellitus, 57.3% had renal insufficiency, and 35.3% had coronary artery disease. Mean lesion length was 71.2 ± 76.5 mm. The Rutherford category improved by 3.0 ± 2.0 ($p < 0.0001$) within 12 months, resulting in a clinical improvement by at least one Rutherford category in 80.2% of the patients. Walking impairment questionnaire score, European Quality of Life index, and patient-reported pain improved significantly from baseline to 6 and 12 months. Primary patency was 68.5%, freedom from target lesion revascularisation 90.6%, and amputation-free survival 83.5% at 12 months.

Conclusion Infrapopliteal drug-coated balloon angioplasty with the ELUTAX SV DCB in patients with critical limb ischaemia was efficacious and safe over the medium term. The study is registered with Clinical.Trials.gov (Identifier: NCT02539940).

Keywords Below the knee · Critical limb ischaemia · Drug-coated balloon angioplasty · Drug-eluting balloon · Infrapopliteal · Paclitaxel · Peripheral artery disease

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Introduction

Patients with critical limb ischaemia (CLI) have a risk of about 50% of major amputation or death within the first year from presentation [1, 2]. Even after major amputation, almost half of those aged 70 and older probably will die in the following year [3].

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CLI is usually a multilevel artery disease, mostly involving the infrapopliteal arteries. The majority of CLI patients concomitantly suffer from diabetes and other cardiovascular diseases, unfavourably reinforcing each other. Guidelines require infrapopliteal revascularisation for limb salvage whenever possible, and endovascular therapy should be considered in patients with stenosis, short occlusions, or at high risk for open surgery [4]. However, infrapopliteal artery disease is characterised by small vessels, particularly prone to elastic recoil [5], low flow, and a diffuse pattern of lesions, frequently accompanied by medial calcification. The incidence of restenosis of about 40–60% at 1 year after standard balloon angioplasty (POBA) is disappointing [6, 7]. Even bare-metal stent implantation does not make a substantial improvement [8]. In short lesions, drug-eluting stents were found to be superior to POBA or bare-metal stents, but did not decrease mortality.

In medium-length lesions, drug-coated balloons (DCBs) tended to prevent restenosis and target lesion revascularisation but did not improve the amputation-free survival [9]. However, advanced technology of DCBs could have improved efficacy and safety. This study aimed to assess the effectiveness of the ELUTAX SV paclitaxel-coated balloon in a real-world setting over a period of 12 months.

Methods

Study Design and Setting

The APOLLO study is a prospective, multicentre, observational, investigator-initiated trial. Recruitment took place over a period of 23 months at nine German sites. Clinical evaluation, duplex ultrasonography (DUS), assessment of quality of life (QoL) measures including Walking Impairment Questionnaire (WIQ) score [10], European Quality of Life-5 Dimensions (EQ-5D) index [11, 12], and patient-reported pain, as well as determination of the ankle–brachial index (ABI) were conducted at baseline and at 6 and 12 months after revascularisation. All target limb-related adverse events, device-related adverse events, adverse cardiovascular events, and all severe adverse events had to be reported by the investigators. The study is registered with ClinicalTrials.gov (Identifier: NCT02539940).

Patients

Patients who were at least 18 years of age and were scheduled for DCB angioplasty with the ELUTAX SV DCB for the treatment of below-the-knee artery stenosis of $\geq$ 70% or occlusion and suffered from critical limb ischaemia (Rutherford category 4–6 or CLI confirmed by photoplethysmography) were eligible. Inclusion was independent of a successful guide wire passage and lesion preparation. All patients provided written informed consent. The inflow artery had to be patent; however, its treatment prior to the index procedure was permitted. Per definition, a target vessel reconstitutes at or above the ankle. Key exclusion criteria were planned major target limb amputation, acute limb ischaemia, or application of DCB other than ELUTAX SV in a target limb artery.

Study Device and Procedure

The semi-compliant ELUTAX SV drug-coated balloon (Aachen Resonance, Aachen, Germany) is coated with a matrix, consisting of two layers of paclitaxel and a seal layer of dextran. Paclitaxel is supposed to inhibit neointimal proliferation and thus to prevent restenosis. The inner paclitaxel layer has an amorphous and the outer layer a crystalline structure. Paclitaxel dose density is 2.2 $\mu g/mm^2$. Dextran protects the paclitaxel layers from abrasion during introduction of the catheter, minimises the paclitaxel wash off by providing a continuous drug transfer to the vessel wall, and supports platelet inhibition. The DCB had to be used according to the manufacturer's instruction and the standard clinical practice of the participating centres. Inflation time recommended by manufacturer is 30 s. Pre-dilation was not mandatory. However, pre-dilation as well as prolonged inflation, bailout stenting, or post-dilation in case of significant residual stenosis or flow-limiting dissection were left to investigator's discretion.

Concomitant study medication had to comply with current guidelines. To prevent systematic vascular events and limb events, long-term treatment with aspirin and, in case of bailout stenting, dual antiplatelet therapy with aspirin and clopidogrel for at least one month was recommended.

Study Outcome Measurements

Primary effectiveness outcome was clinical improvement based on the change in Rutherford category from baseline to 6 and 12 months. Secondary effectiveness outcome was change in QoL, incidence of primary patency, freedom from target lesion revascularisation (TLR), and freedom from target vessel revascularisation (TVR) at 6 and 12 months. QoL was determined by means of WIQ score, EQ-5D index, and patient-reported pain on a scale from zero to ten. Primary patency was given if DUS examination showed sufficient flow upon investigator's assessment without the need of prior TLR. Safety endpoints were freedom from minor amputation, freedom from major amputation, amputation-free survival, and all-cause mortality at 6 and 12 months. Minor amputation was defined as

transmetatarsal or distal amputation and major amputation as above transmetatarsal amputation.

Statistical Analysis

Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as counts and percentages. Differences between variables were assessed with the two-sided sign test or the Wilcoxon sign-rank test. Kaplan–Meier analysis was performed to estimate freedom from TLR, TVR, amputation, or death, as well as primary patency. Results are presented as parameter estimates and their corresponding 95% confidence intervals (CIs). Logistic regression was used to assess predictors of clinical improvement without the need of TLR at 6 months and the composite of death and any amputation at 12 months. Established candidate variables were pre-screened based on univariable analysis with a P value cut-off of 0.25 based on Wald test from logistic regression. Subsequently, variable selection for multivariable modelling was continued by stepwise backward regression with an entry and removal threshold P value of 0.1. A two-sided value of $p < 0.05$ indicated statistical significance. Statistical analysis was performed using SPSS Statistics (version 25.0. IBM, Armonk, NY, USA).

Results

Study Population and Treatment

From November 2015 to September 2017, 164 consecutive CLI patients with 248 infrapopliteal artery lesions were enrolled at nine German centres. All but one underwent DCB angioplasty with the ELUTAX SV DCB. About 80% of the patients had diabetes mellitus and 44% were obese. Fifty-seven per cent of patients had renal insufficiency (Table 1). Mean lesion length was 71.2 ± 76.5 mm. Chronic occlusion and severe calcification were present in 43% and 27% of patients, respectively (Table 2). Inflow intervention was conducted in 31% and pre-dilation in 68% of patients (Table 3). Completion of DUS follow-up was 55.5% (91 of 164 patients) at 6 months and 47.0% (77 of 164 patients) at 12 months.

Table 1 Patient demographics and clinical characteristics (n = 164[a])

Age, years	74.7 ± 9.2
Sex	
Female	55 (33.5)
Male	109 (66.5)
Diabetes mellitus	131 (79.9)
Insulin dependent	82/130 (63.1)
Hyperlipidemia	88/159 (55.3)
Body mass index	29.2 ± 5.4
> 30	71/162 (43.8)
Hypertension	148 (90.2)
Smoking	66/146 (45.2)
Current	17/146 (11.6)
Coronary artery disease	55/156 (35.3)
Heart failure	41/160 (25.6)
Renal insufficiency	94 (57.3)
Cerebrovascular disease	29/154 (18.8)
Stroke	24/154 (15.6)
ABI (n = 83)	0.91 ± 0.46
< 0.5	13/83 (15.7)
≥ 1.3	22/83 (26.5)
Rutherford category	
3—severe claudication	7[b] (4.3)
4—ischaemic rest pain	29 (17.7)
5—minor tissue loss	109 (66.5)
6—major tissue loss	19 (11.6)
Previous amputation	42 (25.6)
Major amputation[c]	7/164 (4.3)
Medication	
Statin	100/162 (61.7)
Platelet inhibitor	64/163 (39.3)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

[a]One patient did not receive the study device. No information about the kind of treatment is available

[b]Photoplethysmography indicated critical limb ischaemia

[c]Above transmetatarsal

Primary Effectiveness Outcome

Rutherford category improved by 2.5 ± 2.0 at 6 months ($p < 0.0001$) and 3.0 ± 2.0 at 12 months ($p < 0.0001$) (Fig. 1A). Clinical improvement by at least one Rutherford category was observed in 74.0% (94 of 127 patients) at 6 months (Fig. 1B) and in 80.2% (85 of 106 patients) at 12 months (Fig. 1C). Excluding patients who did not receive the study device or had peripheral artery diseases (PAD) of Rutherford category 3 at baseline, the 12-month incidence of clinical improvement was 79.0%.

Secondary Effectiveness Outcomes

The WIQ score improved by 7.1 ± 27.9% (p = 0.0119) of the maximum score within 6 months and by 10.7 ± 32.4% (p = 0.0035) from baseline to 12 months (Fig. 2A). The EQ-5D index improved by 0.08 ± 0.30 (p = 0.0013) within 6 months and by 0.07 ± 0.33 (p = 0.0003) over a period of 12 months (Fig. 2B). Patient-reported pain

Table 2 Lesion characteristics[a] (n = 248)

Lesion length, mm	71.2 ± 76.5
Total lesion length, mm	107.2 ± 92.6
Diameter stenosis, %	89.4 ± 10.5
Chronic total occlusion	
Artery based	105/273 (38.5)
Patient based	70/164 (42.7)
Severe calcification[b]	22/83 (26.5)
TASC classification[c]	
TASC A	48/162 (29.6)
TASC B	68/162 (42.0)
TASC C	39/162 (24.1)
TASC D	7/162 (4.3)
Affected arteries	273
Popliteal artery	29 (10.6)
Tibioperoneal trunk	42 (15.4)
Anterior tibial artery	100 (36.6)
Peroneal artery	55 (20.1)
Posterior tibial artery	47 (17.2)
Number of crural arteries with runoff to the foot	
0	27/155 (17.4)
1	73/155 (47.1)
2	43/155 (27.7)
3	12/155 (7.7)

Categorical values are presented as counts (percentages); continuous data are presented as mean ± standard deviation

[a]Adjacent lesions without angiographic evidence of healthy segments 20 mm or greater were considered as single lesion

[b]Assessed by visual estimate or medial calcification indicated by ABI ≥ 1.3

[c]Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC) classification of infrapopliteal lesions

Table 3 Procedure characteristics

Inflow intervention	51/164 (31.1)
SFA	25/51 (49.0)
P1	10/51 (19.6)
P2	11/51 (21.6)
P3	5/51 (9.8)
Pre-dilation (patient-based)	110/163 (67.5)
Pre-dilation (DCB-based)	159/286 (55.6)
Balloon length, mm	88.5 ± 46.6
Nominal diameter, mm	2.7 ± 3.3
Maximum pressure, atm	10.6 ± 3.3
Pre-dilation time, sec	48.5 ± 41.8
Drug-coated balloon[a]	286
DCB/lesion	1.15
Balloon length, mm	86.4 ± 43.8
Nominal diameter, mm	2.9 ± 2.2
Maximum pressure, atm	8.5 ± 2.0
Inflation time, sec	114.4 ± 34.7
Post-dilation	18/163 (11.0)
Scoring balloon	2 (1.2)
Balloon length, mm	63.1 ± 47.1
Nominal diameter, mm	5.0 ± 8.8
Maximum pressure, atm	10.0 ± 3.3
Inflation time, sec	82.8 ± 59.7
Bailout stenting[b]	5/163 (3.1)
Medication at 6 months	
Statin	98/137 (71.5)
Platelet inhibitor	50/136 (36.8)
Medication at 12 months	
Statin	89/119 (74.8)
Platelet inhibitor	33/116 (28.4)

Categorical values are presented as counts (percentages); continuous values are presented as mean ± standard deviation

DCB drug-coated balloon; *SFA* superficial femoral artery; *P1* proximal popliteal artery segment; *P2* mid-popliteal artery segment; *P3* distal popliteal artery segment

[a]One of 164 patients did not receive a drug-coated balloon

[b]Four lesions were stented due to dissection and one lesion due to residual stenosis > 30%

decreased by 1.2 ± 2.1 pain scale units ($p < 0.0001$) within 6 months and by 1.0 ± 2.8 units ($p = 0.003$) within 12 months (Fig. 2C). ABI increased significantly from baseline to 6 months (1.1 ± 0.4, $p = 0.0009$) and from baseline to 12 months (1.2 ± 0.4, $p = 0.0047$).

Freedom from TLR was achieved in 97.1% (standard error [SE] 1.4%) and 90.6% (SE 2.6%) of patients at 6 and 12 months, respectively (Fig. 3A). Freedom from TVR (including TLR) was achieved in 94.9% (SE 1.9%) and 88.4% (SE 2.8%) at 6 and 12 months, respectively (Fig. 3B). Patency at discharge was achieved in 97.8% (176 of 180 lesions). Cumulative incidence of patient-based primary patency was 91.6% (SE 3.0%) and 68.5% (SE 5.2%) at 6 and 12 months, respectively (Fig. 3C). Post hoc multivariable analysis revealed male sex as independent risk factor for worse clinical response at 6 months (odds ratio [OR] 0.17, $p = 0.010$). Inversely, statin medication at 6 months tended to be associated with clinical improvement (OR 3.08, $p = 0.053$) (Fig. 4).

Safety Outcomes

Freedom from minor amputation was 82.5% (95% CI: 75.1–87.9) at 6 months and 77.8% (95% CI: 69.4–84.1) at 12 months. Limb salvage was 97.1% (SE 1.4%) and 95.4% (SE 1.9%) at 6 and 12 months, respectively (Fig. 5A). Survival was 94.5% (SE 1.8%) and 87.8% (SE 2.7%) at 6

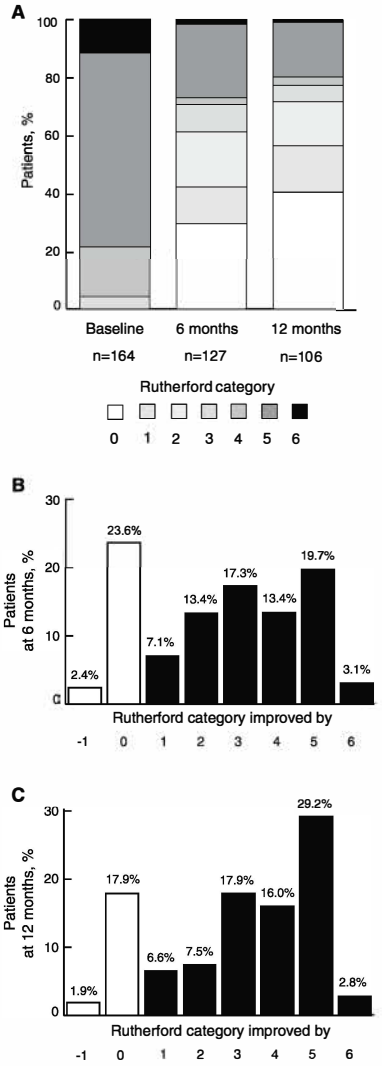

Fig. 1 Distribution of Rutherford categories at baseline and follow-ups (**A**), and clinical improvement from baseline to 6 months (**B**) and to 12 months (**C**)

and 12 months, respectively (Fig. 5B), and major amputation-free survival was 90.7% (SE 2.3%) and 83.8% (SE 3.0%) at 6 and 12 months, respectively (Fig. 5C).

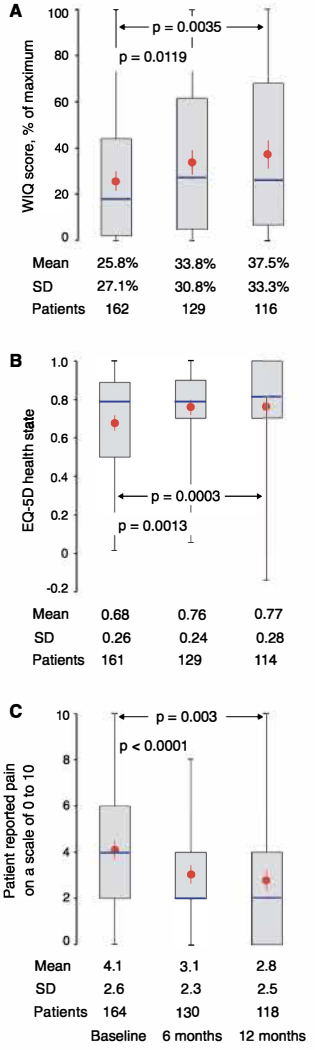

Fig. 2 Quality of life at baseline and at 6- and 12-month follow-ups expressed in Walking Impairment Questionnaire score (**A**), European Quality of Life-5 Dimensions score (**B**), and patient-reported pain (**C**). Box plots indicate median and interquartile range. Whiskers end with the lowest and highest data point. Red dots represent means with their corresponding 95% confidence interval. *SD* standard deviation, *WIQ* Walking Impairment Questionnaire, *EQ-5D* European Quality of Life-5 Dimensions score

A total of twenty patients (15.9%) died within one year of the intervention. Five patients died from heart failure, four from sepsis, two each from stroke, renal failure, pneumonia, or haemorrhage, and one each from myocardial infarction or arrhythmia. One death remained unexplained (Table 4). Without consideration of patients who did not receive the study device or had PAD of Rutherford category 3 at baseline, 12-month incidence of restenosis was 25.7%, of repeat revascularisation 11.3%, of minor or major amputations 26.5% and 5.3%, respectively, and of mortality 15.8%.

Post hoc logistic regression revealed a higher BMI and inflow vessel intervention as independent predictors for a reduced risk of death or amputation at 12 months (OR 0.88 [p = 0.007] and OR 0.37 [p = 0.040], respectively). Renal insufficiency tended to increase the risk of death or amputation (OR 2.2, p = 0.078) (Fig. 6).

Discussion

After angioplasty with the ELUT AXSV DCB, the majority of patients improved clinically. A significant share reported on an improved quality of life that maintained throughout the following year. Repeat revascularisation was needed in about one of eight patients, and minor amputation in one of four. Eighty-four per cent of the patients survived the first year after revascularisation without major amputation.

Clinical Improvement

Clinical improvement and quality of life (QoL) are rarely reported in trials on CLI because limb salvage is paramount. Although QoL is highly subjective, it is a useful complement of clinical effectiveness outcomes. This study found a sustained improvement of QoL in a population with advanced disease and multiple comorbidities. Increased walking ability and activity might have contributed to patency and collateralisation. The favourable impact of statin on clinical improvement is supported by previous results from the CRITISCH registry [13] and a large-scale Swedish registry [14]. Therefore, preventive pharmacological treatment pursuant to guidelines [4] should be strongly recommended. The former registry additionally confirms the worse treatment response in men.

Patency and Repeat Revascularisation

Meta-analysis on three randomised trials that compared infrapopliteal DCB angioplasty with POBA in CLI patients (DEBATE-BTK [15], IN.PACT DEEP [16], BIOLUX P-II [17]) reported on a non-significant trend in favour of DCB angioplasty regarding restenosis [7, 9]. However,

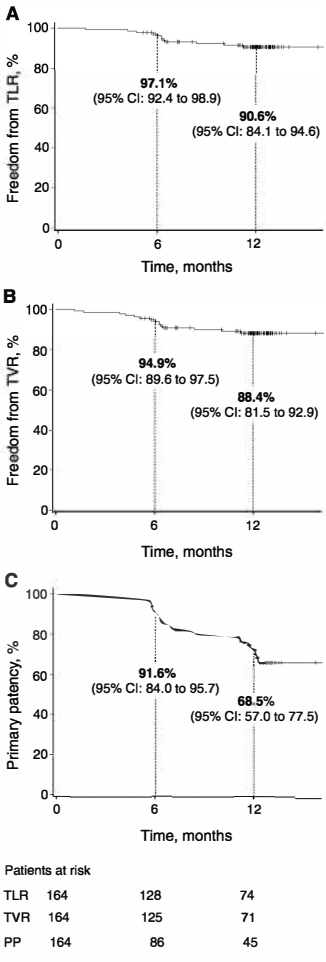

Fig. 3 Kaplan–Meier survival estimates for freedom from target lesion revascularisation (**A**), freedom from target vessel revascularisation (**B**), and primary patency (**C**). *CI* confidence interval, *PP* primary patency, *TLR* target lesion revascularisation, *TVR* target vessel revascularisation

heterogeneity was significant. One-year incidence of restenosis after POBA varied between 47 and 74% [6, 9, 15]. In contrast, incidence of restenosis after DCB is reported with 30% and thus is in line with the findings from this study. This advantage is probably due to inhibition of neointimal proliferation by paclitaxel.

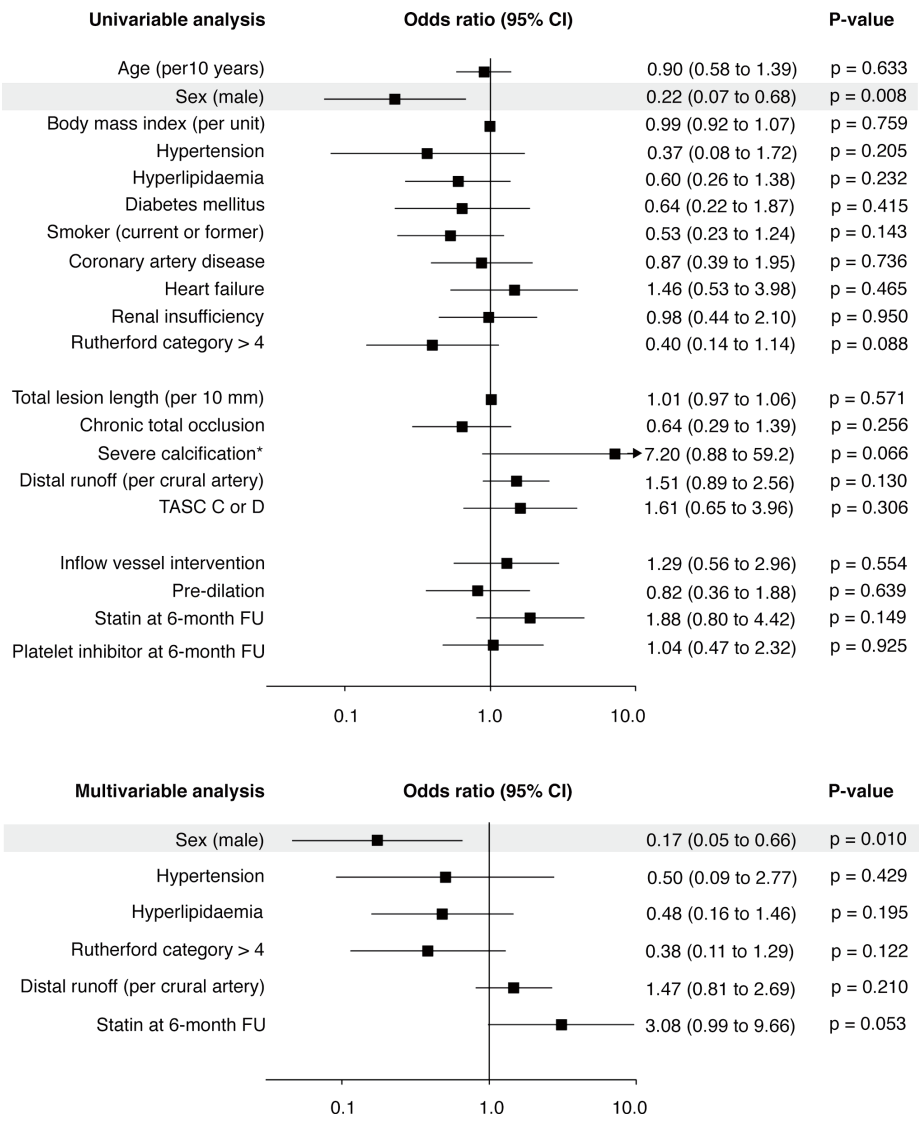

Fig. 4 Probability of improvement by at least one Rutherford category at 6 months without the need of target lesion revascularisation. *Not included into multivariable regression due to numerous missing data. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

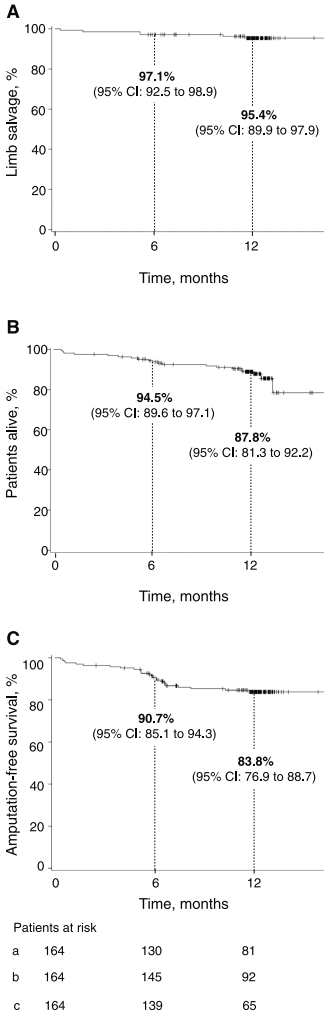

Fig. 5 Kaplan–Meier estimates for limb salvage (**A**), survival (**B**), and major amputation-free survival (**C**). *CI* confidence interval

In this study, TLR was less frequently conducted than in previous DCB studies. It might be assumed that in shorter, less complex lesions, restenosis more rarely needs to be revascularised. The above-mentioned meta-analysis revealed a difference to POBA that was just below statistical significance [9]. From this, one could conclude that with new-generation DCB, there might be a significant advantage over POBA. However, a meta-analysis of 27 trials on infrapopliteal POBA revealed a somewhat lower incidence of TLR with significant heterogeneity [6]. Thus, superiority of DCB angioplasty over POBA remains to be proven by future randomised trials.

Table 4 Incidence of safety outcomes

	At 6 months	At 12 months
All-cause mortality[a]	10/141 (7.1)	20/126 (15.9)
Major target limb amputation[b]	4/137 (2.9)	6/119 (5.0)
Minor target limb amputation[c]	26/137 (19.0)	30/119 (25.2)
Repeat revascularisation[d]	9/137 (6.6)	13/119 (10.9)
Restenosis[e]	10/91 (11.0)	18/77 (23.4)
Thrombectomy	1/163 (0.6)	1/163 (0.6)
Atherectomy	0/162 (0.0)	0/162 (0.0)

Values are given as counts (percentages)

[a]Five patients died from heart failure, four patients from sepsis, two patients each from stroke, renal failure, pneumonia, or haemorrhage, and one patient each from myocardial infarction, or arrhythmia. On death remained unexplained

[b]Above transmetatarsal

[c]Transmetatarsal or distal

[d]Target vessel revascularisation including target lesion revascularisation

[e]No sufficient flow through the target lesion by duplex ultrasonography

Amputation and All-Cause Mortality

Limb salvage is the primary objective of revascularisation in CLI patients. In this study, considerable fewer patients underwent major amputation than during previous studies on infrapopliteal POBA [6] and DCB angioplasty [9].

Incidence of all-cause mortality in this study was slightly higher compared to previous meta-analysis on DCB [9, 18], similar to POBA [6], and lower compared to any kind of CLI revascularisation [19]. Except for renal insufficiency, every single comorbidity statistically was not associated with death or amputation. However, CLI patients frequently suffer from multiple comorbidities which may adversely affect one another and may enhance disease progression. Advanced age, physical constitution, and cardiovascular medication probably carry weight. Finally, mortality and causes of death of patients who withdrew or were lost to follow-up remain unknown.

Shammas et al. [20] reported on a threefold increased risk of major amputation and a 14-fold increased risk of death in diabetic compared to non-diabetic CLI patients. In addition, the above-mentioned Swedish registry supports the finding on an increased risk of death or amputation in

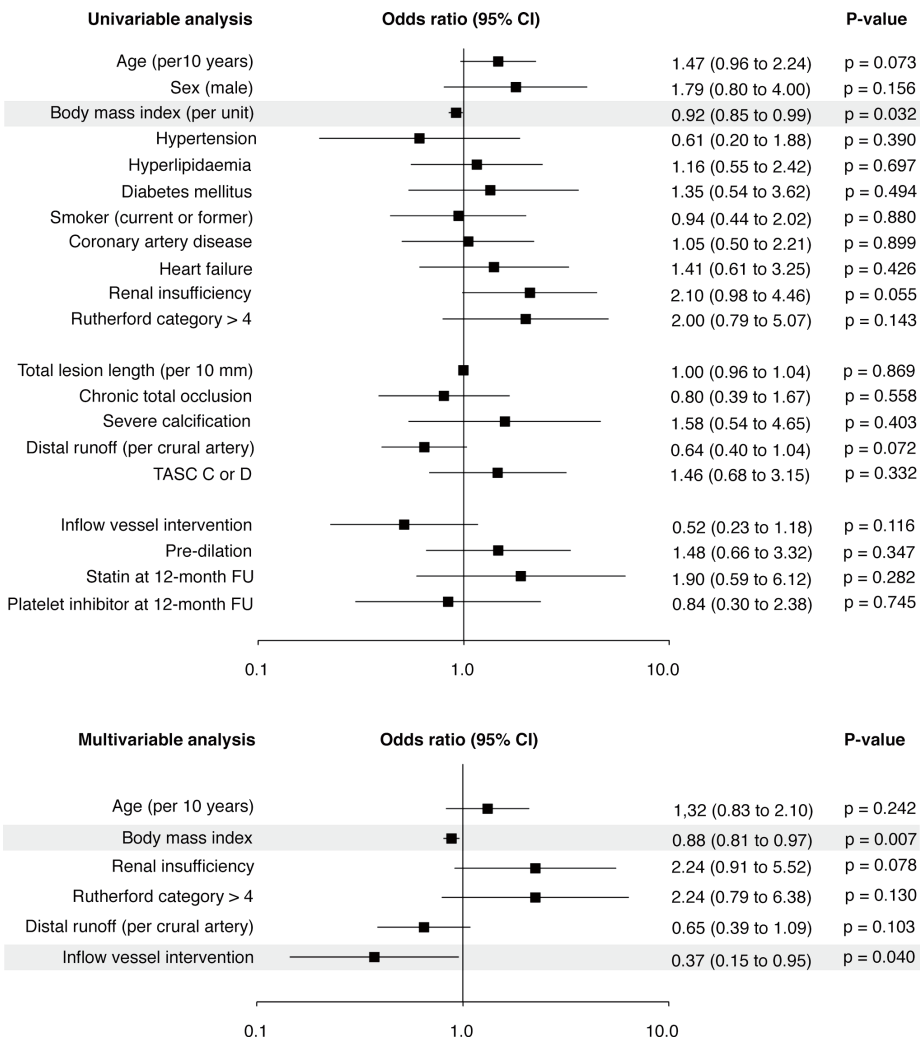

Fig. 6 Probability of death or any amputation at 12 months. *CI* confidence interval, *FU* follow-up, *TASC* inter-society consensus for the management of peripheral arterial disease classification of infrapopliteal lesions

patients with renal insufficiency [14]. In the light of this, mortality in this study was consistent.

A higher BMI was associated with less mortality or amputation. Accordingly, Moussa et al. [21] found a worse in-hospital mortality of underweight compared to normal-BMI patients with severe peripheral artery disease. This might suggest that in CLI patients, downward deviations from the normal BMI may be indicative for poor health. Inflow intervention did not considerably increase clinical improvement but significantly reduced the risk of death or

amputation. This might be attributed to patients who underwent minor amputation and subsequently improved clinically. A previously suggested interaction between diameter stenosis and major adverse events [18] could not be confirmed by this study. Total occlusions at baseline were not associated with death or amputation. Finally, with regard to recent concerns about adverse long-term effects of paclitaxel-coated devices, data from trials that prioritise safety endpoints are needed [22].

Strength and Limitations

The strength of this study is that it provides detailed results on clinical improvement and change in quality of life. Moreover, post hoc analysis identified predictive variables for clinical improvement and risk factors for death and amputation. The study has some limitations. First, return of patients for DUS follow-up was low. Standard errors of primary patency at 6 and 12 months, however, were reasonable. Second, patency was given if flow was clearly demonstrated by DUS. To simplify study-related follow-up evaluations, quantitative measurement was not mandatory. Third, ABI data were obtained by only about half of the patients. In addition, due to medial calcification, a high proportion of ABIs were not suitable to determine the hemodynamic condition. Fourth, severity of calcification was not rated based on an established calcium scoring system but only by investigator's estimate or ABI $\geq$ 1.3. Fifth, classification of wounds and quality of wound care management were not inquired. Sixth, seven patients with PAD of Rutherford category 3 were included. Exclusion of these patients from the analysis led to slightly worse results.

Conclusions

In conclusion, infrapopliteal angioplasty with the ELUTAX SV DCB improved the clinical status and quality of life of CLI patients over a period of 12 months. Restenosis, TLR, and all-cause death were comparable to previous data from infrapopliteal DCB angioplasty in CLI patients and less frequent than known from POBA. Considerably fewer major amputations were necessary than previously reported from any other strategy of revascularisation.

Funding This study was funded by Aachen Resonance.

Compliance with Ethical Standards

Conflict of interest All other authors declare that they have no conflict of interest, except of Prof. Teichgräber who received a funding for the APOLLO study by Aachen Resonance.

Ethical Approval All procedures performed were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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LITERATURE REVIEW

NEURO ELUTAX SV DRUG-ELUTING BALLOON VERSUS WINGSPAN STENT SYSTEM IN SYMPTOMATIC INTRACRANIAL HIGH-GRADE STENOSIS A SINGLE-CENTER EXPERIENCE

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Intracranial stenosis is a major cause of stroke worldwide, prevalent more in Asian populations. The treatment of ICAD (intracranial atherosclerotic disease) remains relatively conservative, owing to the trends following SAMMPRIS trial. SAMMPRIS trial established superiority of conservative management over intracranial stenting. However in SAMPRISS trial, significant re strokes were noted on medical management. Therefore, aggressive medical management does not offer the ideal solution and a novel treatment strategy for ICAD is desired.

Since 1980s, simple angioplasty for ICAD has been tried. Mainly cardiac balloons have been used for intracranial angioplasty however, owing to stiff nature of cardiac hardware these devices are difficult to navigate intracranially. Similar difficulties are encountered in intracranial stenting. This has resulted in higher percentage of procedural and periprocedural complications leading to relatively poor outcome.

Recently a CE certified intracranial drug eluting balloon was compared to Wingspan stents in a study 'Neuro Elutax SV drug-eluting balloon versus Wingspan stent system in symptomatic intracranial high-grade stenosis: a single-center experience.' It was a single-center, open-label, retrospective cohort study of 19 patients with symptomatic atherosclerotic intracranial high-grade stenosis treated with either Elutax DEB (drug eluting balloon) or Wingspan Stent from a tertiary stroke center in Switzerland.

Results: Eight patients received Elutax DEB. Median clinical follow-up was 10 months for the Wingspan Stent and 9.5 months for Elutax DEB (P=0.36). No differences were found in the clinical baseline characteristics, with a median stenosis grade of 80% for the Wingspan stent and 81% for the Elutax DEB (P=0.87). The compound endpoint 'ischemic re-event and/or restenosis' was significantly lower for Elutax DEB (13% vs 64%; P=0.03, OR 0.08 (95% CI 0.007 to 0.93; P=0.043) than for the Wingspan stent.

Compared to previous cardiac hardware Elutax DEB is easy to navigate intracranially and allows delivery of paclitaxel within 30 seconds, which inhibits the ICAD/plaque regrowth. DEB angioplasty is indicated in symptomatic ICAD and stenosis of 70% or more. This study suggests that Elutax DEB angioplasty for ICAD is safe and with less complications as compared to intracranial stenting. This promising treatment option should undergo bigger trials and evaluations.

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ORIGINAL ARTICLE

Systematic review of drug eluting balloon angioplasty for arteriovenous haemodialysis access stenosis

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ABSTRACT

Background: Native or prosthetic arteriovenous (AV) fistulas are preferred for permanent haemodialysis (HD) access. These are marked with circuit steno-occlusive disease leading to dysfunction or even failure. Late failure rates have been reported as high as 50%. Standard angioplasty balloons are an established percutaneous intervention for HD access stenosis. Reported restenosis rates remain high and practice guidelines recommend a wide 6-month primary patency (PP) of at least 50% for any intervention. Neointimal hyperplasia is one of the main causes for access circuit stenosis. Drug eluting balloon (DeB) angioplasty has been proposed as an alternative intervention to reduce restenosis by local drug delivery and possible inhibition of this process.
Purpose: To systematically assess the reported efficacy and safety of DeB angioplasty in percutaneous management of prosthetic and autologous HD access stenosis.
Methods: Protocol for the review was developed following the PRISMA-P 2015 statement. An electronic database (Medline, EMBASE, Clinical Trials.gov and Cochrane CENTRAL) search was conducted to identify articles reporting on the use of DeB intervention in HD AV access. Backward and forward citation search as well as grey literature search was performed. The MOOSE statement and PRISMA 2009 statement were followed for the reporting of results. Data from the included studies comparing DeBs with non-DeBs were pooled using a random effects meta-analysis model and reported separately on randomised and non-randomised studies.
Results: Six studies reported on 254 interventions in 162 participants (mean 27 ± 10 SD). The pooled mean and median duration of follow-up was 12 and 13 months (range 6-24 months). These comprised two randomised control trials (RCTs) and four cohort studies. Participant's mean age was 64 ± 5 years and 61% were male. Target lesions (TLs) ranged from under 2 mm to 5.9 mm and 51 were reported as de novo stenosis. Device failure described as wasting of the DeB was reported in two studies (55% and 92.8%). At 6 months TL PP was reported between 70% to 97% for DeBs in the RCTs and cohort studies, and 0% to 26% for non-DeBs. TLs treated with DeBs were associated with a higher primary patency at 6 months as compared to non-DeB balloons (RCTs: odds ratio [OR] 0.25, 95% CI 0.08 to 0.77 and I^2 = 19%, cohort studies: OR 0.10, 95% CI 0.03 to 0.31 and an I^2 = 20%). No procedure-related major or minor complications were reported.
Conclusions: Current literature reports DeBs as being safe and may convey some benefit in terms of improved rate of restenosis when used to treat AV access disease. However, this body of evidence is small and clinically heterogeneous. A large multicentre RCT may help to clarify the role of DeBs in the percutaneous treatment of AV HD access stenosis.

Keywords: Angioplasty, Arteriovenous fistula, Drug coated material, Drug eluting balloon, Meta-analysis, Systematic review

Introduction

Native or prosthetic arteriovenous (AV) fistulas are preferred for permanent haemodialysis (HD) access as compared to central venous catheters (1-4). These are marked with steno-occlusive disease that leads to access dysfunction and inadequate HD. Late failure rates have been reported as high as 50% (5, 6). Neointimal hyperplasia (NIH) is one of the main causes for access stenosis and resultant failure (7-9). Standard angioplasty balloons are an established percutaneous intervention in access stenosis management. Balloon dilation results in intimal trauma and ensues a cycle of hyperplastic repair and possible further stenosis (10). Reported restenosis rates are high and practice guidelines recommend a wide 6-month access primary patency of at least 50% for any intervention (1-4). Recurrent stenosis and access dysfunction require repeat intervention. This translates in increasing morbidity and healthcare cost (11-13). Access options are limited and further diminish

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with each fistula failure. With conventional dilatation and local drug delivery for NIH, drug eluting balloon (DeB) angioplasty has been proposed as an alternative to reduce time to restenosis in AV access intervention (10, 14, 15).

Objectives

Local delivery of anti-proliferative drugs with coated materials such as balloons and stents have shown promising results in the coronary and peripheral circulation (16-19). Reducing rates of re-intervention may provide benefit of reducing risk from multiple interventions, repeat hospitalizations and perhaps improve long-term patency rates. The safety and efficacy of DeBs in HD access intervention is unclear. The aim of this study is to systematically assess the reported efficacy and safety of DeB angioplasty in percutaneous management of prosthetic and autologous HD access stenosis.

Methods

Study selection

The review advisory group (RAG) developed a protocol for the review following the PRISMA-P 2015 statement (20). Details of the RAG, including their expertise, were provided to the editors of this Journal. The MOOSE and PRISMA statements were followed for the reporting of results (21, 22). Data extraction tables were predefined prior to literature search. An electronic database search strategy with specific keywords, MeSH terms and text words was developed. This was used to identify landmark papers from relevant electronic databases (Medline, EMBASE and the Cochrane Central register of controlled trials). In conjunction with a research librarian, a final strategy was developed and applied (Appendix with search strategies was provided to editors of this Journal). Search was limited to English language and to time period from 1990 to present. Following duplicate removal, abstracts thus identified were screened online, in duplicate and following pre-set eligibility criteria, using Abstrackr® (23). All disagreements were discussed between the screening authors and the RAG. Full text articles were also reviewed in duplicate. Backward and forward citation search of identified full text articles using Google Scholar® was carried out. Grey literature search was guided by the RAG and included content experts. Pre-set criteria for inclusion and exclusion were based on patient population, target disease and index treatment.

Data collection and analysis

Data were extracted in duplicate for each study and populated predefined tables in Microsoft Excel® for Windows® (Microsoft, Redmond, WA, USA). All disagreements and changes were discussed between screening authors and the RAG. Data collection tables were drafted prior to analysis. Primary outcomes were target lesion revascularisation (TLR) rate comparison and access survival. Data were imported into RevMan (RevMan Version 5.2, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) for further synthesis and analysis. Analysis of the randomised controlled trials (RCTs) and cohort studies was carried out separately, following practical guidelines for inclusion of non-randomised trials (24, 25). Where there were concerns regarding missing data, contact with article authors was advised by the RAG. Pooled means and medians for continuous outcome variables was carried out and included range and standard deviation. The odds ratio (OR) for each outcome was calculated from individual studies and pooled with the Mantel-Haenszel random-effects method using RevMan. As selection bias can be a feature of cohort studies, this statistical model was decided to be an appropriate measure of outcome. Statistical heterogeneity was assessed with the Chi^2 test, with p values <0.10 suggesting significant heterogeneity. Inconsistency across the trials was assessed using I^2, where I^2<25% suggests mild, I^2 between 25% and 50% suggests moderate, and I^2>50% suggests extensive statistical inconsistency. Risk of bias assessment was carried out in duplicate using questionnaire assessment provided within RevMan. Results were matched for disagreements and resolved by consensus between authors and the RAG. Publication bias was visual inspection in Deeks' funnel plot. Details of pre-planned subgroup analysis, investigation of heterogeneity and sensitivity analysis were provided to editors of the Journal in following the PRISMA-P statement in the protocol of the study.

Results

Search results are provided in the PRISMA flow diagram (Fig. 1). After removal of duplicates, 638 abstracts were screened. Abstracts were excluded at this stage if they did not meet the pre-set inclusion and exclusion criteria. In total, nine full text articles were reviewed for eligibility. One was excluded as being a publication from the same group with duplicate data, two were reporting on the wrong target disease and two were in the wrong population. Following backward bibliographic and forward citation search and grey literature search, one further article was included.

Description of studies

The use of DeBs was assessed in a total of six original studies published literature (26-30). These collectively reported on 254 interventions in 162 participants (mean 27 ± 10 SD). The pooled mean and median duration of follow-up was 12 and 13 months (range 6-24 months). There were two single-centre RCTs which compared the use of DeBs for recurrent stenosis with standard angioplasty balloons. The remaining were single-centre prospective or retrospective cohort studies.

Randomised controlled trials

The first trial, the "Drug Eluting Balloon Angioplasty for Dialysis Access Treatment" trial randomised 40 patients with venous outflow stenosis between the intervention and control arms (31). They used an IN.PACT balloon dilation catheter (Invatec-Medtronic, Brescia, Italy) for the intervention arm and Ultra-Thin Diamond and Blue Max PTA (Boston Scientific, Natick, MA, USA), Profiler (Angiodynamics, Latham, NY, USA), or Dorado PTA balloon dilator catheter (Bard Peripheral Vascular, Tempe, AZ, USA) for the control arm patients. The

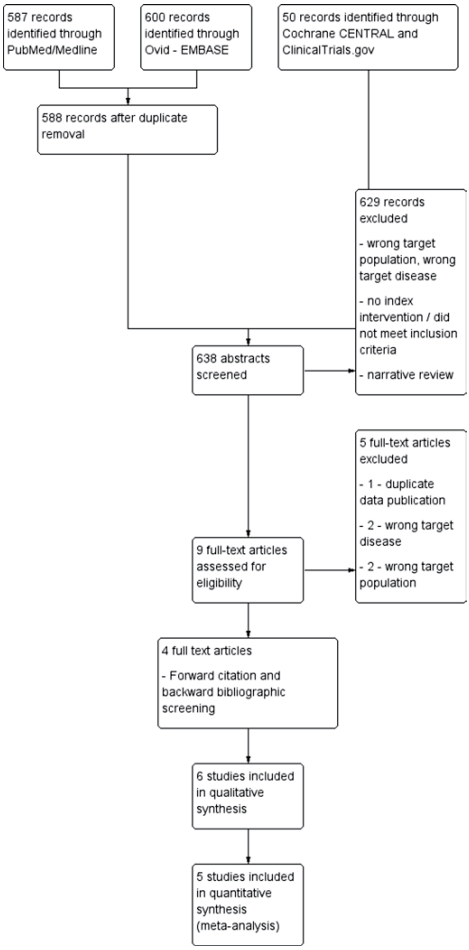

Fig. 1 - PRISMA flowchart of study.

authors described device failure as a need for further post-dilation after use of a DeB, because of suboptimal angioplasty. Technical success was a <30% residual stenosis diameter measured immediately after angioplasty regardless of post-dilation. The second trial, the "Prospective Randomized Trial Comparing DEB Versus Conventional PTA for the Treatment of HD AVF or AVG stenoses (DEBAPTA)" trail randomised 30 patients with a recurrent stenosis anywhere along the access circuit (Tab. I). They used the IN.PACT balloon dilation catheters (Invatec-Medtronic, Brescia, Italy) and compared to conventional balloon. The author described anatomical success as <30% diameter measured immediately after angioplasty.

TABLE I - Characteristics of randomised controlled trials included in analysis

	Kitrou et al (29); Katsanos et al (31)	Teo et al (30)
Study type	**RCT[1], single-centre**	**RCT[1], single-centre**
Number of patients	40	30
Level of TL	Venous outflow	NS
Used for HD	At least 1 session of HD	> 3 months post-formation
Recurrent or de novo	NS	Recurrent
Inflation time	1 min at nominal pressure	NS
Pre- and post-dilation	No predilation post-dilate if necessary	NS
Study device and substance	IN.PACT®[2] FreePac[3]	IN.PACT®[2] FreePac[3]

RCT = randomized controlled trial; TL = target lesion; SG = stent graft; HD = haemodialysis; NS = not stated.
[1] Detailed study protocol available at clinicaltrials.gov and Cochrane register of clinical trials.
[2] IN.PACT® balloon dilation catheters (Invatec-Medtronic, Brescia, Italy).
[3] FreePac 3 µg/mm² a paclitaxel-eluting formulation that contains hydrophilic urea paclitaxel.

Cohort studies

Two prospective studies reported on juxta-anastomotic and venous outflow stenosis intervention; however, one of these studies did not have a comparator arm (28, 32). The results of this non-comparison study reported on survival after radio-cephalic fistulae juxta-anastomotic intervention, and are not included in the meta-analysis (Tab. II). One retrospective cohort reported on the results of a DeB made in-house for non-malignant central venous stenosis (26). The authors reported their experience of using conventional balloons as well as high pressure and cutting angioplasty balloons and compared it to DeBs. The last cohort reported from a prospectively collected database. They reported its use in the case of in-stent stenosis for nitinol stents placed along a vascular access circuit (27). Both functioning and non-maturing fistulas were included in their results (Tab. III).

Clinical outcomes and risk of bias

DeBs were not associated with any major or minor complications. Procedural success rates were reported as 100% across the studies. Anatomical success or failure, device failure or success was described in the studies as wasting of the DeB with or without further post-dilation. In the two RCTs, this was 55% (n = 11/20) and 92.8% (n = 13/14). The second RCT also reported on device failure in the comparator group (81.3% n = 13/16). Target lesions (TLs) ranged

TABLE II - Cohort study patency and survival, not included in meta-analysis

	Time period	TL Primary patency	TL Secondary patency	VA Primary patency	VA Secondary patency
Patanè et al 2014 (28)	6 months	96.1	100	96.1	NS
	12 months	90.9	100	81.8	95.41
	24 months	57.8	94.7	57.8	94.7

TL = target lesion; VA = vascular access; NS = not stated.

TABLE III - Characteristics of cohort studies included in analysis

	Lai et al (32)	Swinnen et al (27)	Massmann et al (26)
Study type	**Prospective**	**Retrospective**	**Prospective**
No. of patients	10	31	25
Level of TL	RC swing	If suitable for DeB	Central venous
Used for HD	NS	On HD = 28 non maturing = 3	All
Recurrent or de novo	Recurrent	Recurrent	Recurrent
Inflation time	1 min	NS	1 min
Pre- and post-dilation	Both	Predilated only	Both[1]
Study device and substance	SeQuentPlease*[2] PACCOCATH*[3]	IN.PACT*[4] FreePac[5]	Custom-made[6] Elutax-SV*[7]

RC = radiocephalic; HD = haemodialysis; NS = not stated.
[1] Post dilated if significant wasting of balloon.
[2] SeQuent Please® (B Braun, Berlin, Germany) balloon catheters.
[3] PACCOCATH – (Bayer Shering Pharma AG, Berlin, Germany) coating is a mixture of iopromide and paclitaxel.
[4] IN.PACT® balloon dilation catheters (Invatec-Medtronic, Brescia, Italy).
[5] FreePac 3 µg/mm^2 a paclitaxel-eluting formulation that contains hydrophilic urea paclitaxel.
[6] Custom made using standard over-the-wire.
[7] Elutax-SV - paclitaxel 2 µg/mm^2 (Aachen Resonance, Aachen, Germany).

from under 2 mm to 5.9 mm and 51 were reported as de novo stenosis. At 6 months, TL primary patency was reported between 70% to 97% for DeBs and 0% to 26% non-DeBs. TLs treated with DeBs were associated with a higher primary patency at 6 months as compared to non-DeB balloons (RCTs: OR 0.25, 95% CI 0.08 to 0.77, p for statistical heterogeneity = 0.27 and I^2 = 19%, cohort studies: OR 0.10, 95% CI 0.03 to 0.31, p for statistical heterogeneity = 0.29 and an I^2 = 20%), (Fig. 2). A similar trend was observed at 12 months with a proportional increase in number of events lower in the DeB group as compared to the control group. This was with a lower number of patients, as not all of the studies had 12-month follow up data reported (Fig. 3). Despite the overall beneficial effect, a wider confidence interval and possibly a reduction of longer-term benefit was noted for the studies at 12 months. Performance and detection bias was considered as high in the non-RCTs. Reporting bias was considered as high or unclear. Risk of bias assessment of the RCTs was low 57% (n = 8/14 questionnaire assessment) or unclear 43% (n = 6/14). The cohort studies were assessed as having a high selection, performance and detection bias (57%, 12/21) (Figs. 2, 3). Visual assessment of publication bias with Deeks' funnel plot is provided in Figure 4 showing the variable results across the studies.

Discussion

Neointimal hyperplasia (NIH) in AV dialysis access is one of the main causes of stenosis and circuit dysfunction or failure. Its pathogenesis is well described in literature as being divided into upstream and downstream events (7, 33). The initial upstream events not only refer to the trauma of surgical creation, but also to the ongoing repeated dialysis needle injury, percutaneous intervention, endothelial dysfunction due to uraemia and circuit haemodynamic disturbances. These in turn lead to downstream endothelial injury and migration of smooth muscle cells (SMCs). For an angioplasty balloon to be effective, baric dilation has to tear the intimal or neointimal layer at the level of the stenosis. Part of the internal elastic lamina and tunica media may also be effectively ruptured in order to avoid elastic recoil of the stenosis. This mechanical trauma is followed by a biological cascade of events for repair of the vessel through formation of a neointima (34). Endothelial cells (ECs) regulate further progression by release of nitric oxide. This decreases the recruitment of inflammatory cells and collagen synthesis by vascular SMCs (35). ECs can lose their ability to release nitric oxide as result, and the neointima formed may be hyperplasic, and in turn result in reoccurrence of the stenosis (34, 36). NIH has also been noted in specimens from immature failing AV fistulas (37). DeBs are coated with

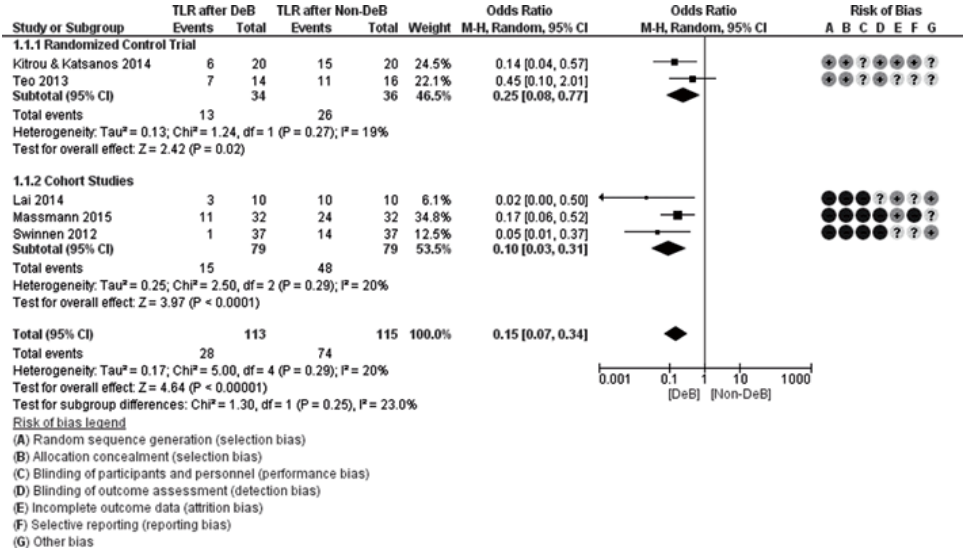

Fig. 2 - Analysis of target lesion revascularisation at 6 months using random effect model. Results of the risk of bias assessment for each study meta-analysed is also included with legend. TLR = target lesion revascularisation; M-H = Mantel-Haenszal model; CI = confidence interval.

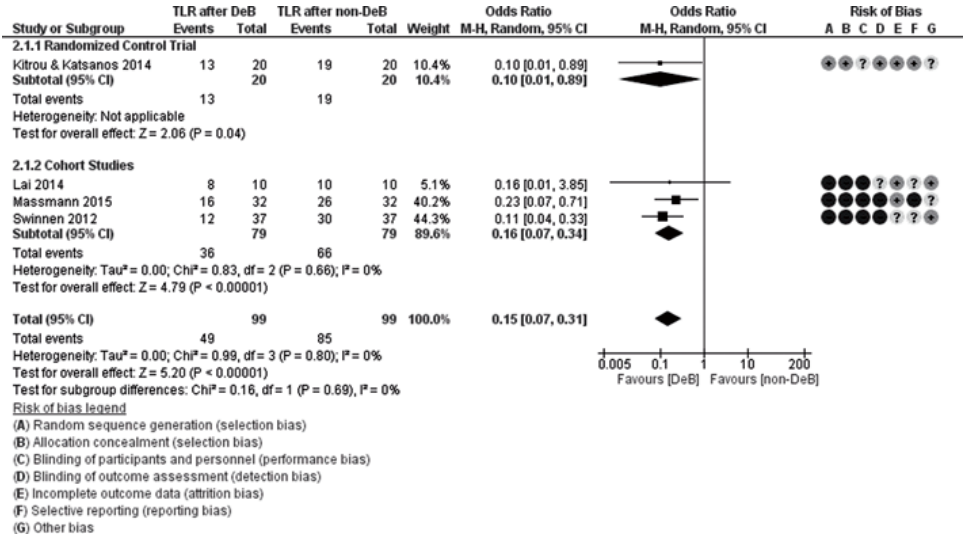

Fig. 3 - Analysis of target lesion revascularisation at 12 months using random effect model and risk of bias assessment results.

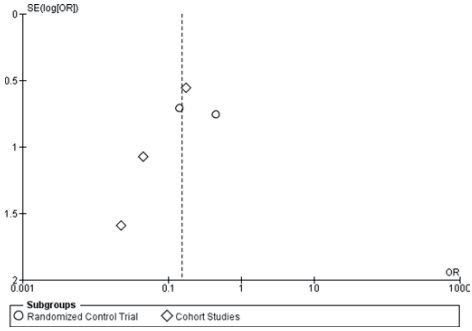

Fig. 4 - Deek's funnel plot of all included studies.

lipophilic rapidly absorbing, cytostatic anti-neoplasic substance. Experimental and *in vitro* studies of AV animal models have shown a sustained antiproliferative effect on vascular SMCs (14, 38-40).

Several publications have commented on safety and a possible superior efficacy of using DeBs in the peripheral and coronary circulation (18, 19, 41). Recent trends from these has peaked interest in their use for dialysis access intervention (10, 42). Their use has anecdotally been reserved for lesions that maybe considered difficult to treat due to recurrence. Our study aimed to present the first summation of its use in AV dialysis access to date in literature and perhaps clarify if further cautious exploration could be advocated. Overall, the use of DeB as compared to non-DeB may confer a benefit by reducing time to re-stenosis and subsequent intervention. Greater benefit was noted in the non-randomised studies; however, the risk of selection bias was understandably higher. At 12 months, the confidence interval for interpretation of beneficial results from RCTs was wider than at 6 months. Whether this would implicate an impact on survival of access circuits will require longer-term follow-up data.

Currently available studies had clinical heterogeneity with non-uniform level of intervention. Larger subgroup exploration may help in identifying lesion characteristics most or least responsive to DeBs. Important subgroups that were mentioned in literature include: fistula fashioning - radiocephalic, brachiocephalic, brachiobasilic, etc.; level of stenosis: juxta-anastomotic, outflow, cephalic arch, central veins; pre- and post-dilation of treated lesions; characteristics of fistula and lesion: primary, recurrent, post-thrombosis, multiple level, mature fistula being used, immature fistula not being used; patient clinical diversity derived from past medical history (43-45). Although these were proposed to be undertaken at protocol development stage, data available from studies could not be explored due to small total cohort size. Other confounders that could be argued include use of different surveillance methods for detection of restenosis (46). These can include clinical examination, dialysis parameters, ultrasonography, CT and MR imaging, or even angiography. With each modality, risks versus benefits and accuracy have to be weighed. An example could be contrast administration in a pre-dialysis patient with residual renal function, or even cumulative radiation exposure (47, 48). Utilising the same clinical and imaging inclusion criteria of a target lesion, for both primary and repeat intervention, could aide in translation of trial results. Functional and clinical parameters in association with imaging have been recommended (46). Further studies may consider inclusion of these variables for exploration. In one study design, the comparator intervention was within the same patient access circuit. This may conflict in outcome results as time to thrombosis is an important outcome measure and multiple level disease would carry a higher risk. Our meta-analysis has several limitations. It is at present underpowered to detect differences and there is clinical heterogeneity. A potential signal of benefit does advocate exploration. Further carefully planned studies may gather to form a stronger body of evidence and repeat meta-analysis with planned subgroup and sensitivity analysis would be beneficial.

Authors' conclusions

Current literature suggests DeBs as safe and may convey some benefit in terms of improved rate of restenosis when compared to standard angioplasty balloons when used to treat AV access disease. However, this body of evidence is small and there is clinical heterogeneity. Interpretation of results from cohort studies is recommended with an appropriate degree of caution. Adequately powered, larger multicentre RCTs may help to clarify the role of DeBs in the percutaneous management of arteriovenous haemodialysis access stenosis.

Disclosures

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Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

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Aims Drug-eluting devices (DED) represent a well-established therapy being widely used for endovascular revascularization (EVR) of peripheral vessels. Recent data indicate a two-fold increased long-term mortality in patients treated with paclitaxel-based DED. The subsequent safety concerns affected international regulatory authorities to enunciate several alerts for further application of DED.

Methods and results In 9.2 million insurants of the German BARMER Health Insurance, data on the application of paclitaxel-based drug-eluting stents (DES) and drug-coated balloons (DCB) were retrieved from their introduction on the market in 2007 until present. All patients with first EVR between 2007 and 2015 were indexed and followed until 31 December 2017. Each subsequently applied DES, DCB, bare-metal stent, and uncoated balloon was included in further analyses. Multivariable Cox regression analysis considered potential non-linear time-dependent hazard ratios (HRs) of DES and DCB over 11 years. We identified 64 771 patients who underwent 107 112 EVR procedures using 23 137 DED. Multivariable Cox regression analysis showed paclitaxel-based DES not to be associated with increased long-term mortality for over 11 years past application (all $P > 0.057$). DCB was associated with decreased long-term mortality for the first year past application (HR 0.92; $P < 0.001$), and indifferent correlation in the years thereafter (all $P > 0.202$).

Conclusion Our real-world analysis showed no evidence for increased mortality associated with paclitaxel-based DED for over 11 years.

Keywords Drug-eluting stent • Drug-coated balloon • Paclitaxel device • Endovascular revascularization • Lower extremity artery disease • Patient safety

Introduction

In the last decade, the technology of drug-eluting devices (DED) for endovascular therapy of patients with lower extremity artery disease (LEAD) rapidly developed. Since its introduction on the US market in 2012,[1–3] the anti-proliferative drug paclitaxel became widely accepted as a coating substance of drug-eluting stents (DES) and drug-coated balloons (DCB).[1,4–7] Randomized clinical trials (RCTs) showed promising results for DES on small-sized selected cohorts to improve late-lumen loss and restenosis rates compared to conventional angioplasty (plain old balloon angioplasty, POBA) or nitinol stents (bare-metal stent, BMS).[1,6,8,9] Unlike DES that release their drug coating over a period of 2–4 weeks to the intimal endothelial layer, DCB-mediated paclitaxel application is a one-off procedure leaving nothing behind. Despite critical voices mainly in the face of weak clinical efficacy and cost-effectiveness,[10,11] DED of various designs expand on the international market.[7,12] Today, DED have become a recommended and commonly used tool for peripheral endovascular revascularization (EVR)[13] exceeding annually 55 000 implanted DCB and over 6600 DES (thereof 97% paclitaxel-eluting) alone in Germany (Federal Statistical Offices DESTATIS, 2016).[14]

Lately, a serious debate on the sensitive issue of patient safety in the use of DED was brought up by unexpected results of a meta-analysis on 28 RCTs ($n = 4663$ patients, thereof 2552 treated with

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DED).[15] The authors stated an increased risk of all-cause death at two [odds ratio (OR) 1.68; 95% confidence interval (CI) 1.15–2.47] and 4–5 years follow-up (FU; OR 1.93; 95% CI 1.27–2.93) by use of paclitaxel-coated compared to uncoated devices in femoro-popliteal LEAD.

As a consequence, two ongoing major RCTs investigating DED technology (BASIL-3 ISRCTN14469736; SWEDEPAD NCT02051088) halted recruitment.[16] Companies of the vascular device sector endeavour to provide preliminary patient-level data in order to address safety concerns of their products.[17] From official site, the US Food and Drug Administration (FDA) released a recommendation appealing for critical indication and informed patient consent in the use of DED,[18] to which international regulatory authorities were further referring.[19] In a recent update, the FDA again tightened its recommendations as a result of preliminary long-term analyses of the three critical RCTs, showing a 'potentially concerning signal of increased long-term mortality in study subjects treated with paclitaxel-coated products'.[20] According to the revalidation of the original trial data, the 5-year mortality risk of DED was 20.1% vs. 13.4% in non-DED treated patients ($n = 975$). However, the FDA stated persistent doubts in the interpretation of these results due to relevant limitations, most notably the small number of long-term cohorts.

These precautions in the use of state-of-the-art technology reflect the current high uncertainty in the face of the pre-eminent importance of patient safety. The ongoing debate points out the need for continuing critical surveillance of new technologies beyond its establishment in clinical routine. Administrative data related to national and health insurance claims may provide an effective approach to answer these demands.

Herewith, we present a real-world safety analysis on 64 771 patients that covers the entire period from the market introduction of DED until today. Our analysis evaluates if the use of paclitaxel-based DES and DCB represent a potential hazard for the actual non-idealised patients in which these devices were applied during the past decade. Exemplified on DED, our work shows the prospects of health services research to assess patient safety without undue delay.

Methods

The German reimbursement system governs the remuneration of healthcare services subject to encoded diagnoses (International Statistical Classification of Diseases, German Modification; ICD-10 GM) and procedures (German procedure classification; OPS) by means of the 'German Diagnosis Related Groups' taxonomy (G-DRG). This obligatory documentation and accounting system is specified and regulated in detail by mandatory coding instructions. Big data derived from national and health insurance claims such as the BARMER are characterized by high transsectoral integrity and validity.[21,22]

Patient selection

We were provided access to the anonymized insurance claims of ~9.2 million patients of the German BARMER Health Insurance. All patients who were encoded in-hospital balloon- or stent-assisted EVR of the lower limbs (OPS 8-836.0*, 8-836.f,g,t,s,h,j*, 8-840.0-5*, 8-841.0-5*, 8-848.0-5*; *codes 9,b,c,q,s) between 1 January 2007 and 31 December 2015 were indexed for further analyses. Patients aged <18 years at index ($n = 32$), with incomplete basic information ($n = 15$), pre-index period <12 months ($n = 456$), implausible exit of database ($n = 11$), or encoded DES of non-paclitaxel or unspecified drug-coating ($n = 519$) were omitted.

Patients were assigned to one of the four sub-groups in hierarchical order according to their first EVR procedure within the index period:

(1) Drug-eluting stents: if ≥1 DES procedure code (OPS 8-836.h*, 8-836.j*, 8-841.0-5*, 8-848.0-5*) combined with paclitaxel material code (OPS 8-83b.03-06) was used.
(2) Drug-coated balloon: if among the remaining patients a balloon angioplasty code (OPS 8-836.0*) combined with ≥1 DCB material code (OPS 8-83b.b2-5, 8-83b.ba-d) was used.
(3) Bare-metal stent: if among the remaining patients ≥1 stent procedure code (OPS 8-840.0-5*, 8-836.f,g,t,s*) was used.
(4) Plain old balloon angioplasty: if among the remaining patients a balloon angioplasty code (OPS 8-836.0*) without any DES, DCB, or BMS codes used.

The selection process including applied ICD-10-GM and OPS codes is presented in detail in the Supplementary material online, *Appendix Figure S1* and *Table S1*.

Cohort characterization

Baseline characteristics were determined for each subgroup according to primary and secondary diagnoses, and procedures during index-hospitalization and within the previous 24 months (*Supplementary Appendix Table S2*). Diagnoses include LEAD, chronic ischaemic heart disease, previous acute myocardial infarction, chronic heart failure, cerebrovascular disease, and ischaemic stroke, chronic kidney disease, hypertension, diabetes, dyslipidaemia, obesity, smoking, and cancer (Supplementary material online, *Appendix Table S2*). These were complemented by previous peripheral and coronary vascular procedures and previous amputation of the lower limbs. Notably, all patients were naive related to paclitaxel-coated peripheral devices, since these were not yet available previous to the index-period (before 2007).

Short-term outcome in the four treatment groups at index (DES, DCB, BMS, and POBA) was assessed based on 30-day mortality, amputations, and other complications (for detailed definitions by coding see Supplementary material online, *Appendix Table S2*).

Follow-up

All patients were continuously followed until death or end of follow-up (FU). All subsequent EVR procedures (inpatient and ambulatory) of individual patients were precisely recorded. For each EVR, the number of applied devices was determined by evaluation of the OPS matrix: the use of up to six BMS (OPS 8-840.0-5), up to six DES (OPS 8-841.0-5, OPS 8-848.0-5), and up to four DCB (OPS 8-83b.ba-bd) per EVR were separately encoded as described in Supplementary material online, *Appendix Table S1*. The cumulative number of applied DES and DCB served as estimate for patients' paclitaxel exposure. Data ascertainment reached until 31 December 2017, providing a median FU of 92 months (2760 days). FU time was 98.8% complete.

Statistical methods

Statistical methods are described in detail in the Supplementary material online, *Appendix*. In brief, logistic regression analyses of 30-day all-cause mortality tested each type of index EVR in hierarchical order (DES, DCB, BMS, and POBA) to evaluate the association between DED and short-

term mortality. The model adjusted for the possible confounders age, sex, pre-existing cardiovascular risk factors, and comorbidities as described above.

To evaluate the association between DED and long-term mortality for up to 11 years FU, a multivariable time-dependent Cox regression analysis was performed that adjusted for patients' risk profile at index and during FU. Per definition, the outcome was the time from index EVR to all-cause death if not censored previously for reaching the end of FU, previous exit of the database ($n = 1020$), exceeding >10 EVR during FU ($n = 345$), or for being treated with a device coated with a drug other than paclitaxel ($n = 456$).

The multivariable Cox regression analysis included all devices that were applied during FU. For each individual device, the analysis accounted for its specific type (DES, DCB, BMS, and POBA) and application date. Particularly, the model allowed for a hazard of DED that is non-constant over time and may alter its effect on long-term mortality past device application. Thereby, also a potentially detrimental effect of DED in the later course of time would become verifiable despite a potentially beneficial effect in the early years or potential aggregation of subsequently applied devices. The hazard ratios (HRs) of individual devices of the same type showed no relevant differences in the time course so that in the final model devices of the same type were cumulated in yearly time intervals to serve as estimates of the patients' paclitaxel exposure. Elementary mortality HRs for each type of device is presented in annual intervals. Combined HRs for any scenario including multiple devices that were applied various years ago can be determined as the product of elementary HRs. Further details of the established Cox model are given in the statistical analysis plan (Supplementary material online, *Appendix*). All analyses were explorative and *P*-values are regarded as noticeable if $P \leq 0.05$. All statistical analyses were performed using SAS (version 9.4 for Windows, SAS Institute Inc., Cary, NC, USA).

Results

We identified 64 771 patients with an index procedure, defined as first EVR of the iliac and lower limb arteries between 2007 until 2015. DED applied in 5.1% of index EVRs with 2648 DCB (4.1%) and 676 DES (1.0%) procedures (*Table 1*, Supplementary material online, *Figure S1*).

Table 1 Patient characteristics at baseline according to index procedure

Characteristics	DES procedure (*N* = 676)	DCB procedure (*N* = 2648)	BMS procedure (*N* = 28 290)	POBA procedure (*N* = 33 157)	All (*N* = 64 771)	*P*
Mean age (year)	73	73	70	74	72	<0.001
Female sex, *n* (%)	293 (43.34)	1249 (47.17)	12 438 (43.97)	15 385 (46.40)	29 365 (45.34)	<0.001
Lower extremity artery disease, *n* (%)						
Lower extremity artery disease (any)	622 (92.01)	2603 (98.30)	26 830 (94.84)	31 416 (94.75)	61 471 (94.91)	<0.001
Lower extremity artery disease (Rutherford Stage 1–3)	364 (53.85)	1517 (57.29)	17 952 (63.46)	15 391 (46.42)	35 224 (54.38)	
Lower extremity artery disease (Rutherford Stage 4)	83 (12.28)	268 (10.12)	3161 (11.17)	3527 (10.64)	7039 (10.87)	
Lower extremity artery disease (Rutherford Stage 5)	88 (13.02)	409 (15.45)	2627 (9.29)	5688 (17.15)	8812 (13.60)	
Lower extremity artery disease (Rutherford Stage 6)	86 (12.72)	407 (15.37)	3059 (10.81)	6763 (20.40)	10 315 (15.93)	
Previous procedures of lower limb arteries, *n* (%)						
Endovascular revascularization	16 (2.37)	76 (2.87)	666 (2.35)	1256 (3.79)	2014 (3.11)	<0.001
Vascular surgery	42 (6.21)	187 (7.06)	1740 (6.15)	2643 (7.97)	4612 (7.12)	<0.001
Amputation	19 (2.81)	71 (2.68)	467 (1.65)	1278 (3.85)	1835 (2.83)	<0.001
Arteriosclerotic co-diagnoses, *n* (%)						
Coronary heart disease	346 (51.18)	1250 (47.21)	13 235 (46.78)	17 222 (51.94)	32 035 (49.49)	<0.001
Previous myocardial infarction	90 (13.31)	318 (12.01)	3560 (12.58)	4405 (13.29)	8373 (12.93)	0.032
Previous coronary revascularization	65 (9.62)	218 (8.23)	2157 (7.62)	2562 (7.73)	5002 (7.72)	0.191
Cerebrovascular disease	239 (35.36)	906 (34.21)	9147 (32.33)	11 332 (34.18)	21 624 (33.39)	<0.001
Previous stroke	109 (16.12)	398 (15.03)	3684 (13.02)	5479 (16.52)	9670 (14.93)	<0.001
Cardiovascular risk factors, *n* (%)						
Atrial fibrillation or flutter	160 (23.67)	588 (22.21)	4548 (16.08)	8217 (24.78)	13 513 (20.86)	<0.001
Chronic kidney disease	207 (30.62)	801 (30.25)	6587 (23.28)	10 604 (31.98)	18 199 (28.10)	<0.001
Chronic heart failure	221 (32.69)	842 (31.80)	7295 (25.79)	11 656 (35.15)	20 014 (30.90)	<0.001
Diabetes mellitus	329 (48.67)	1306 (49.32)	11 589 (40.97)	17 409 (52.50)	30 633 (47.29)	<0.001
Diabetes mellitus (on insulin)	149 (22.04)	595 (22.74)	4337 (15.33)	8257 (24.90)	13 338 (20.59)	<0.001
Dyslipidaemia	512 (75.74)	1975 (74.58)	20 567 (72.70)	23 706 (71.50)	46 760 (72.19)	<0.001
Hypertension	614 (90.83)	2439 (92.11)	24 850 (87.84)	30 393 (91.66)	58 296 (90.00)	<0.001
Nicotine abuse	190 (28.11)	807 (30.48)	10 844 (38.33)	8062 (24.31)	19 903 (30.73)	<0.001
Obesity	158 (23.37)	646 (24.40)	6370 (22.52)	8619 (25.99)	15 793 (24.38)	<0.001
Cancer, *n* (%)	168 (24.85)	607 (22.92)	6197 (21.91)	7734 (23.33)	14 706 (22.70)	<0.001

BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; POBA, plain old balloon angioplasty.

Of those who had no DED at index ($n = 61\,447$), 5184 (8.4%) received at least one DED during FU, and 2064 patients had repeated DED exposure. Baseline characteristics of the four index cohorts are shown in *Table 1*. These illustrate relatively homogeneous subgroups in terms of age (average 71.5 years), sex (45.3% female), and cardiovascular comorbidity. LEAD was encoded in 94.9% of patients as the underlying reason for EVR, thereof 42.7% at critical stages of disease. Every second patient had coronary heart disease at baseline, one-third had cerebrovascular disease. Common comorbidities comprised arterial hypertension (90.0%), dyslipidaemia (72.2%), diabetes (47.3%), chronic heart failure (30.9%), and chronic kidney disease (28.1%). Within two years afore index, amputation of the lower limbs was performed in 2.8% of patients, and vascular surgery was performed in 7.1%. EVR previous to the index-procedure applied in 3.1% of patients, notably none of these with DED.

During the study, in total, 107 112 inpatient and ambulatory EVR procedures were identified, thereof 9401 DCB and 1395 DES procedures (10 796 DED procedures, 10.1%). These correspond to the use of 1973 DES and 21 164 DCB devices (in total ≥ 23 137 DED), accounting for 11.5% of all 200 681 devices being applied (Supplementary material online, *Appendix Figure S2*).

Acute outcomes

Observed 30-day mortality was 1.6% in DED vs. 2.0% in non-DED procedures (2.1% DES, 1.5% DCB, 1.6% BMS, 2.4% POBA; $P < 0.001$; *Table 2*). Multivariable logistic regression was established and detailed model performance is shown in the Supplementary material online, *Appendix Figure S3*). The logistic regression analysis allowing for co-prevalent risk factors showed adjusted 30-day mortality to be independent from the use of DED, both for DES (vs. BMS: OR 0.93, $P = 0.790$) and DCB (vs. POBA: OR 0.79, $P = 0.131$) (*Figure 1*).

Long-term outcomes

Over the entire study period, 41.9% of patients died. A time-dependent Cox regression analysis was performed that adjusted long-term mortality for DED application and cardiovascular risk indicators at baseline and during FU (*Figure 2*). The performance of any stent EVR was associated with increased mortality risk within the first two years (first and second year: HR 1.03; $P = 0.004$ and $P = 0.013$), which was not verifiable in the following years. For the use of paclitaxel-based DES, a tendency towards increased hazards became apparent beyond the fourth year past application. However, these associations with increased long-term mortality could not be statistically confirmed for up to 11 years after DES application (HR between 0.64 and 1.10; all $P > 0.057$). Balloon angioplasty was associated with increased mortality for the first year past balloon EVR (HR 1.10; $P < 0.001$). Paclitaxel coating was not associated with increased long-term mortality for up to 11 years past DCB application. On the contrary, DCB use was associated with decreased mortality for the first year (HR 0.92; $P < 0.001$), which however became irrelevant in the subsequent years. The mortality hazard for the use of multiple devices, e.g. repeated DED exposure, is the product of elementary hazards as illustrated in the example in *Figure 2*. Since none of the elementary hazards for DES or DCB reached statistical noticeability, also multiple DED exposure within the same time period will not result in a statistically noticeable increase of long-term mortality.

Discussion

Based on our analysis, from introduction to the market until present, the use of DED was not associated with exceeding death rates compared to non-DED. Therefore, our study debilitates current safety concerns resulting from previous findings.[15]

Our analysis on 64 771 patients and 107 112 peripheral interventions over a median time period of 92 months (7.6 years) implies high data validity and informational value of the presented results. Compared to the meta-analysis by Katsanos *et al.*[15] that resulted from small-sized selected cohorts of the underlying RCTs, our data reflect the unselected real-world patient collective to which the devices actually apply to. Our cohort is representative compared to

Table 2 In-hospital outcome according to index procedure

In-hospital outcome	DES procedure ($N = 676$)	DCB procedure ($N = 2648$)	BMS procedure ($N = 28\,290$)	POBA procedure ($N = 33\,157$)	All ($N = 64\,771$)	*P*
Cardiovascular events, *n* (%)						
Acute myocardial infarction	6 (0.89)	16 (0.60)	294 (1.04)	375 (1.13)	691 (1.07)	0.070
Acute stroke	<5 (<0.70)	8 (0.30)	140 (0.49)	228 (0.69)	378 (0.58)	<0.001
Lower limb complications, *n* (%)						
Amputation, any	46 (6.80)	183 (6.91)	1199 (4.24)	3282 (9.90)	4710 (7.27)	<0.001
Minor amputation	36 (5.33)	159 (6.00)	917 (3.24)	2605 (7.86)	3717 (5.74)	<0.001
Major amputation	10 (1.48)	24 (0.91)	282 (1.00)	677 (2.04)	993 (1.53)	<0.001
Other complications, *n* (%)						
Acute renal failure	18 (2.66)	40 (1.51)	394 (1.39)	591 (1.78)	1043 (1.61)	<0.001
Bleeding event	73 (10.80)	196 (7.40)	2257 (7.98)	3643 (10.99)	6169 (9.52)	<0.001
Infection including sepsis	15 (2.22)	32 (1.21)	288 (1.02)	595 (1.79)	930 (1.44)	<0.001
Death from any cause, *n* (%)	14 (2.07)	39 (1.47)	440 (1.56)	787 (2.37)	1280 (1.98)	<0.001

BMS, bare-metal stent; DCB, drug-coated balloon; DES, drug-eluting stent; POBA, plain old balloon angioplasty.

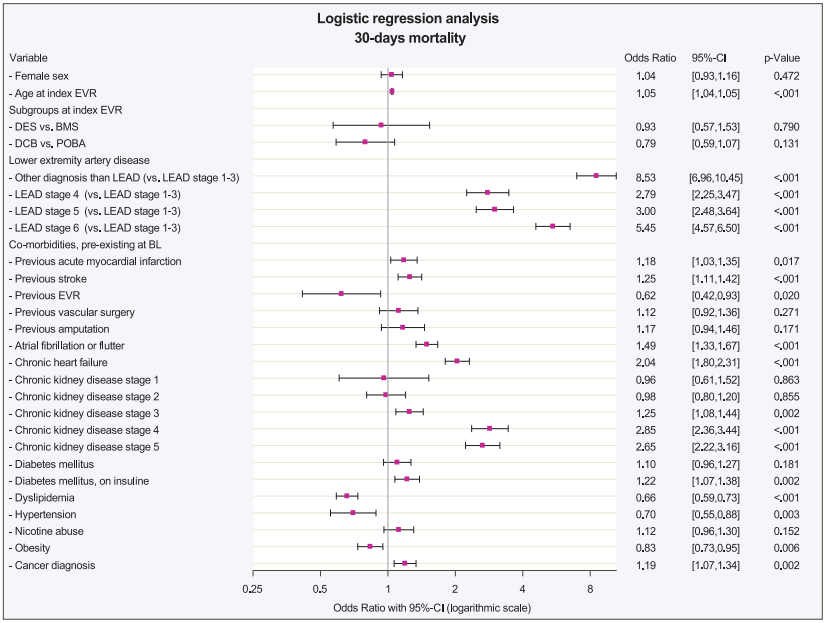


Figure 1 Thirty-day mortality adjusted for baseline risk. Thirty-day mortality after multivariable adjustment for baseline characteristics as assessed within 24 months previous to index EVR. Logistic regression model included co-prevalent cardiovascular risk factors, previous vascular procedures, as well as in-hospital complications and adverse events. Death (from any cause) at 30 days did not differ significantly between stent nor balloon angioplasty with vs. without paclitaxel (DES vs. BMS: OR 0.93, 95% confidence interval 0.57–1.53; $P = 0.790$; drug-coated balloon vs. POBA: OR 0.79, 95% confidence interval 0.59–1.07; $P = 0.131$). BL, baseline; BMS, bare-metal stent; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; EVR, endovascular revascularization; LEAD, lower extremity artery disease; OR, odds ratio; POBA, plain balloon angioplasty.

other large epidemiological studies in terms of age, sex, cardiovascular risk burden, and LEAD severity.[23,24]

Long-term mortality

Our database included a high percentage of patients with chronic limb-threatening ischaemia (CLTI 42.7%) which corresponds well with the 43.5% reported for German nationwide inpatient LEAD cases.[25] Since CLTI is associated with dramatically increased death rates ranging between 40% and 50% within 5 years,[21,24] this explains the observed 41.9% overall mortality during 7.6 years FU in our real-world cohort.

In contrast, Katsanos *et al.*[15] reported markedly lower mortality rates with 14.7% in DED and to 8.1% in non-DED at 4–5 years. The three underlying RCTs, ZILVER-PTX,[1] IN.PACT SFA,[3] and THUNDER[6] included in total $n = 268$ DCB, $n = 214$ DES, and $n = 403$ unspecified non-DED procedures. All procedures were performed on femoropopliteal lesions in patients at moderate LEAD Rutherford stages (ZILVER-PTX: 9% CLTI; IN.PACT SFA: 5.4% CLTI only Rutherford stage, RF 4; THUNDER: mean RF at index 3.1–3.4, no RF 6). Study protocols further limited risk and complexity of the vascular status, as for example, patients with low life expectancy, poor inflow or absence of at least one patent crural artery were excluded upfront from the trials. Importantly, analyses did not include potential subsequent EVR procedures involving paclitaxel exposure outside the frame of the studies.

The hereupon applied meta-analysis resulted in an almost two-fold increased mortality risk for DED (RR 1.93, 95% CI 1.27–2.93) and indicated an increasing risk per paclitaxel dosage. However, reasonable doubts on these results involve methodical issues such as lack of information on the original patient data and a relevant loss of FU in the RCTs. Moreover, a missing discrimination between stent and balloon EVR as well as statistical simplification of bail-out changeovers between treatment arms in ZILVER-PTX were discussed.[26]

Value of health claims data for safety concerns

Large-sized administrative data related to national reimbursement and/or health insurance claims may provide an advantageous approach for surveillance after regulatory approval to address patient

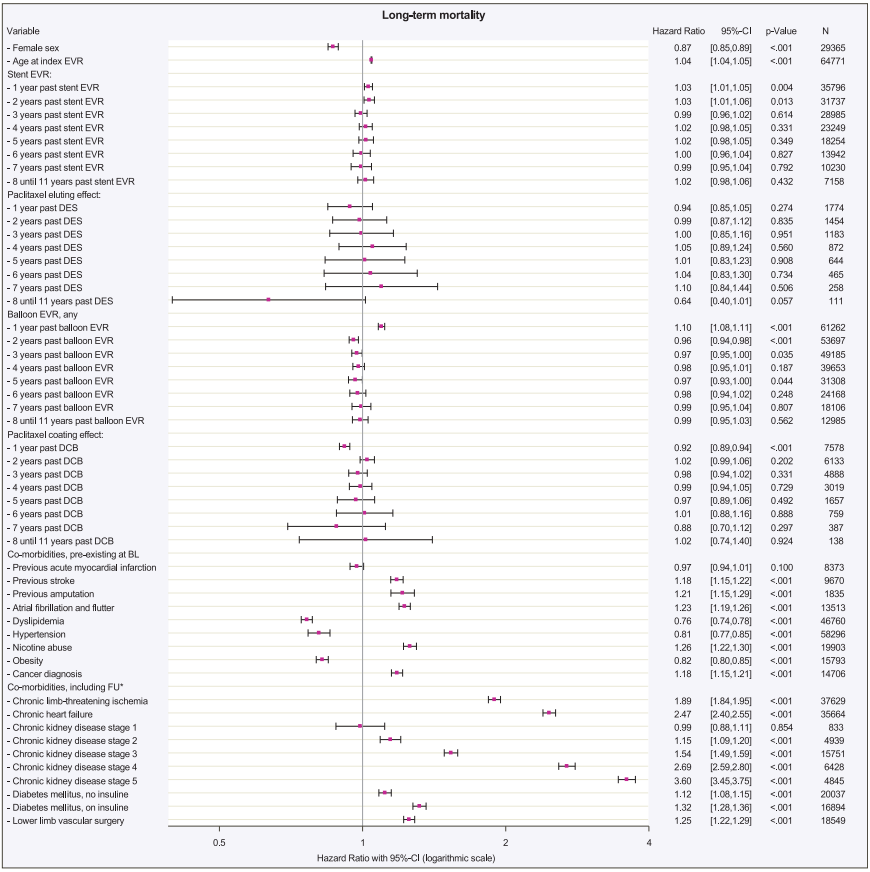
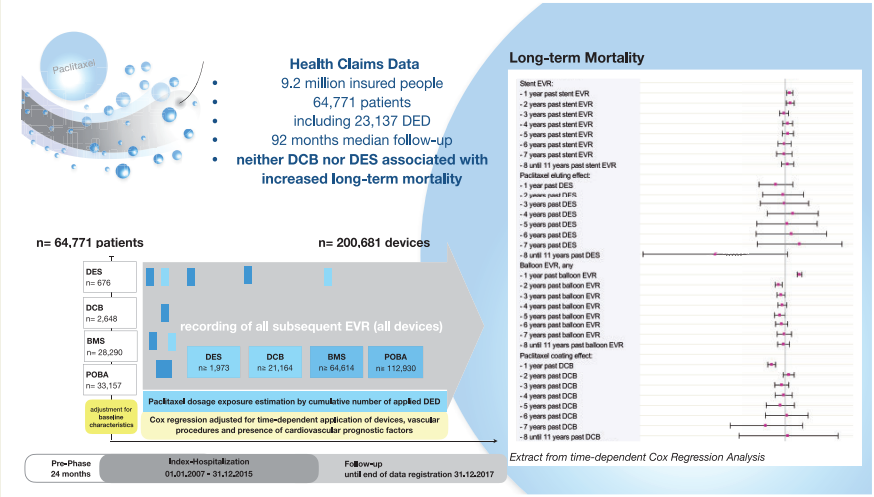


Figure 2 Time-dependent Cox-regression allowing for non-linear and time-dependent hazard ratio of the respective devices. All devices applied between 1 January 2007 and 31 December 2017 were included in the model. HRs for each type of device are given per application of one distinct device over annual time intervals. HR for stent EVR (any device) was increased for the first 2 years (both HR 1.03; $P = 0.004$ and $P = 0.013$), reflecting the procedural risk and general hazard being involved with the need for stent implantation. The additional effect by use of paclitaxel-based DES was not associated with increased mortality in up to 11 years past application. Likewise, balloon EVR (any device) was associated with evident increased mortality in the first year of application (HR 1.10; $P < 0.001$). Paclitaxel coating effect in DCB was associated with a protective effect in the first year of DCB application (HR 0.92; $P < 0.001$), which became irrelevant in the years thereafter. The HR of any combination of applied devices including use of multiple devices in different years and concomitant risk factors can be calculated by multiplying elementary HRs: e.g. a patient with previous stroke, diabetes without insulin and one DES 1 year ago plus two POBA 3 years ago compared to a patient without stroke, without diabetes, only one POBA 3 years ago and identical baseline characteristics (e.g. age and gender) has a HR = [1.18 (previous stroke) * 1.12 (diabetes w/o insulin) * 1.03 (1 stent one year ago) * 0.94 (DES) * 0.97^2 (two POBAs 3 years ago)]/[0.97 (1 POBA three years ago)] = 1.20/0.97 = 1.24. BL, baseline; CI, confidence interval; DCB, drug-coated balloon; DES, drug-eluting stent; EVR, endovascular revascularization; FU, follow-up period; N, number of patients at end of FU. *Time-dependent adjustment of covariates.



Take home figure Safety analysis of paclitaxel based drug eluting devices for application in peripheral arteries.

safety in the long-term. Based on 9.2 million insurants, respectively over 10% of the German population, our data represent the current practice in endovascular treatment of LEAD.

As expected from other trials,[27,28] acute complications and deaths during the first 30 days occurred at relatively low levels irrespective of the devices applied. In the long-term, the categorical risk being involved with medical indication for a repeated EVR was reflected in the slightly increased HR for stent and balloon application in the first year. However, thereafter the EVR the procedure itself had no negative impact on overall mortality anymore. Adjusting for an additional effect by the use of paclitaxel-based DED did not result in increased mortality risks.

DES analysis, based on 1973 encoded devices, indicated slightly decreased mortality in the first year past application. Thereafter, DES indeed trended towards hazardous risks although all of these missed statistical conspicuities. Given the relatively high share of DES (44% of DED cases) in the designated low-risk cohorts, the previous meta-analysis[15] fits in the greater picture drawn by our analysis. However, the reported hazardous effects were likely overweighted due to the afore-mentioned limitations.[26]

DCB, based on 21 164 encoded devices, were associated with an 8% decreased mortality hazard per applied DCB within the first year. Up to 8 years past application, a protective or hazardous association was not verifiable. Beyond the eighth year past DED application, the model faces the limitations of decreasing sample sizes for DES and DCB due to the timeliness of the index period.

Strengths and limitations

Strengths of our analysis are its large and comprehensive database of unselected real-world patients, covering the entire period of DED usage from its introduction on the market until today. Pursuant to the structure of the German health care system and legal framework the study contains no missing values. Since exact coding of each device of DES, BMS, and DCB trigger a markedly increase in reimbursement in the G-DRG-System, completeness of the applicable codes could be expected to be very high. The methodical approach of our analysis overcomes changeover between EVR treatment strategies during FU and further considered any aggregation of subsequently applied devices. To detect any possible detrimental effect of DED in the later course of time against a potential early benefit, the chosen model was also able to consider a non-linear time-dependent effect of DED changing its mortality HR over the time course.

Our study is limited by the general constraints in the use of secondary health care data as previously described in detail.[21] Specifically, real-world administrative data do not provide information on the underlying reason for DED treatment, representing a potential selection bias. Further, the restricted level of detail in some of the codes affected the present study: paclitaxel exposure was estimated by means of the cumulative number of each device. Up to six DES and a maximum of four DCB can be encoded per procedure. However, the collected numbers for DED as estimates for paclitaxel exposure are correct in all probability since the use of more than four DCB or six DES within the same procedure is certainly a rare exception. Further, the OPS coding system does not register the exact product and manufacturer; individual paclitaxel load or length of device are missing.

Our time-dependent Cox regression analysis cumulated devices of each type within annual time intervals. Preliminary working models showed that this methodological simplification was justified as the temporal course of the HR of each device proved to be independent

from the chronological order of its application. Finally, our explorative model needs to be validated externally. We will provide this confirmation in a timely manner in a subsequent publication.

Conclusions

In summary, our analysis found the use of DED to be safe for endovascular therapy of the lower limbs. Particularly with regard to long-term mortality, neither DCB nor DES was associated with increased risk compared to non-DED. Furthermore, our analysis exemplarily demonstrates the significance of health claims data for assessing urgent safety concerns without undue delay.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Image in intervention

Endovascular therapy of symptomatic high-grade stenosis of left internal carotid artery in C6 segment using Elutax "3" Neuro pDEB

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Intracranial atherosclerotic disease (ICAD) is a well-known cause of stroke and is responsible for approximately 5–10% of all strokes [1]. The annual risk of recurrent stroke in symptomatic ICAD is around 9–12% despite optimal medical treatment [2]. Patients presenting with symptomatic ICAD have been managed endovascularly (ET) for over two decades. Still, although initial results of such treatment were encouraging, the rates of periprocedural complications and restenoses were high, 15% and 34%, respectively [2].

Recently, in order to improve the results of ET, novel methods such as drug-coated balloons (DEBs) are increasingly used in these patients. The DEBs are routinely used for the treatment of coronary artery disease, as well as in patients presenting with peripheral arterial lesions. Intracranial arteries (IA) are a new target for this endovascular tool. Since IA differ from the coronary ones and those of the extremities, in terms of their morphology, there are some devices registered for this unique application. The Elutax "3" Neuro drug coated balloon (AR Baltic Medical, Vilnius, Lithuania), which is a hydrophilic balloon covered with paclitaxel trapped in a dextran matrix, is one such device specifically designed for neurovascular applications. Of note, according to the manufacturer, this balloon does not require predilation, since the loss of its unique resistant polymer during the navigation through lesions is not higher than 5%. The balloons are available on a rapid exchange catheter, diameter 1.5–6.0 mm and length 10–40 mm.

In this report we present a case of ET in a 57-year-old patient presenting with stroke resulting from atherosclerotic stenosis in the C5/C6 (clinoid/ophthalmic) segment of the internal carotid artery (ICA), who was managed with this specific endovascular device (first in Poland).

This patient presented with recurrent stroke of the left cerebral hemisphere. Angiography revealed a short critical stenosis in the C5/C6 segment of the left ICA (Figure 1 A) and also 60% stenosis in the C5 segment of the right ICA. Furthermore, there was no adequate collateral inflow to the left cerebral hemisphere from the right side.

Considering the previous history of this patient and angioarchitecture of his IA circle, we decided to address the lesion of the left ICA, endovascularly, using DEB and a proximal protection system. After introduction of the Mo.Ma 8F (Medtronic, Minneapolis, MA, USA) protection system, a Transcend wire (Boston Scientific, Natick, MA, USA) was navigated into the periphery of the left middle cerebral artery. One inflation of the 3.5 × 15 mm Elutax 3 Neuro balloon, inflated under the pressure of 6 atm for 30 s, was performed (Figure 1 B). Of note, the duration of the balloon inflation, in comparison with extracranial arteries, was relatively short. Still, the producer of this particular balloon recommends a 15 s inflation. Considering the characteristics of the lesion, we performed a longer inflation, yet the 30 s time also included a slow and gentle filling of the balloon. The final angiographic result of the procedure was good (Figure 1 C). The post-procedural course of this patient was uneventful. He was discharged home with a recommendation to use dual antiplatelet platelet therapy (DAPT) up to 6 months after the procedure. During the 6-month follow-up, the patient did not develop any new neurological symptoms, and the

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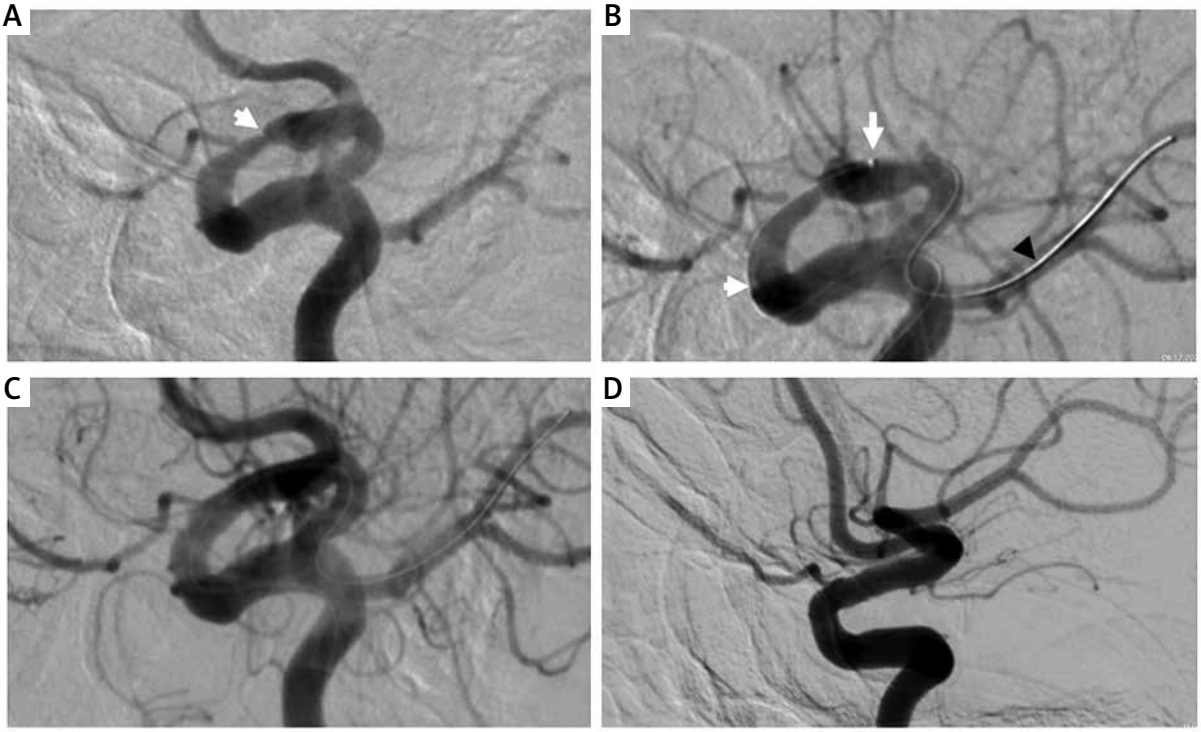

Figure 1. A – Critical stenosis of the left internal carotid artery in the C5/C6 segments (arrow), **B** – Elutax "3" Neuro drug coated balloon angioplasty at the site of the stenosis (balloon between white arrows, black arrow – guidewire in the middle cerebral artery), **C** – final result of angioplasty, **D** – follow-up angiography after 6 months

follow-up digital subtraction angiography examination after 6 months confirmed the good result of the procedure (Figure 1 D).

There are some technical issues associated with ET of such challenging cases that should be discussed. Implantation of stents in the intracranial segments of the ICA is associated with a high rate of severe complications, at the level of 5–15%. Therefore, the use of DEBs seems to be a promising alternative [3, 4]. There is also a high risk of periprocedural peripheral embolization; thus the use of proximal protection devices, which shield the brain during the procedure and allow for the use of any guidewire, seems indispensable. There are also some advantages of the Elutax "3" Neuro balloon. This device is dedicated to the treatment of lesions in the IA. It can also be used without prior predilation, which reduces the risk of dissection and the need for stent implantation [4]. Regarding postprocedural pharmacotherapy after the use of stents or DEB in IA, no widely accepted recommendations exist at the moment. In our patients we routinely use DAPT for 6–12 months. In this case, we asked the patient to take DAPT for 6 months, until the follow-up; then, he received only aspirin.

Finally, it should be emphasized that although ET of symptomatic stenosis of intracranial segments of the ICA can be a life-saving procedure, it should be performed exclusively in centers with high expertise in carotid interventions.

Conflict of interest

The authors declare no conflict of interest.

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Review article

Application of drug-coated balloons for intracranial atherosclerosis disease: a systematic review

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ABSTRACT

Background: Although percutaneous transluminal angioplasty and stenting (PTAS) was an effective and safe alternative treatment for severe intracranial atherosclerosis disease (ICAD), the high rate of restenosis remained a major issue for this endovascular procedure. Recently, the application of drug-coated balloons (DCB) in ICAD was developed to reduce restenosis. This systematic review aimed to evaluate the efficacy and safety of DCB angioplasty for ICAD.

Methods: We searched relevant databases for eligible studies enrolling ICAD patients treated with DCB. The event rates of restenosis and periprocedural complications in the follow-up period were pooled with random-/fixed-effect models using Freeman-Tukey double arcsine transformation. Heterogeneity tests and publication bias tests were performed.

Results: Two hundred and twenty-four ICAD patients treated with DCB from 9 eligible studies were included. Rate of stenosis in the DCB arm before treatment was ranged from 62% to 90% and reported median follow-up was ranged from 3 to 10.7 months. The pooled incidence of restenosis were 5.7% (95% confidence interval [CI] 2.6%−9.7%; $I^2 = 0\%$, $p = 0.516$) and 5.9% for periprocedural complications (95% CI: 2.5–10.3%; $I^2 = 0\%$, $p = 0.649$) in follow-up term.

Conclusion: With the limitation of the low quality of the available evidence, angioplasty with DCB appears to be effective and safe in severe ICAD. Further larger randomized trials are needed to provide more definitive evidence and to address the ideal clinical context for their application.

1. Introduction

Intracranial atherosclerosis disease (ICAD) is a major cause of ischemic stroke, responsible for approximately 17–35% and 10% of ischemic cerebrovascular events in Asians and Whites, respectively [1,2]. It has been demonstrated that patients with ICAD are at high risk of recurrence and poor prognosis especially in high-grade stenosis [3]. Due to the high periprocedural complications rate and high incidence of restenosis of percutaneous transluminal angioplasty and stenting (PTAS) used in ICAD [4,5], best medical treatment (BMT) remains the major preventive measure [6]. However, in a subgroup analysis of Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial, the incidence of recurrent ischemic events beyond 30 days in the BMT group was threefold higher than in the PTAS group (6.2% versus 2.2%) [7]. Poor adherence to strict medical management caused patients to be unable to achieve target blood pressure and low-density lipoprotein cholesterol level. ICAD patients with high-grade stenosis are still confronted with a high risk of stroke recurrence. Thus, PTAS remains a crucial alternative for ICAD. Moreover, recent trials indicated promising results and reconfirmed the safety and efficacy of the application of PTAS in selective ICAD [8,9].

The introduction of balloon dilation with or without the implantation of the stent was able to significantly attenuate the rates of stenosis of intracranial arteries. Nonetheless, stent implantation might lead to

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several certain issues including high restenosis rates and severe bleeding complications led by long-term duration use of dual antiplatelet treatment (DAPT). The underlying mechanism of restenosis could be explained by neointimal hyperplasia and smooth muscle cell proliferation on intracranial arteries [10].

To reduce the incidence of restenosis and shorten the duration of DAPT, drug-coated balloon (DCB) was primarily developed in coronary artery disease (CAD) with combination therapy of angioplasty and antiproliferative drug to the vessel wall [11,12]. By inhibiting the process of neointimal hyperplasia, the use of DCB could reduce the restenosis in long term. Also, with the advantage of avoiding a permanent implant, the application of DCB alone could shorten the duration of DAPT and consequently, reduce the rates of any bleeding complications [13].

Several studies had reported the safety and efficacy of DCB used in ICAD. However, due to fewer enrolled cases, the merged results were needed to clarify the effect. Thus, to review current evidence, we conducted a systematic review to outline studies results with the use of DCB for ICAD and to further elucidate the ideal clinical application.

2. Material and methods

Our systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

2.1. Literature search strategy

We searched published studies up to June 2021 using the following databases: MEDLINE (PubMed), EMBASE, Web of Science, Wanfang Database (Chinese), and references from identified articles and published reviews. We used the following keywords: “drug-coated balloon” or “drug-eluting balloon” and “intracranial atherosclerosis disease” or “ICAD”. We also screened the reference papers from retrieved articles not identified through the initial search. The detailed search strategy was also seen in Data Supplement (Table S1).

2.2. Study selection and eligibility criteria

Two authors (Alvin YC, Wang, and H Lin) decided about inclusion or exclusion according to the following criteria: i) patients with ICAD confirmed by clinical presentation and digital subtraction angiography; ii) studies enrolled ICAD patients undergoing PTA with DCB; iii) at least one of the following outcomes should be reported: restenosis, periprocedural complication, technical failure.

We excluded those studies that 1) case reports with less than 5 cases; 2) reviews or conference papers. Abstracts and titles were screened for potentially relevant studies and assessed for eligibility in full text by two independent reviewers (GM Li and HZ Qiao). Discrepancies were resolved by consulting a third experienced researcher (Alvin YC, Wang). Reference papers management and deduplication were performed in ENDNOTE X9.2.

2.3. Data extraction and methodological quality evaluation

The following variables were extracted by two independent investigators (GM Li and WL Yang) from the included studies and transcribed into a standardized data extraction template. The following information (if available) was extracted from included studies: first author, title, year of publication, region, study design, sample size, age (median or mean), gender(%), rate of stenosis degree before and after angioplasty, time from ischemic event to intervention, devices of DCB used, comparison group, duration of follow up, outcome and frequency of outcome. Restenosis was defined as 1) $>$ 50% stenosis degree during follow-up; 2) with/or without clinical symptoms; 3) assessed by DSA or other reported detection methods. Periprocedural complications were defined as stroke or death within 30 days.

2.4. Statistical analysis

All statistical analyses were performed by the ‘meta’ package [15] running in R version 4.1 [16]. We adopted a narrative approach describing the participant characteristics. To estimate the pooled proportions of restenosis and periprocedural complications, Freeman-Tukey double arcsine transformation was performed as it was suitable for studies with zero event [17]. Study heterogeneity was expressed as % (low [25%], moderate [50%], and high [75%] and Cochrane Q statistic [significance level $<$ 0.05]) [18]. Both fixed- and random-effects summary estimates were reported. Publishing bias was assessed by Begg’s and Egger’s tests [19]. If the two-side p-value of Begg’s and Egger’s test was lower than 0.05, publication bias was considered statistically significant.

3. Result

3.1. Literature research

The flow chart summarized the searching process and study identification (Fig. 1). Initial databases searches yielded 2036 articles after removal of duplicates. After screening titles and abstracts, 2006 articles were excluded for case report, reviews articles, abstract articles or irrelevant to the study. Of these, full texts of 30 potentially relevant studies were retrieved for further identification. According to the inclusion or exclusion criteria, 21 studies were excluded for the following reasons: irrelevant to the current analysis (n = 6), DCB was used in extracranial arteries (n = 10), DCB was used in MCA total occlusion(n = 1), DCB was used for predilation before stent implanting (n = 1), case reports (n = 3). Finally, 9 eligible studies were enrolled for further analysis [20–28].

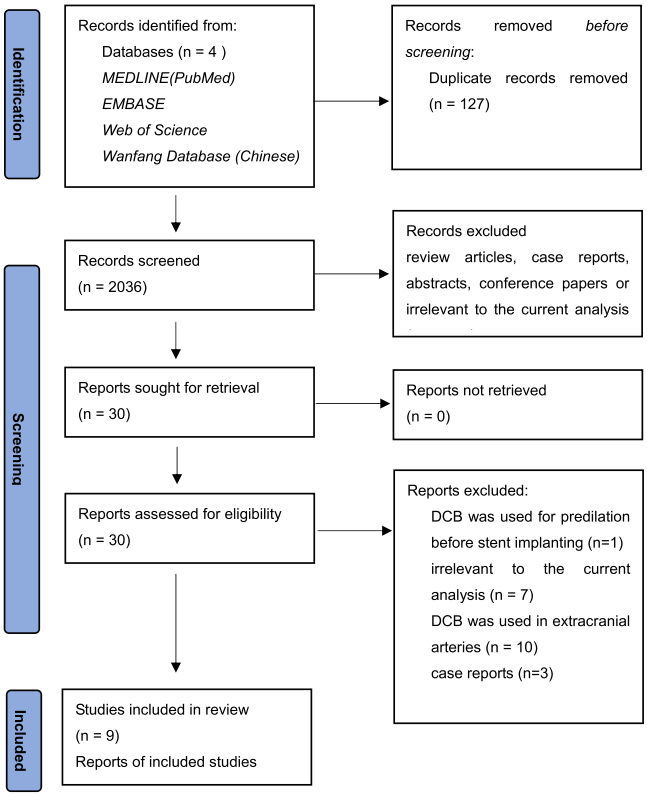

Fig. 1. Flowchart for study screening and selection.

3.2. Study characteristics

Detailed characteristics of 9 included studies were summarized in Table 1 and Table 2. Overall, the studies were published between 2011 and 2020. All studies were retrospective enrolled. Of these, three studies compared DCB with conventional balloons [20], wingspan system [21], any stents [27], and rest of them were single-arm designs. Two studies reported the application of Neuro Elutax SV (Aachen Resonance), a CE certificated DCB, and one study reported unknown DCB devices. Most of the enrolled studies selected SeQuent Please (B Braun, Melsungen, Germany) for angioplasty. Five studies were performed in China, 3 in Switzerland and 1 in Germany.

A total of 224 subjects were identified, with an average age ranging from 56 to 73 years. The proportion of male subjects ranged from 57.1% to 100%. The rate of stenosis in the DCB arm before PTA ranged from 62% to 90%. Median follow-up duration was reported in 8 studies and ranged from 3 to 10.7 months.

3.3. Proportion of restenosis and periprocedural complications in ICAD treated with DCB

Eight studies reported the outcome of restenosis and periprocedural complications in ICAD treated with DCB during follow-up. Proportion of restenosis and periprocedural complications was relatively low in enrolled studies. No restenosis event was described in 2 studies [22,28] while 15% in another study [24]. No periprocedural complication was reported in 1 study [22] and 13% in another paper [21]. Pooled estimates were 5.7% for restenosis (95% confidence interval [CI] 2.6%−9.7%; $I^2 = 0\%$, $p = 0.516$) (Fig. 2) and 5.9% for periprocedural complications (95% CI: 2.5%−10.3%; $I^2 = 0\%$, $p = 0.649$) (Fig.3) in the follow-up term. For both outcomes, the funnel plots were symmetric (Figs.S1–2) and publication bias was not detected as Begg's and Egger's test was not statistically significant in both groups ($P > 0.05$). Technical failure rates were ranged from 0% to 13%.

4. Discussion

Our research found no randomized trial to study the efficacy and safety of DCB use in ICAD. Moreover, the overall quality of the enrolled studies was low due to retrospective, single-arm design and small sample size. Our study provided low-quality evidence to support the promising safety and efficacy of the application of DCB in ICAD.

4.1. DCB for restenosis

Restenosis was considered a crucial risk factor for long-term ischemic events recurrence [20,29]. Age, smoking, lesion location, poor adherence to rigorous medical treatment were contributed to the progression of restenosis [30,31]. Stents implantation was considered as another risk factor leading to restenosis, induced by the development of atherosclerotic plaque inside the stent [32]. Two previous meta-analyses reported that for symptomatic intracranial stenosis, stent implanting (14.8%, 95% CI, 11.9–17.9%) was more likely to develop into restenosis than balloon angioplasty alone (11.5%, 95%CI: 6.9%−19.1%) [33,34]. To our best knowledge, the major underlying mechanism of restenosis was intimal hyperplasia and excessive proliferation of vascular smooth muscle cells [35]. This process, characterized by early foamy macrophage infiltration, atherosclerotic plaque development, and necrotic core plaque formation, was observed in bare-metal stents and occurred earlier and more frequently with drug-eluting stents (DES) [36]. The inflammatory response was also an important potential mechanism for intimal hyperplasia and vascular smooth muscle cell proliferation [37,38]. Furthermore, intracranial arteries might be more susceptible to inflammatory changes and plaque instability due to prominent expression of proinflammatory proteasomes [40].

To lower the rate of restenosis, drug-coated devices, loaded with antiproliferative drugs (e.g., paclitaxel, sirolimus), were firstly developed in CAD, including DES and DCB. Those anticancer agents could inhibit the proliferation of smooth muscle cells and reduces intimal hyperplasia [41], as well as alleviate inflammatory response. The application of DES in CAD significantly reduced the incidence of restenosis [42–44]. Also, for ICAD subjects, a meta-analysis reported the encouraging effect of DES to reduce the incidence of restenosis (5.2%, 95%CI:1.5–11.1%) [45]. However, DES might be associated with an increased incidence of late thrombotic complications, most likely due to the prolonged endothelization process resulting from the sustained drug

Table 1
Characteristics of participants from enrolled studies.

Author	Year of Publication	Region	Participants	No. of Cases Enrolled	Male, %	Age (mean or median)	Rate of stenosis in DCB arm before PTA, %	Devices of DEB	Comparison group	DAPT Duration
H. Henkes	2011	Germany	ICAD with ISR	51	72.5	67	62%	SP	Conventional Balloon	1 year
Luca Remonda	2018	Switzerland	ICAD	8	62.5	68.5§	81%	NESV	Wingspan System	unknown duration for DCB alone and 6 months for stents
Luca Remonda	2018	Switzerland	ICAD	10	100	73§	78%	SP	None	3 months
Wei Wang	2018	China	ICAD	30	80	57.4	82%	SP	None	3 months for DCB alone and 6 months for stents
Philipp Gruber	2020	Switzerland	ICAD	33	81.2	72§	80%	SP or NESV	None	3 months
Alvin Yi-Chou Wang	2020	Taiwan, China	ICAD	35	57.1	61.3	77%	SP	None	3 months
Sheng Guan	2020	China	ICAD with ISR	11	90.9	56	76%	SP	None	3 months
Ju Han	2020	China	ICAD	42	71.4	57.6	90%	SP	Any stents	3 months for DCB alone and 6 months for stents
Ximeng Yang	2020	China	ICAD	16	93.8	63.1	75%	Unknown	None	3 months

§ expressed in median

Abbreviation: ICAD: intracranial atherosclerosis disease; ISR:in-stent restenosis; PTA: percutaneous transluminal angioplasty; SP: SeQuent Please; NESV: Neuro Elutax SV; DAPT: Dual antiplatelet therapy; DCB: drug-coated balloon.

Table 2
Outcome of interest reported in ICAD patients treated with DCB during follow-up.

Author	Year of publication	Rate of restenosis, % (DEB vs. comparison group)	Duration of follow up, months	Rate of periprocedural complications, n (%) (DEB arm)	Rate of technical failure, n (%) (DEB arm)	Rate of vessel dissection, n (%)(DEB arm)	Remedial stent for dissections, n (%) (DEB arm)	Remedial stent for elastic coil, n (%) (DEB arm)
H. Henkes	2011	9 vs 50	7.5	DNR	8	DNR	DNR	DNR
Luca Remonda	2018	13 vs 55	4	1(12.5)	1(12.5)	0	DNR	DNR
Luca Remonda	2018	0	3	0	0	0	DNR	DNR
Wei Wang	2018	3.2	7	2 (6.5)	0	2 (6.5)	0	2 (6.5)
Philipp Gruber	2020	15	9	4 (11.4)	DNR	1 (7.6)	0	0
Alvin Yi-Chou Wang	2020	8.3	10.7	4 (11.4)	1 (3)	2 (5.1)	2 (5.1)	1 (2.5)
Sheng Guan	2020	DNR	DNR	1 (9.1)	1 (9.1)	1 (9.1)	DNR	DNR
Ju Han	2020	4.8 vs 27.4	6	1 (2.4)	DNR	2 (4.8)	2 (4.8)	10 (23.8)
Ximeng Yang	2020	0	5.5	1 (6.2)	DNR	1 (6.2)	DNR	DNR

Abbreviation: DNR, did not report

release and chronic inflammatory response [46,47]. More importantly, stent implantation required prolongation of DAPT which was associated with more bleeding complications.

DCB was a drug delivery system by balloon dilation. As previously discussed, the application of DCB might achieve a lower incidence of restenosis by means of antiproliferative effect and no stent requirements. Beyond that, balloon inflation provided a broader area of surface contact and ensured homogeneous delivery of the drug to the vessel wall. DCB also had the benefits of potential improvement in delayed arterial healing, luminal gains, and early restoration of normal vessel anatomy [48]. Moreover, the application of DCB was less likely to develop into bleeding complications since a shorter duration of DAPT was allowed for 1–3 months for DCB use alone [49].

Our review reported relatively lower rate of restenosis for 5.7% (95% CI: 2.6%−9.7%) compared with one-year restenosis of 17.6% (18/102) in WOVEN (Wingspan One-year Vascular Events and Neurologic Outcomes) study [50] and one-year symptomatic in-stent restenosis of 9.6% (95%CI: 6.1%−14.9%) in the SAMMPRIS stent cohort [51]. Although post-procedure residual stenosis indices were slightly high (0–50%) in the DCB group, the stenosis rates in long-term follow-up were lower than the post-procedural term in 2 reported studies (absolute luminal gain: 7.4%−10%) [25,27]. This was supposed to be associated with the role of vascular healing of DCB. The SEDUCE study also demonstrated the potential arterial healing effect of DCB with the usage of optical coherence tomography (OCT) in CAD. It suggested that DCB was associated with a good healing pattern at late follow-up [52].

4.2. Duration of DAPT for DCB alone

Although the evidence regarding the duration of DAPT following treatment with a DCB in ICAD was lacking. eight of enrolled studies reported 3 months duration of DAPT except for one study [20] that adopted a 1-year duration of DAPT (Table 1). One of enrolled studies reported that shorter-term DAPT (3 months) did not increase the rate of recurrent ischemic events (13.2% vs 2.6%, $P = 0.219$), compared with stent implantation with longer-term DAPT (6 months) [27]. Currently, clinical trials in CAD treated with DCB alone suggested 1–3 months duration without significantly increasing ischemic events [11,53]. Another review also recommended 4 weeks duration for DCB treatment alone in stable coronary disease [54]. Thus, a shorter duration of DAPT was acceptable for ICAD with DCB alone, especially in those patients with a high risk of bleeding complications.

4.3. Periprocedural complications in application of DCB

In our systematic review, we found that the pooled proportion of periprocedural complications in ICAD treated with DCB was 5.9% (95% CI: 2.5%−10.3%), which was lower than stent implantation from a previous study (16%) [55]. Additional stenting procedure was considered to be the major factors for higher periprocedural complications. However, balloon angioplasty without stent implantation also had a similarly high rate of periprocedural complications in ICAD (16.3%, 95% CI: 9.9%−26.8%) [33]. Moreover, in our enrolled studies, predilation with conventional balloons was needed for the introduction of DCB as well as stent implant procedure. The additional procedure might not be the major reason for the high incidence of periprocedural complications in ICAD. Several studies indicated that high periprocedural complications had been criticized for the study designs, including short lead-in phase, low volume of institutions, the inexperience of the operator, and inadequate patient selection [56,57]. Recent trials with modified inclusion criteria had reported a lower rate of periprocedural complications with 2% [58], 2.4% [8], 4.3% [59], respectively.

Arterial dissection was another complication that should be noticed in the application of DCB in ICAD since the arterial wall needed to sustain at least twice dilations by the balloon catheters. The incidence of arterial dissection was ranged from 4.8%− 9.1% and only 4 cases

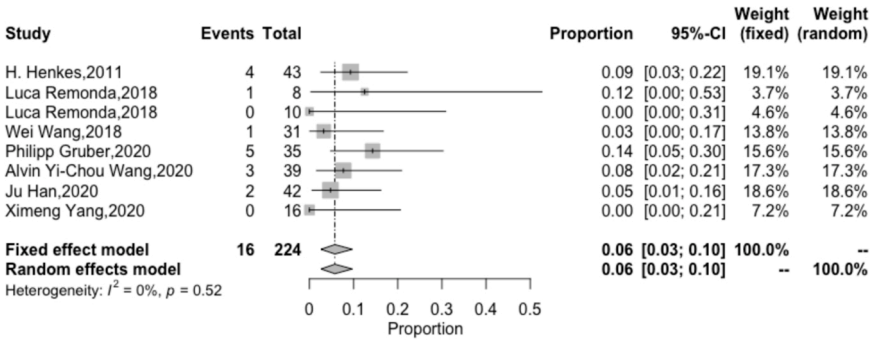

Fig. 2. Forest plot summarizing the proportion of restenosis in ICAD patients treated with DCB during follow-up.

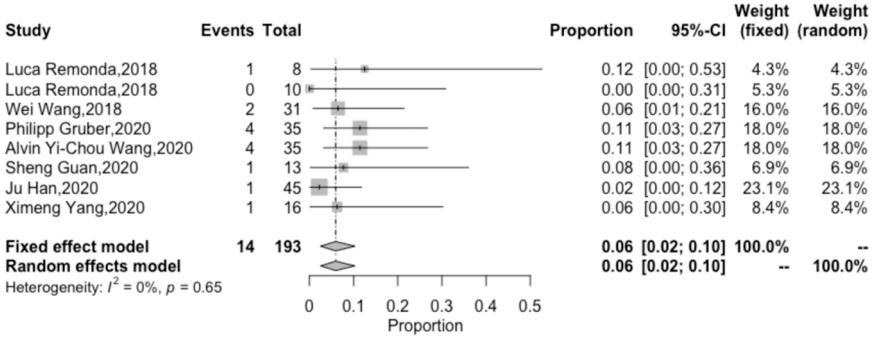

Fig. 3. Forest plot summarizing the proportion of periprocedural complications in ICAD patients treated with DCB during follow-up.

required immediate remedial stents [25,27]. We had discussed previously that mild or moderated dissection needed no intervention as it might heal by itself and facilitate a later luminal gain [25]. Also, the rate of dissection in our enrolled studies was relatively lower than balloon angioplasty alone (13.8%, 95%CI: 9.6%−19.8%). Nonetheless, the remedial stent was still needed for severe dissection causing flow limiting or arterial occlusion. To avoid dissection, submaximal angioplasty technique was recommended in two enrolled studies [21,22] and no dissection was reported. Although submaximal angioplasty might lead to high residual stenosis, < 50% residual stenosis was sufficient to meet the metabolic demands of the ischemic territory distal to the occlusive lesion with the advantage of luminal gain from DCB application [60]. Moreover, excessively faster inflation and oversize of the balloon were crucial risk factors for arterial dissection. In our review, DCB was slowly inflated for 30–60 s allowing adequate drug transfer and then slowly deflated. The diameter of DCB was selected based on 80–100% of the normal vessel diameter. A post-interventional angiogram was also needed for 10–15 min later following the initial angioplasty to detect any flow-limiting dissection or thrombus formation.

4.4. *Technical success in the application of DCB*

The technical failure rate was ranged from 0% to 13% in the enrolled studies. Currently, the rigidity of the drug-loading balloon catheter prevented itself from passing the tortuous vascular anatomy was the major reason for technical failure. In the earlier phase, DCB was used as predilation followed by the implantation of stent systems [61] or as direct angioplasty without predilation [24] in ICAD. However, DCB predilation was failed in 19% of the cases instead of conventional balloon predilation. Thus, current studies reported lesions should be predilated with a more flexible, smaller diameter conventional balloon to facilitate the subsequently attempted advancement of DCB over the stenotic vessel lesion. Tortuous intracranial vasculature was also thought to be another reason for technical failure. For those patients, we had previously recommended applications of intermediate catheters for providing proximal support. For extremely tortuous anatomy, we reported the balloon anchor tracking (ANTRACK) technique to advance the intermediate catheter close to the lesion [62].

Elastic recoil causing more than 50% residual stenosis rate required immediate remedial stent implantation. Compared to coronary arteries, instead of lipid infiltration, proliferative fibrosis of the intima or adventitia was more commonly seen in intracranial atherosclerosis [63,64]. That could be the reason for elastic recoil in angioplasty for ICAD. Although twice dilation could provide adequate mechanical force to the lesion, the incidence of bail-out stent for elastic recoil was relatively high in two enrolled studies (2 cases, 6.5%; 10 cases, 23.8%). Severe elastic recoil remained a major issue for the application of DCB in ICAD.

4.5. *Implications for future researches with DCB*

To date, currently available data indicated that DCB angioplasty was effective and safe for ICAD. However, there were still some issues that needed to be solved. First of all, DCB angioplasty for ICAD was not approved in some countries. The off-label use of DCB in ICAD might lead to certain ethic issues and discouraged the clinical application of DCB. Although Neuro Elutax SV was certified for the treatment of intracranial lesions, SeQuent Please without intracranial indication was the most widely used DCB device in our enrolled studies. Secondly, the number of studies and sample sizes to evaluate the efficacy of DCB in the ICAD was limited. Also, most of the currently enrolled studies set restenosis as outcome of interest whereas other randomized clinical trials used stroke, death or disability as main outcome variable. Although the incidence of restenosis was highly related to ischemic events, it was still unable to clarify whether DCB was more effective than other treatments or not. Thirdly, the potential neurotoxicity of the anti-cancer drug loaded on the balloon causing damage to the brain remained concerned.

Thus, to further demonstrate the efficacy and safety of DCB in ICAD, prospective and larger sample sizes clinical trials are urged to be performed. Advance evidence for DCB in ICAD is still required before widespread clinical utilization. We notice that a prospective,

multicenter, randomized controlled clinical trial is ongoing to evaluate the efficacy and safety of intracranial DCB catheters in the treatment of symptomatic intracranial atherosclerotic disease (NCT04631055). This study plans to enroll 180 ICAD patients with 70–99% degree stenosis and compare the incidence of restenosis between DCB angioplasty and stent implantation.

In future clinical trials, we advised high-resolution magnetic resonance (HRMR) to evaluate the characteristic of intracranial plague before DCB angioplasty. With the underlying mechanism of the anti-inflammatory effect of anti-proliferative agents [65,66], DCB could show another potential benefit during the inflammatory state in the plaque. HRMR might help us to differentiate unstable plaque or dissections and characterize the inflammatory status of intracranial plague. Contrast enhancement on plaque indicated a high inflammatory burden [67] and we considered it should be treated with DCB to further reduce the restenosis by inhibiting the inflammatory response. HRMR might be useful in patient selection to distinguish the ICAD subjects who were needed to be treated by DCB. Likewise, the use of HRMR helped us to identify the anatomical relationship between intracranial lesions and branch arteries and guided us to avoid the 'snow-plowing' effect [68].

Another issue is that the paclitaxel is considered a cytotoxic agent which might lead to some neurotoxic events [69]. Sirolimus was another widely used effective anti-proliferative drug. Preclinical studies indicated that higher dosages of paclitaxel might lead to a more unstable phenotype of the plaque due to increased apoptosis in the vessel wall compared with sirolimus [70]. In hypoxic conditions, the anti-proliferation effect of paclitaxel was significantly weaker than sirolimus in inhibiting hypoxic cell proliferation and the potential mechanism was related to inhibitions of HIF-1α expression and glycolysis [71]. Sirolimus was also thought to be no neurotoxic in the canine cerebral vasculature [72]. Therefore, sirolimus-coated devices may be safer and more effective in the hypoxic territory from plaque given the condition of restricted blood flow to the brain tissue in mostly ICAD.

Recently, newer-generation sirolimus-coated balloons (SCB) had been developed with advanced delivery technologies and they exhibited similar efficacy and safety compared with paclitaxel-coated balloons (PCB) in the treatment of coronary DES in-stent restenosis [73]. Lower major adverse cardiovascular events (MACE) and target lesion revascularization (TLR) rates were observed in other SCB used prospective registry studies [74,75]. Although no report about the application of SCB in cerebral arteries diseases, SCB may have an emerging role in treating ICAD in terms of preclinical studies and CAD reports.

5. Conclusions

From our comprehensive study, we considered that DCB angioplasty was an effective and safe procedure for ICAD. It might become a promising alternative treatment for ICAD. DCB angioplasty alone had some potential advantages in treating ICAD from literature review, including anti-restenotic effect, the introduction of no stent implant, and shorter duration of DAPT. Nonetheless, the current studies did not support widespread application in clinical utilization. Further prospective clinical trials were needed to address the effectiveness of DCB angioplasty in ICAD. Also, the development of newer DCB devices with advanced anti-proliferative drugs and a more flexible catheter was necessary for intracranial use.

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Disclosure statement

The authors declare no conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2021.107065.

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Mechanical rotational thrombectomy with Rotarex system augmented with drug-eluting balloon angioplasty versus stenting for the treatment of acute thrombotic and critical limb ischaemia in the femoropopliteal segment

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Abstract

Introduction: *Mechanical thrombectomy is an alternative to local thrombolysis for the treatment of severe ischaemia in the femoropopliteal segment, but stent implantation is usually required after this procedure. The use of drug-eluting balloons (DEBs) may overcome long-term problems associated with stents, but it remains unclear how often such a treatment is technically feasible and efficient.*
Aim: *This post hoc single-centre study was aimed at assessment of the feasibility, safety and efficacy of mechanical thrombectomy followed by application of DEBs.*
Material and methods: *Fifty-one patients, aged 69.1 ±11.6 years, were managed for acute thrombotic or chronic critical ischaemia in the femoropopliteal segment using the Rotarex device. Following mechanical thrombectomy, on condition that there was no significant residual stenosis or dissection, lesions were managed with paclitaxel-coated DEBs, which was a desired strategy (24 patients). The remaining 25 patients underwent stent implantations, which was regarded as bailout treatment. Final follow-up was scheduled 12 months after the procedure.*
Results: *The primary-assisted patency rate after mechanical rotational thrombectomy with additional balloon angioplasty and/or stenting was 97.1% (49 patients). The early mortality rate was 2.0% (1 patient) and the amputation rate was 4.1% (2 patients). There were no late mortalities or limb amputations at 12-month follow-up, but significant restenoses occurred in 13 (27.1%) patients. These restenoses were more frequent in patients who underwent stent implantation (45.5%) than those managed with DEBs (12.5%), and in patients managed for secondary lesions.*
Conclusions: *In selected patients mechanical rotational thrombectomy in the femoropopliteal segment followed by application of DEB is a safe, effective and long-lasting method of revascularisation.*

Key words: *critical ischaemia, stent, drug-eluting balloon, mechanical thrombectomy, acute limb ischaemia.*

Introduction

Both acute thrombotic and chronic critical lower limb ischaemia are associated with high morbidity and mortality, and also with a high risk of unsuccessful revascularisation of the limb, requiring its amputation. Routine management of both types of limb ischaemia consists of anticoagulation followed

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by open surgical repair of occluded arteries (usually bypass grafting) [1–4]. Yet, such a treatment in patients with acute thrombotic ischaemia is associated with an amputation rate at the level of 10–70% and in-hospital mortality even as high as 15% [5]. In patients with critical limb ischaemia the amputation rate after surgical revascularization is at the level of 20–25% and the 2-year mortality rate in these patients is about 50% [2, 5, 6]. Although local thrombolysis is associated with better clinical outcomes and currently it is preferred to surgical revascularization [7–10], not all occlusions can be opened by thrombolytic agents. Those primarily atherosclerotic poorly respond to thrombolysis. Moreover, even if thrombolysis is successful, these arteries usually re-occlude and stent implantation is often required, which carries another problem – in-stent stenosis or occlusion, primarily associated with intimal hyperplasia within the stent. Mechanical thrombectomy seems to be an alternative treatment modality [5, 11–14], but stent implantation with similar late problems is usually required after this endovascular procedure. The use of drug-eluting balloons (DEB) instead of stents may theoretically overcome clinical problems associated with stents, but it remains unclear how often such a treatment is technically feasible in these challenging patients and how efficient mechanical thrombectomy not augmented with stent implantations is in the long run.

Aim

This post hoc single-centre study was aimed at assessment of the feasibility, safety and efficacy of mechanical thrombectomy followed by application of DEBs for acute thrombotic or chronic critical ischaemia of the lower limbs in the femoropopliteal segment. We also analysed how often the use of rotational thrombectomy enabled an endovascular procedure not accompanied by stent implantation, and whether the utilisation of DEBs instead of stents was associated with a better clinical outcome.

Material and methods

We reviewed our register of endovascular interventions and identified patients with acute thrombotic ischaemia or chronic critical lower limb ischaemia due to occlusions in the femoropopliteal segment, who were managed using mechanical rotational thrombectomy (Rotarex®s device; Straub Medical AG, Wangs, Switzerland). Technical success of mechanical rotational thrombectomy was defined in terms of absence of relevant post-procedural residual stenosis, with cutoff at the level of 50%. Primary-assisted patency rate was defined as exempt from significant stenosis (cutoff at the level of 30%) in the target artery following rotational thrombectomy and additional endovascular interventions during the primary procedure, such as balloon angioplasty and stenting.

Potential risks and benefits associated with such a procedure were discussed with the patients, and all patients gave their written informed consent. Clinical indications for mechanical rotational thrombectomy in our centre included:

– occlusions and/or critical stenoses of the distal femoral artery (distally from the profunda femoris artery) or the popliteal artery (with or without involvement of its branches);
– atherosclerotic, atherothrombotic and atheroaneurysmatic lesions;
– primary lesions and secondary lesions after previous balloon angioplasty or stent implantations.

Exclusion criteria comprised: highly calcified lesions, no adequate vascular access, contraindications for antiplatelet therapy, and lack of the patient's consent.

In this study we did not include patients presenting with arterial emboli. From June 2014 to November 2016 there were 51 eligible patients, 26 men and 25 women, with a mean age of 69.1 ±11.6 years. Thirteen (25.5%) patients were managed for acute non-embolic occlusions of the distal femoral artery and/or popliteal artery and its branches. Out of these patients, 6 (46.2%) presented with an acutely occluded stent. Thirty-eight (74.5%) patients were admitted to the hospital because of critical limb ischaemia resulting from atherothrombotic lesions at the same level as patients with acute ischaemia. In this group there were 5 (13.2%) patients with thrombotic occlusions after balloon angioplasty and 18 (47.4%) patients with chronically occluded stents. A majority of patients presented with grade 4 and 5 (21 and 25 patients, accordingly) of the Rutherford classification, and 5 patients presented with severe ischaemic ulcers (grade 6 in this classification). The demographic profile of both groups of patients and their co-morbidities are presented in Table I, while localisations and characteristics of arterial lesions are described in Table II.

Table I. Clinical characteristics of patients

Parameter	All patients (*n* = 51)	Critical limb ischaemia (*n* = 38)	Acute non-embolic limb ischaemia (*n* = 13)
Male/female ratio	26/25 (51.0/49.0%)	17/21 (44.7/55.3%)	9/4 (69.2/30.8%)
Patients' age [years]	69.1 ±11.6	70.2 ±11.8	67.9 ±15.5
Diabetes mellitus type 2	20 (39.2%)	12 (31.6%)	8 (61.5%)
Cigarette smoking	17 (33.3%)	13 (34.2%)	6 (46.2%)
Hypercholesterolaemia	22 (43.1%)	16 (42.1%)	6 (46.2%)
Arterial hypertension	44 (86.3%)	34 (89.5%)	10 (76.9%)
Family history cardiovascular disease	9 (17.6%)	7 (18.4%)	2 (15.4%)
History of myocardial infarction	11 (21.6%)	7 (18.4%)	4 (30.8%)

Table II. Localisations and characteristics of arterial lesions

Variable	All patients (*n* = 51)	Critical limb ischaemia (*n* = 38)	Acute non-embolic limb ischaemia (*n* = 13)
Distal part of femoral artery	12 (23.5%)	10 (26.3%)	2 (15.4%)
Popliteal artery	14 (27.5%)	10 (26.3%)	4 (30.8%)
Distal part of femoral artery and popliteal artery	16 (31.4%)	13 (34.2%)	7 (53.8%)
Popliteal artery and its branches	7 (13.7%)	5 (13.2%)	2 (15.4%)
Popliteal artery with aneurysmatic dilatation	3 (5.9%)	1 (2.6%)	2 (15.4%)
Distal part of femoral artery and popliteal artery with aneurysmatic dilatation	2 (3.9%)	2 (5.3%)	0
Mean length of the lesion [mm]	247.0 ±135.8	253.2 ±129.9	303.8 ±140.0
Thrombosis in the area of lesion	34 (66.7%)	22 (57.9%)	12 (92.3%)
Total occlusion of the target artery	44 (86.3%)	31 (81.6%)	13 (100%)
Degree of stenosis (%)	93 ±3.1	92 ±2.2	100
Ankle/brachial index at baseline	0.2 ±0.1	0.4 ±0.15	0.2 ±0.15
Primary lesion	26 (51.0%)	19 (50.0%)	7 (53.8%)
Restenotic lesion	25 (49.0%)	19 (50.0%)	6 (46.2%)

Endovascular procedures were performed through ipsi- or contralateral femoral access. Before intervention all patients received 300 mg of clopidogrel and 75 mg of aspirin. During endovascular intervention patients were administered intravenously unfractionated heparin. Dosing of heparin depended on the duration of the procedure. We used 110 cm or 135 cm long 6 Fr Rotarex®s catheters. Firstly we navigated through the occluded segment with a 0.018" guidewire and then performed 2–6 passages of the Rotarex system. After at least 2 passages of the rotational catheter, control catheter angiography was performed. If there was still over 50% stenosis, balloon angioplasty was performed. Afterwards, if there was no major residual stenosis (over 40%) in the target artery and no significant dissection, this area was managed with paclitaxel-coated DEBs, such as Elutax SV (Aachen Resonance, Aachen,

Germany) or Luminor (iVascular, Barcelona, Spain). This was a desired strategy, which was possible in 24 patients (49.0%). In 25 (51.0%) patients arteries revealed significant stenoses despite balloon angioplasty, or there were severe (grade C or higher) dissections. These patients underwent stent implantations, which was regarded as a bailout treatment. In addition, 6 (11.8%) patients presenting with over 60% residual stenosis following balloon angioplasty and/or significant peripheral embolisation received alteplase intra-arterially (5 mg as a bolus, and then 15 mg during 12 h). Details regarding results of rotational mechanical thrombectomy with the Rotarex system are given in Tables III and IV.

All patients were assessed before discharge from the hospital. They were discharged with the recommendation of dual antiplatelet therapy with aspirin (75–150 mg daily) and clopidogrel (75 mg daily). Their follow-ups were scheduled 30 days, 6 and 12 months after the procedure. Since there was 1 death and 2 amputations during the hospital stay, only 48 patients were followed up (24 patients managed

Table III. Results of rotational mechanical thrombectomy with Rotarex system in patients with acute vs. critical leg ischaemia

Variables	All patients (n = 51)	Critical limb ischaemia (n = 38)	Acute non-embolic limb ischaemia (n = 13)
Number of passages of the Rotarex system	3 ±2	4 ±2	3 ±1
Degree of stenosis after mechanical thrombectomy (%)	54 ±15	55 ±15	45 ±13
Duration of mechanical thrombectomy [min]	5 ±2	7 ±2	5 ±2
Patients finally managed with drug-eluting balloons	24	19	5
Degree of residual stenosis after drug-eluting balloons (%)	13.5 ±4	10.5 ±6	12.5 ±9
Patients finally managed with stents	27	19	8
Degree of residual stenosis after stenting (%)	11.5 ±4	10.5 ±6	10.5 ±6
Ankle/brachial index at hospital discharge	0.73 ±0.10	0.75 ±0.12	0.75 ±0.14

Table IV. Results of rotational mechanical thrombectomy with Rotarex system in patients finally managed with drug-eluting balloons vs. those managed with stents.

Variable	All patients (n = 51)	Patients managed with drug-eluting balloons (n = 24)	Patients managed with stents (n = 27)
Patients presenting with critical limb ischaemia	38 (74.5%)	19 (79.2%)	19 (70.4%)
Patients presenting with acute non-embolic limb ischaemia	13 (25.5%)	5 (20.8%)	8 (29.6%)
Number of passages of the Rotarex system	4 ±2	3 ±1	4 ±1
Degree of stenosis after mechanical thrombectomy (%)	47 ±20	41 ±18	45 ±13
Degree of residual stenosis after balloon angioplasty and/or stenting (%)	14.3 ±6	21.5 ±12	10.5 ±6
Ankle/brachial index at hospital discharge	0.71 ±0.14	0.72 ±14	0.70 ±0.12

with DEBs and 22 patients who underwent stent implantation). At each visit patients underwent physical examination, evaluation of degree of limb ischaemia according to the Rutherford classification and duplex sonography of the recanalised arteries. Patients were also evaluated in a case of clinical worsening or delayed wound healing. Clinical worsening, restenosis revealed by sonographic examination and delayed healing of an arterial ulcer were the indications for control angiography and reintervention.

Statistical analysis

Multivariate stepwise backward conditional logistic regression analysis was used to determine independent predictors of restenosis/occlusion. The significance of this analysis was set at $p < 0.05$.

Results

Technical success of mechanical rotational thrombectomy alone was achieved in 20 (19.6%) patientsand there was a 97.1% primary-assisted patency rate (49 patients) after additional balloon angioplasty and stenting. In 2 (4.1%) patients despite recanalisation of the target artery and stenting this procedure clinically failed and in both of them amputations of ischaemic limbs were performed during the hospital stay. Such an unfavourable outcome occurred in 1 patient presenting with acute thrombotic limb ischaemia and in 1 with chronic critical ischaemia. In both patients, in addition to occlusions of the distal femoral artery and popliteal artery, there were occlusions of the branches of the popliteal artery. There was one in-hospital death (mortality rate: 2.0%). This patient died because of intracranial bleeding, which probably was associated with infusion of alteplase. There were local complications associated with mechanical thrombectomy in 5 (9.8%) patients – distal embolisation in 4 patients, which was successfully managed with aspiration and local infusion of alteplase, and perforation of the artery in 1 case, which required implantation of a covered stent. There were neither mortalities nor major adverse events, such as myocardial infarction, stroke or limb amputation in all 48 remaining patients during 12 months of follow-up. At 12 month follow-up the clinical status of the majority of ischaemic limbs had improved. Only 1 (2.1%) patient suffered from rest pain and 7 (14.6%) patients from severe claudication. There were no patients presenting with ischaemic ulcers. Details are given in Figure 1. In 13 patients (27.1%, excluding deceased and amputated patients) duplex sonography revealed occlusions or severe stenoses in the target arteries. These lesions primarily occurred in patients managed for secondary lesions (12 limbs). There was only 1 patient with restenosis after primary intervention. Also, restenoses and occlusions at follow-up were significantly more frequent in patients who underwent stent implantation (10 patients; 45.5%) than in those managed with DEBs (3 patients; 12.5%) – Figure 2. The risk of recurrent lesions was higher in patients with chronic critical lower limb ischaemia (11 patients; 30.6%) than those managed for acute thrombotic occlusions (2 patients; 16.7%). Details are described

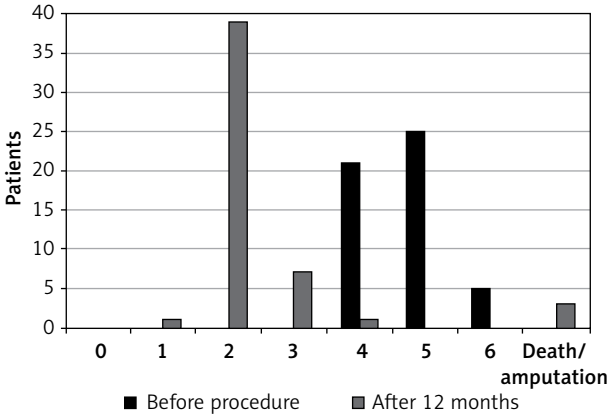

Figure 1. Degree of ischaemia according to the Rutherford classification before intervention and at 12-month follow-up

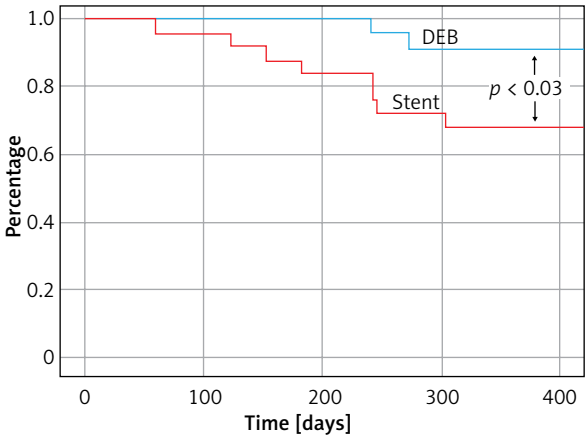

Figure 2. Kaplan-Meier event-free curves displaying the freedom from restenosis/reocclusion in patients managed with drug-eluting balloons (DEB) vs. those managed with stents

Table V. Number of patients presenting with severe restenoses and occlusions at 12-month follow-up (patients who died or had their limbs amputated during first hospitalization were excluded)

Parameter	All patients	Critical limb ischaemia (n = 36)	Acute non-embolic limb ischaemia (n = 12)
All patients (n = 48)	13 (27.1%)	11 (30.6%)	2 (16.7%)
Patients managed with drug-eluting balloons (n = 24)	3 (12.5%)	3 (15.8%)	0
Patients managed with stents (n = 24)	10 (41.7%)	8 (47.1%)	2 (28.6%)
Patients managed for primary lesions (n = 22)	1 (4.5%)	1 (6.7%)	0
Patients managed for secondary lesions (n = 26)	12 (46.2%)	10 (47.6%)	2 (40.0%)

in Table V. The logistic regression analysis revealed that peripheral embolisation during the procedure and more than 4 passages of the Rotarex system were significantly associated with a higher risk of restenosis/occlusion (hazard ratio: 5.6 and 5.0; p = 0.018 and 0.025 respectively).

Discussion

In this post-hoc analysis we have demonstrated that the majority of severe atherothrombotic lesions in the femoropopliteal segment that result in acute or chronic critical limb ischaemia, and are not highly calcified, can be reopened using mechanical rotational thrombectomy. In our patient series the primary-assisted patency rate after thrombectomy augmented by balloon angioplasty and stenting was as high as 97.1%. in the in-hospital amputation rate was 4.1%. Such management was also safe. In-hospital mortality was 2.0%, which was significantly lower than after an open surgical revascularization. Moreover, in 49% of patients it was possible to avoid stent implantation and instead to manage the area of occlusion with DEB.

Analysis of the clinical outcome of our patients at 12-month follow-up demonstrated that mechanical rotational thrombectomy with the Rotarex system followed by DEB was not inferior to such a thrombectomy assisted by stent implantation. Actually, the results after DEB were better; there were fewer restenoses and no amputations. Yet, stents were implanted in patients with more advanced pathology and therefore these differences should be interpreted with caution. Similarly, although we identified peripheral embolisation during the procedure and more than 4 passages of the Rotarex system as risk factor of reocclusion, these events were probably predictors of more advanced arterial disease, and thus the risk of reocclusion in these patients was higher. Similarly worse late results in patients who required local fibrinolysis in addition to mechanical thrombectomy have already been reported by Kronlage [5].

Large epidemiological studies have revealed a significant risk of major amputation and/or mortality associated with open surgical revascularization for acute and critical leg ischaemia [1–3, 15]. Consequently, local fibrinolysis or endovascular thrombectomy is currently suggested to be a preferred treatment modality [16–20]. In the large study by Freitas *et al.*, who managed with Rotarex 525 patients presenting with acute and subacute ischaemia, with an average length of occluding lesions of 159 mm, there was 1.1% mortality and a 2.3% major amputation rate during 30-day follow-up. Adverse events associated with the treatment occurred in 6.9% of patients and mortality after 1 year was 8% [19]. Similar outcomes were reported by Kronlage *et al.* They managed 202 patients and in this group amputation-free survival was 94.3% [5].

Although mechanical thrombectomy with the Rotarex system has been demonstrated to be both relatively safe and efficient [5, 7–9, 14, 16–19], it remains to be established how to optimize such treatment. Even if short-term results are encouraging, long-term patency rates in the femoropopliteal segment after standard balloon angioplasty or stent implantation are relatively low. The 1-year reocclusion rate after balloon angioplasty is at the level of 60% [21–28]. Stents do not seem to be a proper solution either. When implanted in this part of the arterial system, especially in the distal part of the popliteal artery or in its branches, a significant proportion of currently available stents occlude in the long run, either because of a fracture, or due to thrombosis and intimal hyperplasia [21–29]. Although novel wire-in-

terwoven Nitinol or helically shaped stents, exhibiting a swirling flow, try to overcome these problems, they are not yet routinely used and their actual long-term advantage remain to be proven [30–35]. On the other hand, long-term patency rates in the femoropopliteal segment after DEBs are higher than after standard balloon angioplasty [36–47], while the problems associated with stents are avoided.

The results of our study suggest that the use of DEB after mechanical thrombectomy for thrombotic acute or critical leg ischaemia resulting from arterial occlusion in the femoropopliteal segment could be a desired treatment strategy. However, it should be emphasized that it was a retrospective analysis and the groups of patients were not fully comparable. A larger prospective study should be designed and performed in order to fully compare the clinical value of DEBs with stents in these challenging patients. Also, probably some novel area-dedicated stents (such as the aforementioned helically shaped ones) should be applied in such a trial.

Conclusions

The short and intermediate term results from this nonrandomised study indicate that the combination of mechanical thrombectomy with DEB is safe and feasible for the treatment of intermediate to long superficial femoral artery/popliteal artery lesions in selected patients with severe limb ischaemia. The DEB group had higher rates of primary patency and freedom from restenosis than the group of patients with stent implantation.

Conflict of interest

The authors declare no conflict of interest.

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NEW RESEARCH PAPER

CORONARY

Long-Term Outcome of Drug-Coated Balloon vs Drug-Eluting Stent for Small Coronary Vessels

PICCOLETO-II 3-Year Follow-Up

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ABSTRACT

BACKGROUND Native vessel coronary artery disease represents 1 of the most attractive fields of application for drug-coated balloons (DCBs). To date, several devices have been compared with drug-eluting stents (DESs) in this setting with different outcomes.

OBJECTIVES The authors sought to compare the short- and long-term performance of the paclitaxel DCB with the everolimus-eluting stent in patients with de novo lesions in small coronary vessel disease.

METHODS PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) was an academic, international, investigator-driven, multicenter, open-label randomized clinical trial in which patients were allocated to a DCB (n = 118) or DES (n = 114). We previously reported the superiority of DCBs regarding in-lesion late lumen loss at 6 months. Herein we report the final 3-year clinical follow-up with the occurrence of major adverse cardiac events (MACEs), a composite of cardiac death, nonfatal myocardial infarction, target lesion revascularization, and its individual components.

RESULTS The 3-year clinical follow-up (median 1,101 days; IQR: 1,055-1,146 days) was available for 102 patients allocated to DCB and 101 to DES treatment. The cumulative rate of all-cause death (4% vs 3.9%; $P = 0.98$), cardiac death (1% vs 1.9%; $P = 0.56$), myocardial infarction (6.9% vs 2%; $P = 0.14$), and target lesion revascularization (14.8% vs 8.8%; $P = 0.18$) did not significantly differ between DCBs and DESs. MACEs and acute vessel occlusion occurred more frequently in the DES group (20.8% vs 10.8% [$P = 0.046$] and 4% vs 0% [$P = 0.042$], respectively).

CONCLUSIONS The long-term clinical follow-up of the PICCOLETO II randomized clinical trial shows a higher risk of MACEs in patients with de novo lesions in small vessel disease when they are treated with the current-generation DES compared with the new-generation paclitaxel DCB. (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment [PICCOLETO II]; NCT03899818) (J Am Coll Cardiol Intv 2023;16:1054–1061) © 2023 by the American College of Cardiology Foundation.

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In the last decade, the necessity of developing newer therapies to mitigate the potential risk of long-term adverse events after percutaneous coronary interventions (PCIs) has emerged. Although drug-eluting stents (DESs) represented a terrific improvement from the technological point of view, leading to the treatment of theoretically any complex coronary anatomy,[1] their performance in some lesion settings, including small vessel disease (SVD), is lower and associated with an almost 2-fold risk of target lesion failure (TLF) at 1 year.[2-4] Moreover, with the currently available DESs, the long-term fate remains associated with a low but constant increase in adverse events.[5] In this regard, some devices have been developed aimed at reducing late-occurring adverse events. Among them, drug-coated balloons (DCBs) have been increasingly adopted for de novo coronary lesions, particularly in SVD.

Several DCBs have been tested in the native coronary artery disease setting with good angiographic and clinical results compared with first- or second-generation DESs,[6-8] but only a few of them have long-term clinical data available.

The aim of PICCOLETO II (Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment) was to test the long-term efficacy and safety of 1 of the latest-generation paclitaxel DCBs in comparison with 1 of the most widely used DESs (Xience everolimus-eluting stent, Abbott Vascular) in patients with de novo SVD.

METHODS

STUDY DESIGN AND POPULATION. PICCOLETO II (NCT03899818) is an academic, investigator-driven, randomized, multicenter, open-label, clinical trial performed at 5 European centers. The study protocol was presented and approved at the coordinating center (ASST Fatebenefratelli-Sacco), and all participating centers' ethics committees in 2015. Patients included in this study were enrolled between May 2015 and May 2018. The protocol was designed in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines. All participants provided written informed consent before being enrolled in the study.

We included patients hospitalized either for stable or unstable coronary artery disease scheduled for PCI. The angiographic inclusion criterion was native coronary vessel disease with a reference diameter between 2 and 2.75 mm and stenosis >70% (by investigator's judgment and visual estimation). The exclusion criteria have been reported elsewhere.[6] In brief, they are recent ST-segment elevation myocardial infarction (<48 hours), highly calcific coronary artery, highly tortuous target vessel, index lesion located in the left main trunk, aorto-ostial lesion, previous stent implantation at target vessel, target lesion with chronic total occlusion or longer than 25 mm, high thrombus burden, and target lesion involving a major bifurcation. Figure 1 shows the study flowchart.

INTERVENTION. The open-label randomization was performed just after coronary angiography, and patients were randomized 1:1 between the DCB (Elutax SV) and the DES (Xience everolimus-eluting stent), allowing 1 single lesion per patient. In case of the necessity of additional lesion treatment, this should have been performed before the study lesion with any device deemed necessary by the operator. The study protocol strongly encouraged predilatation with any device in both arms in order to ensure optimal angiographic results. The DCB inflation time had to be at least 30 seconds. If the lesion preparation or the DCB in the DCB arm led to major, flow-limiting dissection or vessel recoil, the investigator was allowed to implant a DES as a bailout. Conversely, investigators were encouraged not to stent the type A-B coronary dissections according to previous experiences. In case of bailout stenting, the protocol suggested using stents shorter than the DCB previously used.

The PCI procedure and antithrombotic agent used were performed according to current European Society of Cardiology guidelines.[9] The subsequent antithrombotic regimen in the DCB arm followed the GISE (Italian Society of Interventional Cardiology) Consensus Document with a minimum of 30 days of dual antiplatelet treatment in case of stable coronary artery disease and 6 to 12 months in case of acute patients. In DES-treated patients, we followed the European guidelines with a minimum of 6 months of dual antiplatelet therapy (12 months in acute coronary syndrome patients).

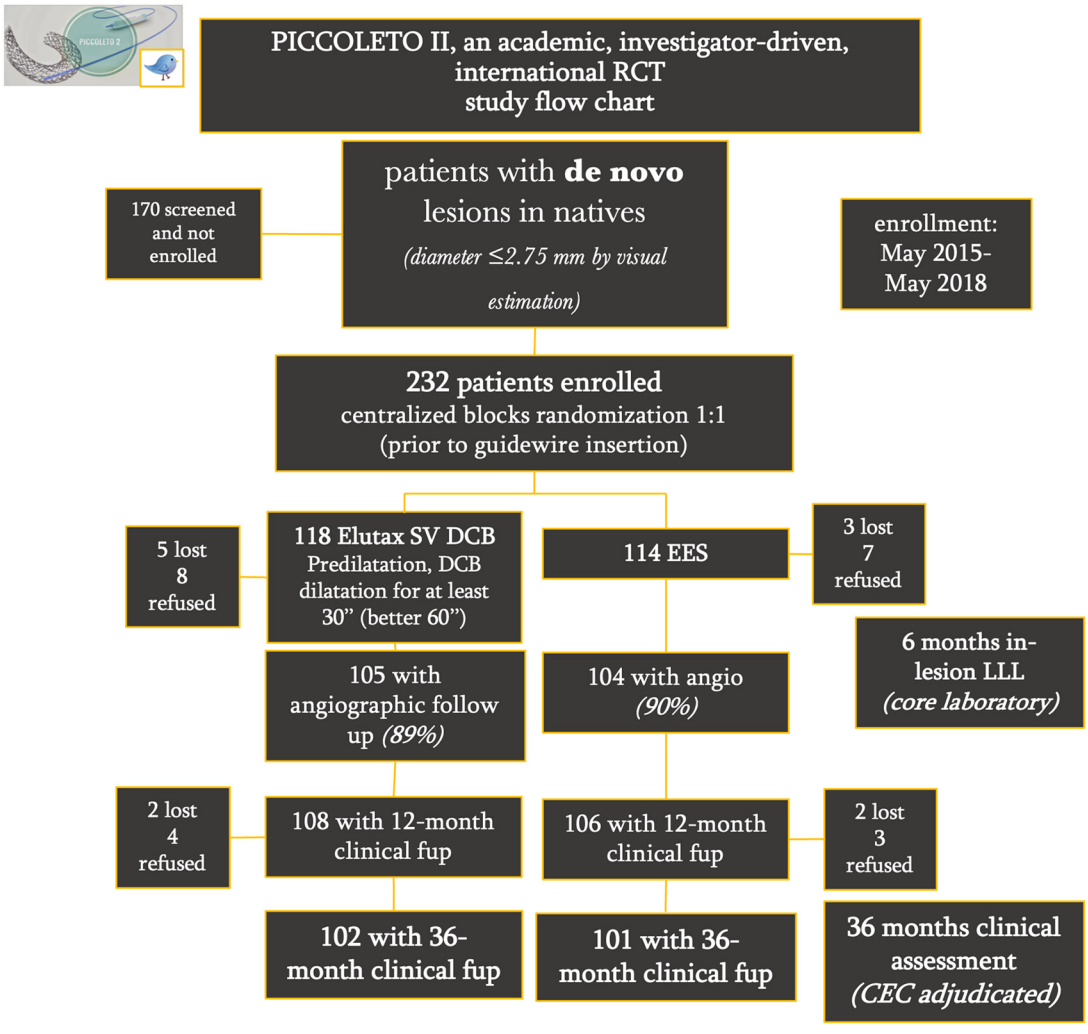
STUDY DEVICE. The technical characteristics of the study devices have been described previously.[10] This DCB elutes paclitaxel loaded on a folded balloon at a dosage of ≅2.2 μg/mm^2 (tolerance of 1.4-3.00 μg/mm^2). The drug is added with the matrix dextran aiming at preserving paclitaxel delivery to the vessel wall, ensuring tissue persistence for the following days.[10]

STUDY ENDPOINTS. The primary endpoint of this study was the angiographic in-lesion late lumen loss (LLL) assessed by an independent core laboratory

ABBREVIATIONS AND ACRONYMS

DCB = drug-coated balloon
DES = drug-eluting stent
LLL = late lumen loss
MACE = major adverse cardiovascular event(s)
MI = myocardial infarction
PCI = percutaneous coronary intervention
SVD = small vessel disease
TLF = target lesion failure
TLR = target lesion revascularization

FIGURE 1 Study Flowchart and Follow-Up of PICCOLETO II Study



CEC = clinical events committee; DCB = drug-coated balloon; EES = everolimus eluting stent(s); fup = follow-up; LLL = late lumen loss; SV = small vessel.

(University of Ferrara), and noninferiority was hypothesized. The other study endpoints were procedural success, which was defined as angiographic success and the absence of in-hospital cardiovascular complications, and major adverse cardiovascular events (MACEs), a composite of cardiac death, all myocardial infarctions (MIs), target lesion revascularization (TLR), and the individual components of MACEs at 1 and 3 years. All clinical events have been censored and assessed by an independent clinical events committee after blindly reviewing all documents. The 3-year clinical follow-up was prespecified in the study protocol.

STATISTICAL ANALYSIS. The study hypothesis was that the DCB was noninferior to the DES in terms of in-lesion LLL. Accordingly, we assumed an LLL of 0.20 mm in the DES arm with a delta of 0.35, alpha of 5%, power of 90%, and a noninferiority margin of 0.25 mm. Thus, a total of 230 patients to be enrolled in the PICCOLETO II trial, including a possible attrition rate of 10%, was calculated. Cox proportional hazards models and Kaplan-Meier curves were used to analyze time-related events. HRs were presented with 95% CIs. For baseline characteristics, continuous variables were reported as mean ± SD (Mann-Whitney *U* test) and categoric variables as frequency with

TABLE 1 Clinical Characteristics of the Study Population at Baseline

	DES (n = 114)	DCB (n = 118)	*P* Value
Male	87 (76.9)	83 (70.3)	0.25
Age, y	66 (50-82)	64 (48-80)	0.32
Hypertension	76 (67.2)	77 (65.2)	0.74
Diabetes	40 (35.4)	45 (38)	0.65
Insulin-dependent diabetes	15 (13.3)	21 (17.8)	0.66
Smoke	19 (16.7)	23 (19.5)	0.84
Dyslipidemia	63 (55)	72 (61)	0.66
Renal failure (eGFR <60 mL/min)	12 (10.6)	4 (3.3)	0.03
Previous MI	34 (30)	45 (38)	0.19
Previous CABG	4 (3.5)	4 (3.3)	0.95
Previous PCI	60 (53)	59 (50)	0.33
LVEF	58 [7]	58 [10]	0.89
Clinical presentation			
Stable angina	63 (55.7)	64 (54.2)	0.81
Unstable angina	18 (16)	17 (14.4)	0.74
NSTEMI	23 (20.3)	25 (21.1)	0.87
STEMI, late comers	9 (8)	12 (10.3)	0.34

Values are n (%) or median (IQR) unless otherwise indicated.

CABG = coronary artery bypass grafting; DCB = drug-coated balloon; DES = drug-eluting stent; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

TABLE 2 Lesion Characteristics and Procedural Aspects

	DES (n = 114)	DCB (n = 118)	*P* Value
SYNTAX score	17 [12]	16 [11]	0.36
Bifurcation lesion	14 (12.3)	15 (12.7)	0.94
Multivessel disease	86 (76)	86 (72.8)	0.5
Target vessel LAD	44 (39)	47 (40)	0.31
Target vessel LCX	35(31)	44 (37.2)	0.12
Target vessel RCA	34 (30.2)	27 (22.8)	0.19
Total contrast use, mL	155 [67-289]	152 [75-301]	0.37
Total fluoroscopy time, min	11 [4-67]	13 [5-59]	0.22
Predilatation	78 (69)	99 (84)	0.007
Postdilatation	66 (59.4)	4 (3.3)	0.001
Scoring balloon use for lesion preparation	18 (15.8)	26 (22)	0.13
Number of devices used	1.12 [1-1.41]	1.03 [1-1.12]	0.004
Length of device used, mm	18.3 ± 6.9	21.8 ± 8.2	0.006
Mean inflation pressure, atm	13.7 ± 2.5	11.4 ± 3.3	0.03
Mean duration of inflation, s	21.4 ± 11.8	49.2 ± 14.5	0.002
Bailout stenting	–	8 (6.7)	–
Angiographic success	113 (99.1)	116 (98.3)	0.88
Procedural success	112 (98.2)	116 (98.3)	0.92
Intracoronary imaging use	11 (9.6)	12 (10.2)	0.62
Peak troponin I after the intervention, ng/mL	6.14 ± 5.80	3.6 ± 3.21	0.09

Values are mean ± SD or n (%) unless otherwise indicated.

LAD = left anterior descending; LCX = left circumflex; RCA = right coronary artery; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery; other abbreviations as in Table 1.

percentage, with 95% CIs determined by the Wilson score method. Adjusted odds ratios were calculated with the logistic regression model and the HR with the Cox model. All analyses were performed by intention-to-treat. All *P* values <0.05 were considered statistically significant. All statistical analyses were performed with SPSS software (version 26, SPSS, Inc).

RESULTS

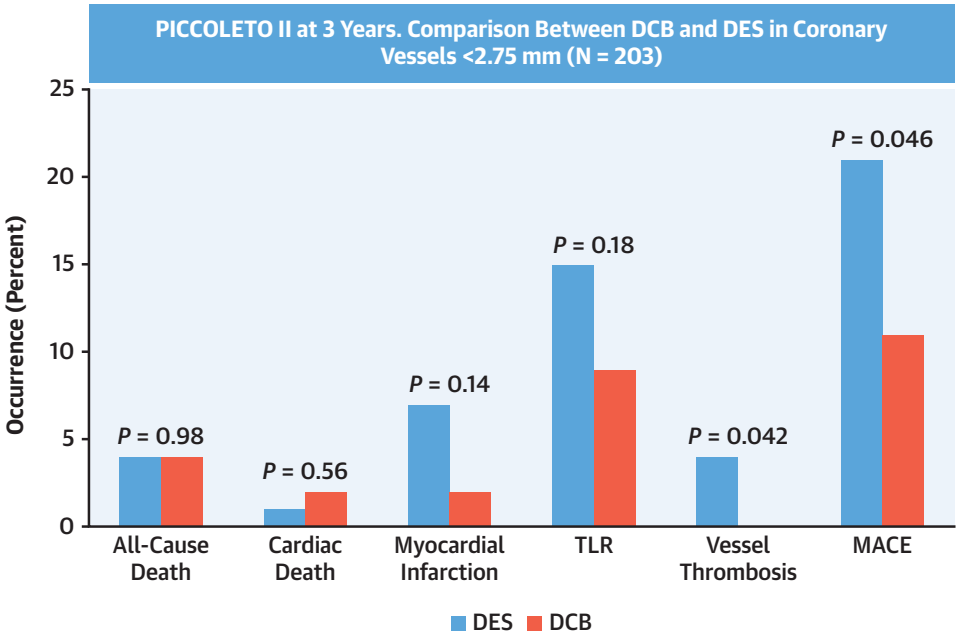
Of the 232 patients enrolled in the study, 114 patients were allocated to the DES and 118 to the DCB group. Importantly, group allocation was performed before lesion preparation. Significant differences between groups regarding the main clinical characteristic of the population enrolled were not observed (Table 1). Table 2 describes the procedural characteristics, with more patients undergoing lesion predilatation in the DCB arm and longer devices used in the DCB arm. The bailout stenting rate, which was always performed with the DES, was only 6.7%.

We previously reported the primary endpoint of the PICCOLETO II study, which showed the superiority of the DCB vs the DES in terms of in-lesion LLL (0.04 ± 0.28 mm vs 0.17 ± 0.39 mm; $P = 0.03$).[6] Other angiographic and procedural parameters were not significantly different between the 2 study groups as well as the 12-month clinical outcome.[6]

After a median of 1,101 days (IQR: 1,055-1,146 days), 102 patients (86%) in the DCB arm and 101 (88.5%) in the DES arm underwent the scheduled clinical follow-up or had available clinical information. All-cause mortality occurred in 4 patients per group ($P = 0.98$); 2 patients died of cardiac causes in the DCB group (1 fatal MI not related to the target vessel and 1 end-stage heart failure) and 1 in the DES group (unexplained and unwitnessed sudden death) ($P = 0.56$). Four cases of target vessel thrombosis in the DES arm and none in the DCB arm ($P = 0.042$) were observed. TLR was not significantly lower in the DCB arm (9 patients [8.8%] vs 15 [14.8%] in the DES arm; $P = 0.18$). The MACE rate (ie, the primary endpoint of the present study) was significantly lower in the DCB arm compared with the DES arm (n = 11 [10.8%] vs n = 11 [20.8%]; $P = 0.046$) (Central Illustration, Table 3).

Figure 2 depicts the Kaplan-Meier curves of MACEs according to treatment allocation for the entire length of follow-up.

CENTRAL ILLUSTRATION **Long-Term Study Findings**



Cortese B, et al. J Am Coll Cardiol Intv. 2023;16(9):1054–1061.

Comparison between drug-coated balloons (DCBs) and drug-eluting stents (DES) in coronary vessels <2.75 mm. MACE = major adverse cardiac event(s); PICCOLETO II = Drug Eluting Balloon Efficacy for Small Coronary Vessel Disease Treatment; TLR = target lesion revascularization.

DISCUSSION

SUMMARY OF THE STUDY RESULTS. PICCOLETO II was a multicenter, multinational, open-label investigator-driven, randomized clinical trial aiming at assessing the short angiographic performance of a novel paclitaxel DCB and its long-term outcome compared with a new-generation DES. The similar angiographic performance of the 2 strategies (but superiority in the case of the primary endpoint LLL for the DCB) was previously reported. The results of the latest clinical follow-up of PICCOLETO II, herewith presented, confirm the safety and the efficacy of this device with DCB, showing for the first time a significant reduction in MACEs and target vessel thrombosis at 3 years compared with the modern DES.

LONG-TERM EVENTS WITH DESs. The currently available DESs are highly performing devices in terms of safety and efficacy. However, in the very long-term, they still remain associated with a very low but constant risk of adverse events such as TLF every year. In a recently reported very long-term outcome study, this event rate with current DESs eventually reached 43.8% after 10 years, with a yearly rate of 3.3% after year 1.[5] On top of this, in the case of more complex lesion subsets, such as SVD or in case of long stenting, this late failure can lead to a 2-fold rate in TLF.[2-4] The current patient population routinely treated in all catheterization laboratories shares a high bleeding risk, a phenomenon also associated with higher rates of adverse clinical events after DESs.[11]

COULD DCB PREVENT LONG-TERM EVENTS?. Theoretically, DCB angioplasty could be associated with a flattening of the adverse event curve in the long-term because this technology does not require any prosthesis implantation, and DESs are associated with adverse events, probably related to the permanent metallic prosthesis itself. Moreover, some paclitaxel DCBs have shown a late positive vessel remodeling effect when used in native vessel disease, eventually leading to an LLL proximal to 0 mm.[12,13]

TABLE 3 Clinical Outcome After 3 Years (Kaplan-Meier Estimates)

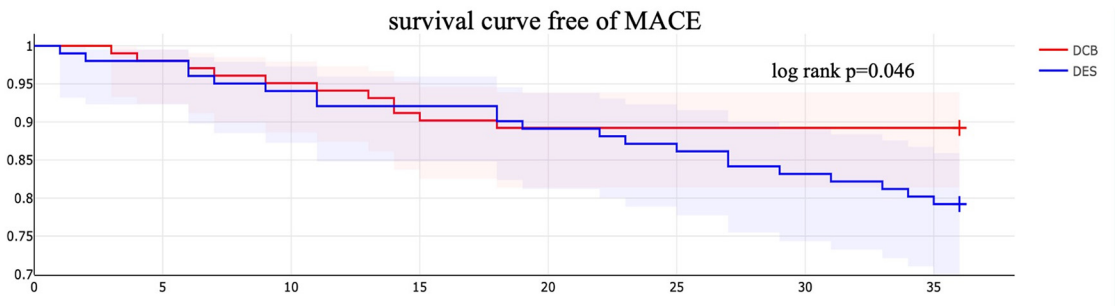
	DES (n = 101)	DCB (n = 102)	*P* Value
All-cause death	4 (3.96)	4 (3.92)	0.98
Cardiac death	1 (1)	2 (1.96)	0.56
Myocardial infarction	7 (6.9)	2 (1.96)	0.14
TLR	15 (14.8)	9 (8.8)	0.18
Vessel thrombosis	4 (3.96)	0	0.042
MACE	21 (20.8)	11 (10.8)	0.046

Values are n (%) unless otherwise indicated.
MACE = major adverse cardiac event(s); TLR = target lesion revascularization; other abbreviations as in Table 1.

Of note, this effect can be particularly appealing in small- or midsize vessels like the ones treated in the current study. Other studies have previously shown a drastic reduction in TLF after the first 9 to 12 months after DCB application. In the BELLO (Balloon Elution and Late Loss Optimization) randomized trial, the In-Pact Falcon paclitaxel DCB (Invatec-Medtronic) showed a significant reduction in the rate of MACEs compared with first-generation DESs (14% vs 30%; $P = 0.015$) with very few events after 7 months from the index procedure.[14] Similarly, a meta-analysis of 4,590 patients treated with the paclitaxel DCB vs other treatment options showed reduced rates of cardiac (risk ratio [RR]: 0.53; 95% CI: 0.33-0.85; $P = 0.009$) and total (RR: 0.73; 95% CI: 0.53- 1.00; $P = 0.047$) mortality with few adverse events after 12 months.[15] The long-term follow-up of PICCOLETO II shows a divergence between the curve of events after 20 months, with an almost straight line in the DCB arm. It is difficult to speculate on the behavior of the DCB after the first months from intervention, with 1 possibility being the quiescence of any effect related to a DCB PCI, compared with some detrimental effects of the permanent prostheses implanted on the vessel wall at the long-term clinical follow-up. However, the findings of this report should be put into the context of a study not powered for clinical endpoints, with 14% of patients lost at follow-up and with more patients with renal failure (glomerular filtration rate <60 mL/min) in the DES arm. Moreover, the low use of intravascular imaging (10% in each group) might be responsible for a higher risk of stent underexpansion, leading to a higher risk of stent thrombosis.

MORTALITY AFTER DCB USE. A few years ago a meta-analysis shed light on a hypothetical increase in mortality after paclitaxel application for peripheral interventions.[16-19] Conversely, a meta-analysis on "coronary" applications for DCBs and other large reports and data sets showed no association between paclitaxel DCB use and mortality.[15,20] The 3-year outcome of the BASKET SMALL II (Basel Stent Kosten Effektivitäts Trial Drug Eluting Balloons vs Drug Eluting Stents in Small Vessel Interventions) study shows similar cardiac (HR: 1.29; 95% CI: 0.63-2.66; $P = 0.49$) and all-cause mortality (HR: 1.05; 95% CI: 0.62-1.77; $P = 0.87$) between DCBs and DESs.[21] Our current 3-year findings reported here further confirm the lack of any association between all-cause mortality and paclitaxel application in the coronary field, with 4 cases both in the DCB and the DES arm but none of them related to a potentially toxic effect of

FIGURE 2 Kaplan-Meier Curves of the Study Endpoint MACEs According to Treatment Allocation for the 3-Year Follow-Up



number at risk								
group DES	114	108	99	98	95	90	85	80
group DCB	118	116	105	102	101	96	95	91

MACE = major adverse cardiac event(s); other abbreviations as in Figure 1.

this drug in other organs. All these findings corroborate the thesis that a correlation between the currently available paclitaxel DCB and mortality does not exist in the coronary field.

STUDY LIMITATIONS. As previously stated,[6] this study has several limitations. First, treatment assignment was performed in an open-label fashion; thus, biases in the initial reports and the clinical follow-up cannot be completely eliminated despite the blinded clinical event committee and the independent core laboratory used. Second, the selection of centers to participate in PICCOLETO II was done according to a 5-year experience using DCBs for native vessel disease, which was also reflected by the low bailout stenting rate; thus, such results might not be reproducible in other settings. Another limitation is that we decided to include the MACE rate as the cumulative secondary endpoint instead of target vessel failure, with the inherent limitation of including MI and not target vessel MI as an endpoint. At the time of protocol drafting, we did not expect a major role determined by this endpoint at the long-term follow-up. Finally, and most importantly, we report a 3-year clinical outcome that was prespecified in the study protocol, but the study design and the final population were not powered enough for drawing definitive conclusions on the long-term clinical outcome. A study including a larger population and an ad hoc clinical primary endpoint is necessary to confirm our preliminary findings.

CONCLUSIONS

PICCOLETO II long-term data show for the first time a reduction in late adverse clinical events with DCBs compared with current era DESs in de novo lesions, mainly driven by a reduction of vessel thrombosis and MACEs after 1 year with DCBs. An adequately powered study should be conducted to confirm these preliminary findings.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

PICCOLETO II is an investigator-driven study endorsed by the Italian Society of Interventional Cardiology GISE. The role of GISE was to coordinate the centers and submit the protocol to the ethics committees. GISE had no other role, including protocol drafting, data analysis, and manuscript writing. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Small vessel coronary artery disease still represents a challenging subset for DESs with an increase in long-term adverse events.

WHAT IS NEW? This is the first randomized study between the new-generation DCB vs the DES in small vessels to show 1) an improved angiographic outcome at 6 months and 2) reduced clinical events (MACEs and acute vessel closure) after 3 years.

WHAT IS NEXT? A larger study adequately powered for hard clinical endpoints is needed in order to confirm these findings in a larger data set of patients.

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KEY WORDS drug-coated balloon, everolimus-eluting stent(s), long-term comparison with drug-eluting stent(s), native vessel disease, small coronary vessel disease

Results of New Dual-Drug Coated Balloon Angioplasty versus POBA for Femoropopliteal Lesions

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Background: The study aimed to assess the 24-month safety and effectiveness of a new generation drug-coated balloon (DCB) (Elutax; AR Baltic Medical, Vilnius Lithuania—also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) for the treatment of patients with femoropopliteal lesions.

Methods: From January 2019 to January 2020, DCB angioplasties using Elutax were performed on 53 consecutive patients (53 limbs) with femoropopliteal lesions (group A) and compared with a noncontemporary control group (group B) consisting of 71 patients (71 limbs) treated with plain old balloon angioplasty (POBA) between January 2017 and January 2018. Before performing the angioplasty, both groups underwent clinical examination, ultrasound evaluation, and computed tomography angiography to delineate subject clinical and baseline lesion characteristics. Primary end point was primary patency rate at 24 months. Secondary end points included clinically driven target lesion revascularization (CD-TLR), overall survival and limb salvage rates.

Results: In both groups technical success rate was 100% with bailout stenting performed in 16.9% (9/53) of lesions in group A, while stenting was necessary in 22.5% of lesions (16/71) in group B. Patients treated with Elutax exhibited lower 24-month restenosis/reocclusion rate and improved primary patency compared to those treated with POBA (restenosis/reocclusion rate: 9.4% vs. 25.3%, CI 95% 0.01−0.30, $P = 0.034$; primary patency: 88.2% vs. 71.5%, log rank $P = 0.03$). Twenty-four-month CD-TLR rate was 7.5% for DCB versus 18.3% for POBA. No device or procedure-related deaths occurred, and no 30-day mortality was observed in either group. During the follow-up period, the limb salvage rate was 94.9% for A group and 92.1% for B group. All minor amputations occurred in limbs presented with chronic limb threatening ischemia (CLTI). Overall survival was 91.7% for group A and 89.4% for group B.

Conclusions: Paclitaxel + Dextran DCB angioplasty proved safe and effective in managing chronic lesions of femoropopliteal arteries. Our experience has shown superior primary patency rate for Elutax when compared to POBA.

Conflicts of interest: There are no financial conflicts of interest to disclose.

Authors contribution: All authors contributed to (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

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INTRODUCTION

European guidelines[1] recommend an endovascular strategy for lesions <25 cm in both artery symptomatic femoropopliteal disease and below knee artery disease as a first-line treatment. For chronic limb threatening ischemia (CLTI), the guidelines recommend a revascularization strategy in accordance with lesion complexity.

Surgical revascularization was once the only strategy available but in recent years endovascular approaches have gained popularity due to their faster recovery times and correspondingly lower morbidity and mortality rates, particularly in patients with multiple medical comorbidities.

That being said, higher restenosis rates and low long-term patency rates remain limiting factors for the endovascular approach. In order to improve the primary patency rate following plain old balloon angioplasty (POBA), bare-metal stents may be implanted, even if the presence of a permanent metallic scaffold seems to increase restenosis and occlusions.

Over the last years, Paclitaxel-based drug-coated balloons (DCB) and drug-eluting stents (DES) have been showing promise for the treatment of peripheral artery disease and have been introduced to help with lowering restenosis and improving patency rates.[2] Several meta-analyses have reported the superior performance of paclitaxel-based DCBs compared to standard POBA for femoropopliteal peripheral artery lesions,[3,4] causing some authors to consider DCB a first choice for treatment of de novo stenosis. Many commercial devices are available and a new generation of DCBs can combine two drugs to improve results.

A published meta-analysis of randomized controlled trials has shown an increased risk of mortality within 5 years following application of paclitaxel-coated DCB and DES in femoropopliteal lesions,[5,6] postulating a dose-dependent relationship between the death and paclitaxel administration. However, it remains unclear whether treatment of femoropopliteal lesions with a paclitaxel-coated DCB leads to an increase in all-cause mortality in a real-world setting.

The objective of this study is to analyze the safety and effectiveness of a new generation DCB (Elutax; AR Baltic Medical, Vilnius Lithuania—also marketed as Emperor in some European countries; Aachen Resonance, Germany, and AB Medica, Italy) for femoropopliteal lesions and to demonstrate a reduction in restenosis rates and need for reintervention compared to standard POBA, using a case-control study as a model.

MATERIALS AND METHODS

We retrospectively reviewed for a case-control study a prospectively maintained registry of all patients with symptomatic femoropopliteal artery lesions treated with Elutax between January 2019 and January 2020 and POBA between January 2017 and January 2018. Approval from the investigational review board of the Interuniversity Center of Phlebolymphology, International Research and Educational Program in Clinical and Experimental Biotechnology (approval number: ER.ALL.2018. 49 A) was obtained. Inclusion criteria were Rutherford class from 3 to 5, significant femoropopliteal stenosis or occlusion >40 mm in length with patency of at least 1 below-the-knee vessel, and life expectancy >1 year. Exclusion criteria were occlusion longer than 25 cm, occlusion of all below-the-knee vessel, multilevel atherosclerotic disease requiring additional procedures (i.e., iliac angioplasty/stenting, common femoral artery endarterectomy, and so on), and preplanned major amputation (Table I). Indications for intervention included the following: lifestyle-limiting intermittent claudication (Rutherford 3), ischemic rest pain (Rutherford 4), minor tissue loss-nonhealing ulcer, and focal gangrene with diffuse pedal ischemia (Rutherford 5). All patients had a computed tomography angiography to study the features of the arterial lesions and plan the intervention.

Prior to procedure, patient demographics, clinical presentation, and ankle-brachial index (ABI) assessment and comorbidities were identified and recorded (Table II).

Fifty-three consecutive patients (36 males) treated with Elutax were enrolled and defined as group A, and 71 consecutive patients (47 males) treated with POBA were defined as group B. Subjects were followed for a total of 24 months and underwent duplex ultrasonography evaluationat 30 days and 6, 12, and 24 months, thereafter. We performed additional ultrasonographic evaluation, for patients who clinically needed re-evaluation due to recurrent symptoms and/or worsening pain at rest in the limb treated, and nonhealing lesions. Ultrasound performance and interpretation was blinded. Assessments at 1, 6, 12, and 24 months included the occurrence of reintervention (target vessel recanalization, target lesion revascularization (TLR), and amputation), major adverse cardiovascular and cerebrovascular events (MACCE) and health status. Primary patency, defined as freedom from restenosis (duplex ultrasonography peak systolic velocity ratio ≤2.4) and/or reocclusion, was

Table I. Study enrollment criteria

Inclusion criteria	Exclusion criteria
Rutherford 3−4−5	Rutherford 0−1−2−6
Significant femoropopliteal stenosis or occlusion >40 mm in length	Occlusion longer than 25 cm
At least 1 below-the-knee vessel with distal runoff	Poor distal runoff (occlusion of all below-the-knee vessel)
Life expectancy >1 year	Multilevel atherosclerotic disease requiring additional procedures
	Preplanned major amputation

analyzed throughout 24 months per study protocol and considered as the primary end point. Secondary end points included the following: clinically driven target lesion revascularization (CD-TLR) rate, defined as rate of patients with restenosis/reocclusion of the target vessel with need for revascularization due to recurrence of symptoms; overall survival and limb salvage rate.

Statistical analysis was carried out with version April 1, 1106 2009−2021 RStudio, PBC. Continuous variables (age, body mass index, ABI, target lesion reference vessel diameter and length, sheath size, predilation balloon diameter, length and pressure, number of treatment balloons per subject) and outcomes (ABI, procedural time, follow-up time and hospital stay) were analyzed with a Welch two sample *t*-test, while categorical variables (males, current smoker, hypertension, diabetes, insulin-dependent diabetes, dyslipidemia, coronary artery disease, prior myocardial infarction, chronic kidney disease, previous amputation and stenting, Rutherford category, popliteal involvement, total occlusion, no. of patent runoff vessels, contralateral femoral access, type of lesion and need for stenting) with a two-sample test for equality of proportions with continuity correction. Categorical outcomes (restenosis/reocclusion, CD-TLR, target limb major amputation, all-cause death and MACCE-related death) were analyzed with Fisher's test.

The Kaplan−Meier method was used to evaluate time-to-event data. Difference in the survival curves between the treatment groups was assessed using the log-rank test.

The DCB used for our study was Elutax, a third-generation balloon that is the newest of its kind, which enables a long-term drug release over a period of months with only a single inflation. The balloon integrated two different drugs (Dextran + Paclitaxel) on its surface: Dextran, which provided an antithrombotic effect to reduce erythrocyte aggregation, platelet adhesiveness and function while activating plasminogen with a thrombolytic effect, and Paclitaxel which blocked progression of cellular mitosis inhibiting cell division and proliferation to reduce restenosis.[6−8]

Local anesthesia was administrated to all patients. An ipsilateral or contralateral femoral approach was used to perform procedure. After the introducer sheath was successfully inserted, 3500 UI heparin sodium was administrated. In all cases we used plain balloon with a diameter of 1 mm undersized to the reference vessel diameter (RVD) to predilate target lesion. After that, the lesions were dilated with Elutax balloon using a diameter 1:1 ratio to the RVD, which ranged from 4.0 to 6.0 mm. Elutax was inflated at 10 atmospheres for at least 180 sec according to manufacturer's instructions for use. As flow limiting dissection is a significant risk factor for restenosis/occlusion, in cases of a flow-limiting dissection or >50% residual stenosis after Elutax angioplasty, a bailout stent (Everflex Self-Expanding Peripheral Stent System; ev3 Inc. Plymouth, Minnesota, United States) was deployed. Following procedure, all patients were prescribed with a dual antiplatelet therapy, acetylsalicylic acid (aspirin, 100 mg/d) and clopidogrel (75 mg/d) for 24 months, and a single antiplatelet therapy was indefinitely prescribed thereafter. No significant difference about the adherence to anti-platelet therapy between the POBA and Elutax groups was observed. Standard and advanced wound care was continued after intervention until healing was achieved. Primary and secondary end points were assessed at 24 months and no patients were lost to follow up during this period.

RESULTS

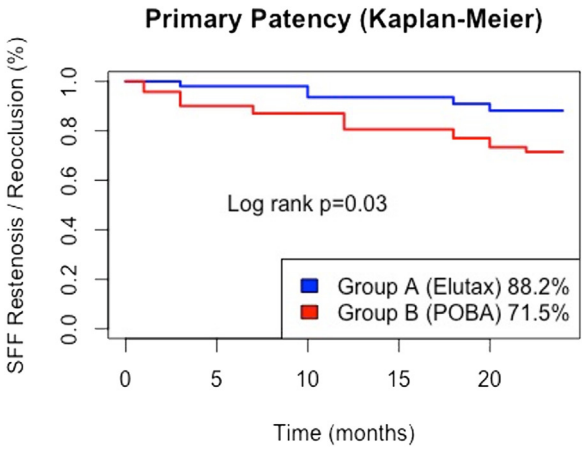
Both treatment groups had similar demographics, comorbidities, and lesion characteristics at baseline (Table II). Cardiovascular risk factors were prevalent in the patients included in the study (Table II), and 13.7% of patients suffered from chronic kidney disease. Half the patients presented with CLTI (Table II). Mean lesion length was 121.5 ± 58.1 mm in

Table II. Subject clinical, baseline lesion, and procedural characteristics

Subject clinical characteristics	Overall ($N = 124$)	Group A (Elutax) $n = 53/124$	Group B (POBA) $n = 71/124$	CI 95%	*P*-value (<0.05)
Age (years)	67.3 ± 8.1	67.3 ± 9.0	67.2 ± 7.4	[−3.15; 2.88]	0.927
Males	83/124 (66.9%)	36/53 (67.9%)	47/71 (66.1%)	[−0.20; 0.16]	0.992
BMI (kg/m^2)	27.0 ± 3.3	26.8 ± 3.4	27.2 ± 3.2	[−0.81; 1.60]	0.515
Current smoker	51/124 (41.1%)	19/53 (35.8%)	32/71 (45%)	[−0.09; 0.28]	0.396
Hypertension(SAP>140 mm Hg and/or DAP>90 mm Hg)	102/124 (82.2%)	43/53 (81.1%)	59/71 (83%)	[−0.13; 0.17]	0.963
Diabetes (glycemia>125 mg/dL and/or use of HD/insulin)	76/124 (61.2%)	31/53 (58.4%)	45/71 (63.3%)	[−0.14; 0.23]	0.713
Insulin-dependent diabetes	30/76 (39.4%)	13/31 (41.9%)	17/45 (37.7%)	[−0.29; 0.20]	0.900
Dyslipidemia(Tot. Chol.>240 mg/dL and/or TGL>150 mg/dL and/or use of LLD)	84/124 (67.7%)	35/53 (66%)	49/71 (69%)	[−0.15; 0.21]	0.875
CAD	47/124 (37.9%)	19/53 (35.8%)	28/71 (39.4%)	[−0.15; 0.22]	0.825
Prior MI	16/124 (12.9%)	9/53 (16.9%)	7/71 (9.8%)	[−0.21; 0.06]	0.368
CKD (GFR<60 ml/min/1,73m^2)	17/124 (13.7%)	5/53 (9.4%)	12/53 (16.9%)	[−0.06; 0.20]	0.351
Previous amputation	4/124 (3.2%)	3/53 (5.6%)	1/71 (1.4%)	[−0.12; 0.04]	0.416
Previous stenting	12/124 (9.6%)	8/53 (15.1%)	4/71 (5.6%)	[−0.22; 0.03]	0.145
ABI	0.52 ± 0.09	0.51 ± 0.08	0.52 ± 0.09	[−0.02; 0.04]	0.527
Rutherford 3	57/124 (45.9%)	26/53 (49%)	31/71 (43.6%)	[−0.24; 0.13]	0.678
Rutherford 4	41/124 (33%)	16/53 (30.1%)	25/71 (35.2%)	[−0.13; 0.23]	0.692
Rutherford 5	26/124 (20.9%)	11/53 (20.7%)	15/71 (21.1%)	[−0.14; 0.15]	1.000
Baseline lesion and procedural characteristics					
Popliteal involvement	32/124 (25.8%)	13/53 (24.5%)	19/71 (26.7%)	[−0.14; 0.19]	0.941
Target lesion RVD (mm)	5.1 ± 0.6	5.1 ± 0.6	5.1 ± 0.6	[−0.21; 0.23]	0.938
Target lesion length (mm)	117 ± 55.2	121.5 ± 58.1	113.6 ± 53.2	[−28; 12.3]	0.441
Total occlusion	96/124 (77.4%)	42/53 (79.2%)	54/71 (76%)	[−0.19; 0.13]	0.839
No. of patent runoff vessels					
1	45/124 (36.2%)	18/53 (33.9%)	27/71 (38%)	[−0.14; 0.22]	0.781
2	36/124 (29%)	14/53 (26.4%)	22/71 (30.9%)	[−0.13; 0.22]	0.722
3	43/124 (34.6%)	21/53 (39.6%)	22/71 (30.9%)	[−0.27; 0.10]	0.418
Contralateral femoral access	107/124 (86.3%)	47/53 (88.6%)	60/71 (84.5%)	[−0.17; 0.09]	0.686
Type of lesion					
De novo	101/124 (81.4%)	41/53 (77.3%)	60/71 (84.5%)	[−0.08; 0.22]	0.435
Restenosis/reocclusion	19/124 (15.3%)	9/53 (16%)	10/71 (14%)	[−0.17; 0.11]	0.848
Intrastent restenosis/reocclusion	4/124 (3.2%)	3/53 (5.6%)	1/71 (1.4%)	[−0.12; 0.04]	0.416
Sheath size (French)	5.8 ± 0.7	5.8 ± 0.8	5.8 ± 0.7	[−0.31; 0.22]	0.735
Predilation balloon diameter (mm)	4.3 ± 0.7	4.3 ± 0.8	4.2 ± 0.7	[−0.31; 0.24]	0.806
Predilation balloon length (mm)	74.7 ± 27.3	75.8 ± 28	73.9 ± 26.9	[−11.8; 8.01]	0.704
Predilation balloon pressure (atm)	8.5 ± 2.7	8.5 ± 2.9	8.5 ± 2.6	[−1.07; 0.92]	0.885
No. of treatment balloons per subject	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	[−0.13; 0.08]	0.603
Need for stenting	25/124 (20.1%)	9/53 (16.9%)	16/71 (22.5%)	[−0.10; 0.21]	0.591

BMI, body mass index; SAP, systolic arterial blood pressure; DAP, diastolic arterial blood pressure; HD, hypoglycemic drugs; TGL, triglycerides; LLD,lipid-lowering-drugs; CAD, coronary artery disease; MI, myocardial infarction; CKD, chronic kidney disease; GFR, glomerular filtration rate; RVD, reference vessel diameter.

the Elutax group versus 113.6 ± 53.2 mm in the POBA group ($P = 0.441$). Forty-two (79.2%) of 53 Elutax-treated lesions and 54 (76%) of 71 POBA-treated lesions were occlusions. Thirty-three-point nine percent and 38% of the lesions in groups A and B respectively, had only 1 distal outflow vessel with the remainder having at least 2 distal outflow vessels. Owing to the >50% residual stenosis (CLTI limbs, 4) and flow-limiting dissections (CLTI limbs, 5), 9 superficial femoral lesions in group A and 16 in group B required stent placement, resulting in a stent-assisted technical success rate of



groups=Elutax

time	n.risk	n.event	survival	std.err
3	51	1	0.980	0.0194
10	44	2	0.936	0.0359
18	35	1	0.909	0.0437
20	33	1	0.882	0.0503

groups=POBA

time	n.risk	n.event	survival	std.err
1	71	3	0.958	0.0239
3	67	4	0.901	0.0357
7	60	2	0.871	0.0403
12	54	4	0.806	0.0485
18	45	2	0.770	0.0526
20	42	2	0.734	0.0561
22	39	1	0.715	0.0577

Fig. 1. The Kaplan-Meier estimate of primary patency.

100%. Technical success, defined as residual diameter stenosis ≤50% for non-stented patients or ≤30% for stented patients, was achieved in 100% of the subjects in both groups.

The restenosis/reocclusion rate at 24-months was significantly lower with Elutax than with POBA (restenosis/reocclusion rate: 9.4% vs. 25.3%, odds ratio [OR] 0.30, 95% confidence interval [CI]: 0.08−0.95, $P = 0.034$). The Kaplan−Meier estimate of primary patency was 88.2% for Elutax compared to 71.5% for POBA (log rank $P = 0.03$; Fig. 1). Elutax-treated patients showed no significant difference in CD-TLR rate at 24 months (7.5% vs. 18.3%, OR: 0.36, 95% CI: 0.08−1.28, $P = 0.114$) compared with patients treated with POBA (Table III, Fig. 2). The mortality rate at 24-months was similar in both groups (5.6% vs. 8.4%, OR 0.65, 95% CI: 0.10−3.23, $P = 0.731$). The Kaplan−Meier estimate of overall survival was 91.7 % for Elutax compared to 89.4% for POBA (log rank $P = 0.5$; Fig. 3). Four were MACCE-related deaths (1.8% vs. 4.2%, OR: 0.43, 95% CI: 0.008−5.64, $P = 0.635$) while 3/124 and 2/124 were respiratory insufficiency- and septic state-related deaths.

During the follow-up period of 24 months, 2 above-the-knee amputations in group A versus 5 amputations in group B were observed (3.7% vs. 7%, OR: 0.52, 95% CI: 0.04−3.33, $P = 0.697$). The Kaplan−Meier estimate of limb salvage was 94.9% for Elutax compared to 92.1% for POBA (log rank $P = 0.4$; Fig. 4).

No deaths or other major complications (i.e., rupture, perforation, embolization of distal arteries, and contrast nephropathy) were observed in any of the patients within 30 days after procedure in either group.

DISCUSSION

Several randomized trials report on the superior benefits/major advantages of employing DCB over POBA in patients with femoropopliteal disease,[7,9,10] denoting higher patency rates compared to uncoated balloons.

Our study demonstrates that performing endovascular DCB angioplasty with Elutax can be safe and effective in treating patients with atherosclerotic femoropopliteal lesions leading to high levels of technical success, limb salvage and patency rates as well as low prevalence of procedure-related complications, even in limbs presenting CLTI and long-segment occlusion lesions.

Elutax has been used in several trials to treat de novo coronary and intracranial artery stenosis resulting in a more favorable angiographic outcome of ''new generation'' DCBs versus other DCBs, thereby demonstrating their feasibility and safety in patients with symptomatic high-grade stenosis and is supported by significantly lower rates of ischemic re-events or restenosis.[11,12]

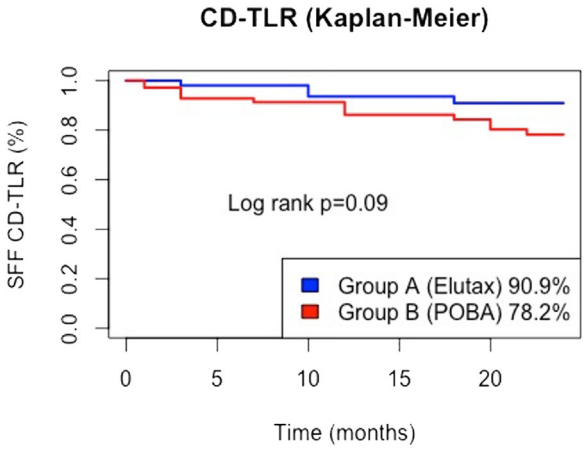
Treatment of long steno-occlusive femoropopliteal lesions is associated with a high risk of dissection to rechannel vessel increasing the impact of future restenosis, so it could be necessary stents implantation even if in short no flow limiting dissections it should be unnecessary.[13] Long-segment occlusions typically treated with subintimal recanalization using balloon cause tears and dissections. In such cases the use of DCB could improve angioplasty result and late vascular remodeling.[14]

Because flow-limiting dissection is a significant risk factor for restenosis/reocclusion,[14] 25 out of the 124 treated cases in our study required stent placement due to flow-limiting dissections. Moreover, it was found that, when compared to POBA, DCB was associated with decreased arterial wall fibrosis after

Table III. Safety and effectiveness outcomes (24-months)

Safety and effectiveness outcomes (24 months)	Overall	Group A (Elutax)	Group B (POBA)	Odds ratio	CI 95%	*P*-value (<0.05)
	N = 124	*n* = 53/124	*n* = 71/124			
Restenosis/reocclusion (No. of restenosis or reocclusions/total limb treated)	23/124 (18.5%)	5/53 (9.4%)	18/71 (25.3%)	0.30	[0.08; 0.95]	0.034
CD-TLR	17/124 (13.7%)	4/53 (7.5%)	13/71 (18.3%)	0.36	[0.08; 1.28]	0.114
Target limb major amputation	7/124 (5.6%)	2/53 (3.7%)	5/71 (7%)	0.52	[0.04; 3.33]	0.697
All-cause death	9/124 (7.2%)	3/53 (5.6%)	6/71 (8.4%)	0.65	[0.10; 3.23]	0.731
MACCE related death	4/124 (3.2%)	1/53 (1.8%)	3/71 (4.2%)	0.43	[0.008; 5.64]	0.635
ABI	0.8 ± 0.12	0.85 ± 0.12	0.77 ± 0.12	-	[−0.11; −0.03]	<0.001
Procedural time (min)	86.4 ± 34.5	85.1 ± 36.5	87.4 ± 33.2	-	[−10.2; 15.0]	0.711
Hospital stay (days)	2 ± 1.8	2 ± 2	2 ± 1.7	-	[−0.71; 0.65]	0.934
Follow-up time (months)	24 ± 0	24 ± 0	24 ± 0	-	NA	NA
Technical success	124/124 (100%)	53/53 (100%)	71/71 (100%)	NA	NA	NA

CD-TLR, clinically-driven target lesion revascularization; MACCE, major adverse cardiovascular and cerebrovascular events; NA, not applicable.



groups=Elutax

time	n.risk	n.event	survival	std.err
3	51	1	0.980	0.0194
10	44	2	0.936	0.0359
18	35	1	0.909	0.0437

groups=POBA

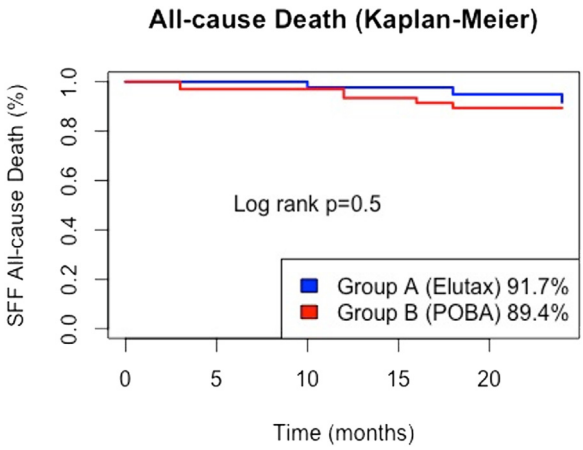
time	n.risk	n.event	survival	std.err
1	71	2	0.972	0.0196
3	67	3	0.928	0.0309
7	60	1	0.913	0.0340
12	54	3	0.862	0.0429
18	45	1	0.843	0.0461
20	42	2	0.803	0.0519
22	39	1	0.782	0.0545

Fig. 2. The Kaplan-Meier estimate of CD-TLR.

overstretch injuries by balloon angioplasty and reduced degrees of constrictive remodeling and neointimal hyperplasia.[11,15] Notwithstanding these findings, however, the effects of various DCBs or stents on the subintimal channel require further investigation.

Severe calcification reducing the antirestenotic effect of the drug is considered a risk factor for restenosis in the femoropopliteal segment[16] following DCB angioplasty,[17] and to support this 5 reocclusion episodes did occur in our Elutax group while in the POBA angioplasty group the reocclusion rate was even higher (18/71). These patients had been elected for surgical or hybrid procedures benefiting from the complementary role of endovascular and surgical treatments which compensated for unsatisfactory results of both approaches.[18,19]

Infrapopliteal outflow is considered a significant factor potentially affecting the primary patency rate of femoropopliteal occlusive diseases. Salapura et al.[20] reports that restenosis or reocclusion occurred in 23% of subjects with compromised outflow and 11% of patients with good runoff 1 month after femoropopliteal angioplasty, though restenosis or reocclusion incidence increased at approximately identical rates in both groups after 6 months (49% vs. 43%) and 12 months (57% vs. 52%) leading the authors to conclude that patients are predisposed to early restenosis or reocclusions if there is a compromised postprocedural infrapopliteal outflow. A retrospective review[21] of 86 patients treated with angioplasties for femoropopliteal occlusions found that a decreased primary patency and limb salvage rate was significantly associated with isolated popliteal artery outflow or one tibial vessel outflow during a mean follow-up time of 2.4 years (880 ± 68.84 days), suggesting that the impact of infrapopliteal outflow on long-term patency after



groups=Elutax

time	n.risk	n.event	survival	std.err
10	44	1	0.977	0.0225
18	35	1	0.949	0.0351
24	29	1	0.917	0.0467

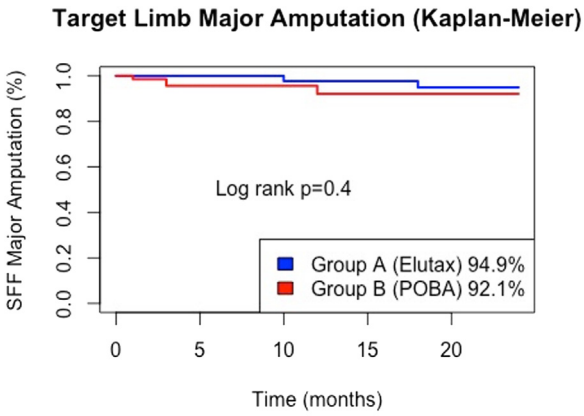
groups=POBA

time	n.risk	n.event	survival	std.err
3	67	2	0.970	0.0208
12	54	2	0.934	0.0320
16	47	1	0.914	0.0370
18	45	1	0.894	0.0413

Fig. 3. The Kaplan-Meier estimate of overall survival.

popliteal DCB angioplasty requires a longer follow-up period. A systematic review and meta-analysis by Katsanos et al. reported an increased risk of all-cause mortality following the application of paclitaxel-coated balloons and stents in the femoropopliteal artery.[6] In our study, no coating related adverse events were observed at 12- and 24-months follow-up with the Elutax approach. Moreover, overall survival at 24 months was higher in the Elutax group than in the POBA one (91.7% vs. 89.4%, log-rank $P = 0.5$; Fig. 1C). Due to the limited follow-up period, we were unable to evaluate the long-term safety of Elutax angioplasty in femoropopliteal artery lesions and further research with a longer follow-up duration is undoubtedly required for safety concerns. Several studies have proven that paclitaxel-DCB is also effective in treating limbs with CLTI caused by infrapopliteal lesions as evidenced by relief of rest pain and promotion of ulcer healing, citing that they give better results in outcomes when compared to POBA angioplasty.[3,4,9]

Due to the favorable results revealed by our analysis and reported herein, we can conclude that paclitaxel + dextran DCB is considered a safe and effective modality for treating femoropopliteal lesions, albeit a longer follow-up period is necessary to confirm its long-term efficacy.



groups=Elutax

time	n.risk	n.event	survival	std.err
10	44	1	0.977	0.0225
18	35	1	0.949	0.0351

groups=POBA

time	n.risk	n.event	survival	std.err
1	71	1	0.986	0.0140
3	67	2	0.956	0.0246
12	54	2	0.921	0.0341

Fig. 4. The Kaplan-Meier estimate of limb salvage.

CONCLUSIONS

New generation DCBs have firmly secured their propitious role in femoropopliteal disease proving excellent short-term patency and low TLR rates when compared to POBA alone. They have also been shown to be safe. Given the reduction in TLR and its ease of use, new generation DCBs can be considered an attractive alternative to conventional POBA. More randomized trials are necessary to optimize the drug dosage needed so as to ensure better long-term outcomes. This can be done by evaluating paclitaxel + dextran-based DCBs and establishing their safety in femoropopliteal disease.

The results of our study lead us to conclude that, when compared with POBA, treatment with Elutax provides superior clinical benefits throughout early and midterm follow-up bearing in mind, however, that longer-term outcomes are as yet uncertain and need to be studied further.

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ORIGINAL ARTICLE

Treatment of In-stent Restenosis of the Internal Carotid Artery Using Drug-eluting Balloons

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Abstract

Purpose In-stent restenosis (ISR) following internal carotid artery (ICA) stenting is relatively common with an estimated incidence of 5%. Treatment options include repeat angioplasty with conventional or drug-eluting balloons (DEB), repeat stent angioplasty and surgical intervention. Application of DEB in ISR of the coronary and peripheral arteries is an established method; however, data on DEB treatment of ICA ISR are sparse. In this work, results from a retrospective cohort of 45 patients harboring 46 ICA ISR lesions treated with DEB angioplasty are presented.

Methods Clinical, procedural and imaging data from DEB angioplasty treatment of 46 high-grade ICA ISR lesions in 45 patients, performed between 2013 and 2021 were collected. A single type of DEB (Elutax, Aachen Resonance, Aachen, Germany) was used in all procedures. Imaging follow-up was performed by regular Doppler ultrasound (DUS), verified by computed tomography angiography (CTA) in cases suspicious for a recurrent ISR.

Results Technical success was 100%. Intraprocedural and postprocedural complications were not encountered. Clinical follow-up was obtained in all patients. Recurrent stroke in the affected territory was not encountered. A recurrent ISR following DEB treatment was confirmed by DUS and CTA in 4/46 (8.7%) of the lesions and were retreated with DEB. A third recurrent ISR occurred in a single case (2%) and following a second DEB retreatment there were no signs of a fourth recurrence after 36 months follow-up.

Conclusion The use of DEB angioplasty is a safe and effective treatment of ICA ISR lesions, yielding significantly better results compared to other modalities. Randomized multicenter studies are warranted.

Keywords Stent · Carotid · Restenosis · Intervention · Drug-eluring balloons

Introduction

Atherosclerotic stenotic lesions of the proximal internal carotid artery (ICA) are responsible for up to 20% of severe acute ischemic stroke cases [1] and despite the advances in medical treatment, the invasive treatment of these lesions by an endovascular or surgical approach remains an important option of stroke prevention, in symptomatic and asymptomatic cases alike [2]. The recent large randomized trials comparing the safety and efficacy of carotid stenting (CAS) vs. endarterectomy (CEA) [3–5] showed similar outcomes in stroke prevention with both methods, initiating a shift in the treatment paradigm from favoring endarterectomy towards equal acceptance of both modalities [6].

A drawback of both CEA and CAS is the development of neointimal hyperplasia resulting in a progressive, significant in-stent recurrent stenotic lesion (ISR). The underlying pathology and the composition of the material causing lumi-

Availability of Data and Material Questions regarding details not seen in the manuscript should be addressed to the corresponding author, who maintains the clinical research files and provides access to the data upon reasonable request.

Code Availability Not applicable.

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nal narrowing is completely different compared to the original atherosclerotic plaque. The neointimal tissue is covered with endothelium and there is no debris material within the plaque, therefore the risk of increased thrombogenicity and embolization is minimal [7]; however, rapid progression of the luminal narrowing can lead to decreased blood flow velocity and may ultimately result in a thrombotic occlusion of the ICA. Accordingly, a significantly increased risk of ipsilateral stroke has been reported in patients with in-stent restenosis by multiple randomized trials [2, 4, 8, 9], underlining the importance of timely diagnosis and effective treatment of ISR lesions.

The literature on the treatment of ICA ISR is relatively sparse and randomized trials are lacking. Available treatment options include repeated CAS, endarterectomy or re-angioplasty (percutaneous transluminal angioplasty) (re-PTA) using a conventional or a drug-eluting balloon (DEB) [10]. Although the safe and effective application of paclitaxel-eluting DEBs is well established for the treatment of ISR in other vascular territories including the coronary [11], peripheral [12] and intracranial [13] arteries, results of a mere 33 DEB re-PTA procedures of ICA ISR have been published in case series in the literature altogether [14].

In the present retrospective study, we report our single center experience in the treatment of ICA ISR with re-PTA using a paclitaxel-eluting balloon in 46 ICA ISR lesions.

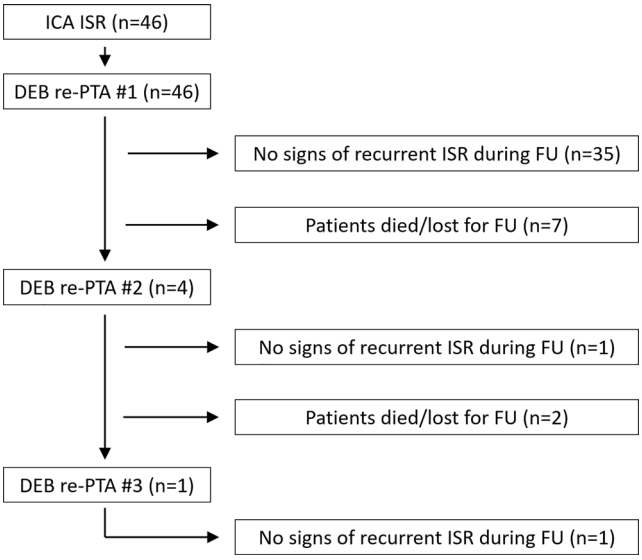

Fig. 1 Schematic drawing illustrating the treatment and follow-up algorithm of recurrent stenotic lesions following carotid artery stenting. *ICA* internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *PTA* percutaneous transluminal angioplasty, *FU* follow-up

Methods

Patient Cohort, Detection of ISR and Preprocedural Imaging

This is a single center retrospective cohort study based on clinical and imaging data obtained from Moritz Kaposi Teaching Hospital, Kaposvár, Hungary. The flow chart for patient inclusion is shown in Fig. 1. Between March 2013 and March 2021 a total of 950 stent-PTA procedures were performed in the institution, using Wallstent (Boston Scientific, Natick, MA, USA) and Roadsaver (Terumo, Tokyo, Japan) stents, following multidisciplinary team (MDT) decisions. Postprocedural follow-up included outpatient visits every 3 months in the first year and every 6 months thereafter. Carotid Doppler ultrasound (DUS) examination was performed at each visit, with Doppler velocity measurements using proper angle correction techniques and B-mode imaging assisted by color duplex. Peak systolic velocity (PSV) ratios in the stented ICA segment and the common carotid artery (CCA) greater than 2 were used as cut-off values for significant (>50%) in-stent restenotic lesions, as described elsewhere [15, 16]. In the case of a suspected ISR lesion, verification was achieved by supra-aortic intracranial CTA performed on a dual-source CT scanner (SOMATOM Definition Flash, Siemens, Erlangen, Germany) (Fig. 2).

Procedure

Patients with high-grade (>50%) ISR lesions were scheduled for DEB re-PTA. The advantages and disadvantages as well as risks of the application of conventional or drug-eluting balloons were thoroughly discussed with the patients prior to the procedure and written informed consent was obtained in each case. Procedures were performed with the patient under local anesthesia, with an anesthesia team present in stand-by, using a 6 French femoral or radial access. All patients received an IV dose of 5000 IU Na-heparin after access was secured. The degree of ISR lesions was first verified with selective injection of the common carotid artery on the affected side, followed by the insertion of a 6F guide catheter into the CCA. A filter device was not applied. A 0.014-inch microwire was advanced through the ISR lesion into the petrosal segment of the ICA, 0.5 mg atropine was administered IV as premedication for the prevention of extreme bradycardia/asystole during the dilatation of the ICA bulbus and a 6 × 30 mm paclitaxel-eluting balloon (Elutax, Aachen Resonance, Aachen, Germany) was inflated under manometer control to nominal pressure (6 atm) for 30 s. The inflation time was shortened and the balloon was deflated immediately if the patients' heart rate fell under 50 bpm. Following deflation, the balloon was removed and control angiographic series were performed to document the

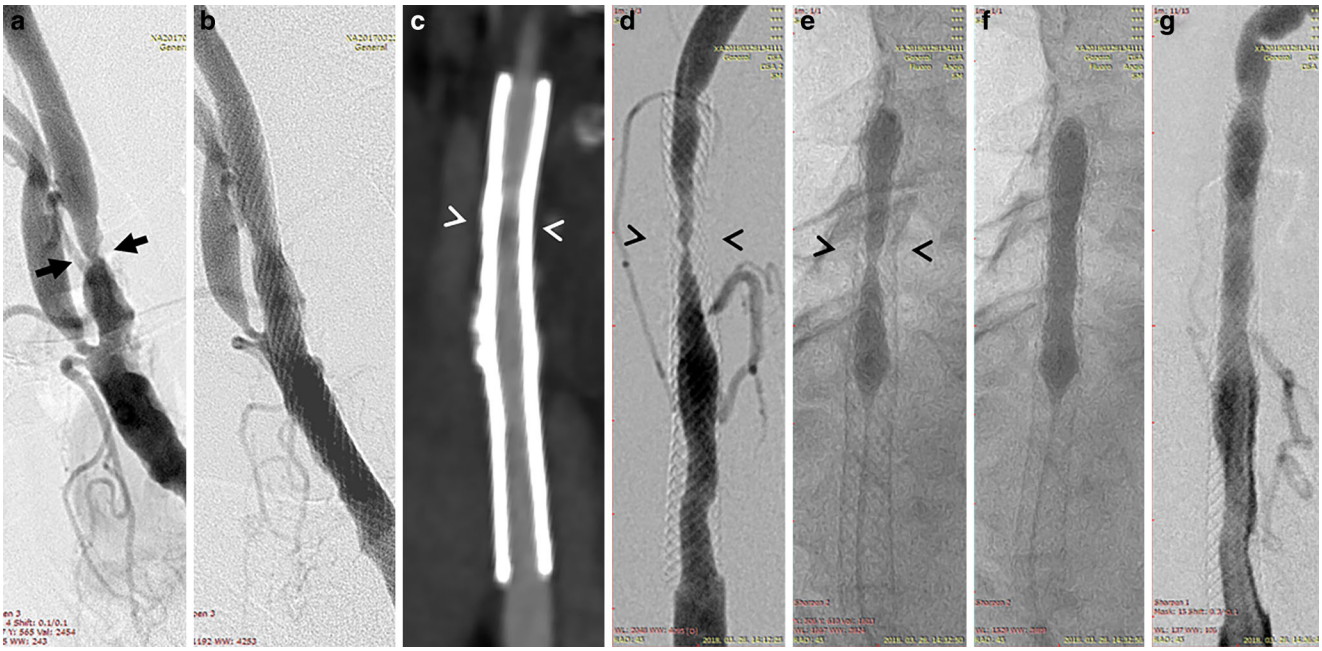

Fig. 2 Illustrative case demonstrating the DEB re-PTA procedure of an ISR lesion of the right-sided ICA in a 63-year-old female patient. A high-grade stenotic lesion in the proximal portion of the right ICA (*arrows* in **a**) was treated with stent implantation, followed by angioplasty with good result (**b**). The DUS after 6 months suggested a high-grade ISR in the location of the original lesion, which was verified by dual-source CTA (**c**) and catheter angiography (**d**, *arrowheads* in **c**–**e** point to the stenotic lesion). **e**, **f** Angioplasty using a paclitaxel eluting balloon was performed with good morphological results (**g**). The patient had the last follow-up DUS 52 months after the DEB re-PTA procedure, showing no signs of a recurrent ISR. *ICA* internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *DUS* Doppler ultrasound, *PTA* percutaneous transluminal angioplasty, *CTA* computed tomography angiography

effect of re-PTA and to exclude intracranial emboli. At the end of the procedure, the femoral access sites were closed by closure device (Angio-Seal, Terumo, Tokyo, Japan) and the radial access sites were closed by manual compression.

Medication

All patients received 5000 IU sodium heparin IV at the beginning of the procedure. Oral dual antiplatelet therapy with 100 mg of acetylsalicylic acid and 75 mg of clopidogrel was maintained for 6 months and clopidogrel monotherapy was continued thereafter. Patients managed with long-term single or dual anti-platelet treatment (SAPT or DAPT) were always examined with Multiplate test (Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany) to evaluate the efficacy of SAPT/DAPT treatment and if necessary, to provide treatment with another type of anti-aggregation drug.

Postprocedural Follow-up

Postprocedural follow-up was similar to that following the initial stent-PTA and included outpatient visits every 3 months in the first year and every 6 months thereafter. Carotid Doppler ultrasound (DUS) examination was performed at each visit. Peak systolic velocity (PSV) values of 220 cm/s and 300 cm/s were used as cut-off for luminal narrowing rates of >50% (moderate) and >70% (severe) ISR, respectively. In cases of a suspected repeated ISR lesion, verification was achieved by CT angiography (CTA). Thin slice (0.6 mm) series were reviewed using multiplanar reformatting (MPR). The axis of the stented segment was identified in two perpendicular planes and axial images, perpendicular to this axis were reviewed throughout the entire stented segment. The relatively small diameter of the ICA still did not allow exact determination of the percentage of the luminal narrowing, therefore a binary paradigm was used (ISR confirmed or rejected). If CTA confirmed a recurrent ISR lesion, the clinical and imaging data were reviewed by a MDT consisting of neurologists, vascular surgeons and interventional neuroradiologists for treatment decision. According to the MDT decision, an additional re-PTA procedure using the same technique and DEB balloon was performed, as described above.

Primary endpoints were death resulting from vascular disease, transient ischemic attack (TIA), and stroke related to the treated ICA. The secondary endpoint was a recurrent ISR lesion during follow-up.

Table 1 Patient data, lesion characteristics and risk factors of the cohort

Patient nr.	Age (years)	Gender	Time of ISR detection after CAS (months)	ISR ECST (%)	Risk factors
1	62.8	m	4.1	80–90	HT, DM, hBMI
2	63.4	m	69.1	50–70	HT, smoking
3	47	m	8.2	70–80	HT, DM, smoking
4	73	m	43.8	50–70	HT, hBMI, HL
5	71.4	m	9.7	60–70	HT, smoking, hBMI
6	70.1	f	186.2	80–90	HT, DM, HL
7	67.9	m	14	70–80	HT, smoking, hBMI, HL
8	66.1	m	34.3	60–70	HT, DM, smoking, hBMI, HL
9	69.2	m	8.5	80–90	HT, smoking
10	66.6	f	7.4	80–90	HT, smoking, HL
11	73.9	m	3.4	70–80	HT, smoking, HL
12	67.4	f	3.7	60–70	HT, DM
13	63.2	m	3.9	70–80	HT, smoking, HL
14	68.5	m	7.4	50–60	HT, smoking
15	62.1	f	4.8	60–70	HT, smoking, hBMI
16	57.3	m	19.8	50–60	HT, smoking, HL
17	71	m	3	70–80	Smoking, hBMI
18	62.2	m	9.7	50–60	HT, smoking, hBMI
19	60.6	m	14.3	80–90	HT, smoking, hBMI
20	75.9	m	12.1	80–90	HT, Smoking
21	67.7	m	1.4	70–80	HT, DM, smoking, hBMI, HL
22	71.2	f	8.9	60–70	HT, smoking, hBMI, HL
23	59.2	m	10	80–90	HT, smoking, hBMI
24	60.7	m	66.4	50–60	HT, smoking, hBMI
25	62	m	17.1	60–70	HT, DM, smoking, hBMI, HL
26	69.1	m	6.2	70–80	HT, smoking
27	64.6	m	6.3	60–70	HT, DM, smoking, hBMI, HL
28	56.5	m	5.9	60–70	HT, DM, hBMI, HL
29	55.8	m	5.4	60–70	HT, DM, smoking, hBMI
30	67.3	m	9.3	50–60	HT, smoking, HL
31	51.2	m	8.6	60–70	HT, DM, hBMI, HL
32	61.4	m	5.5	50–60	HT, smoking, hBMI, HL
33	67.9	m	6.5	80–90	hBMI
34	52	m	5.3	60–70	HT, DM, HL
35	65.1	m	8.4	70–80	HT, DM, hBMI, HL
36	58.3	f	13	60–70	HT, HL
37	65.7	f	4.2	50–60	HT, smoking, hBMI, HL
38	67.8	m	6.3	60–70	HT, smoking, hBMI, HL
39	69.9	m	7.7	60–70	HT, DM, hBMI, HL
40	63.3	f	6.2	80–90	HT, smoking, hBMI
41	68.6	m	9.5	70–80	HT, smoking, hBMI, HL
42	64.9	m	46.6	50–60	HT, smoking, hBMI, HL
43	61.1	f	18.6	50–60	HT, smoking, hBMI
44	59.9	f	11.6	70–80	HT, DM, hBMI, HL
45	65.4	f	4.9	90–99	HT, smoking, hBMI, HL
46	52.3	m	3.7	70–90	Smoking, hBMI

ISR in-stent restenosis, *CAS* carotid artery stenting, *ECST* European Carotid Surgery Trial, *HT* hypertension, *DM* diabetes mellitus, *hBMI* high body mass index, *HL* hyperlipidemia

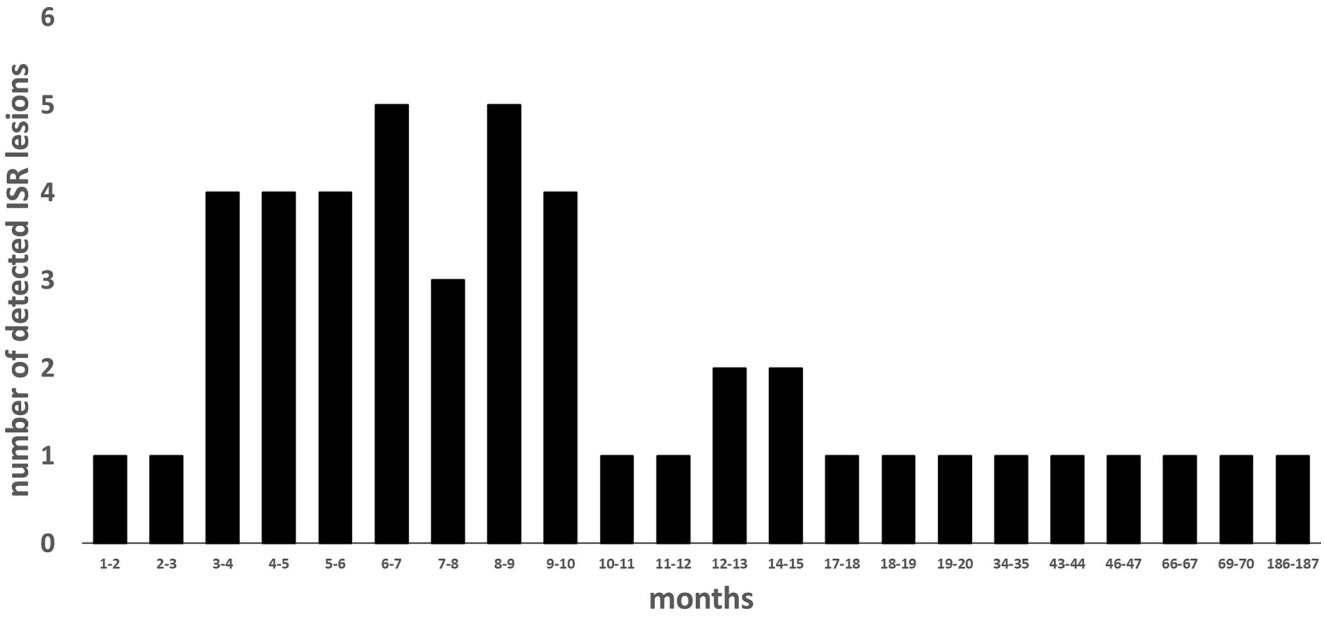

Fig. 3 Diagram showing the frequency of newly detected ISR lesions in the follow-up period following CAS. *ISR* in-stent restenosis

Data Collection and Statistical Analysis

Recorded baseline data included age, sex, history of hypertension, atrial fibrillation, diabetes, dyslipidemia, history of smoking and presence of a neoplastic disease at the time and following the re-PTA intervention. Collected preprocedural parameters included the type of stent and dates of the initial stent-PTA, detection of ISR and the re-PTA procedure.

The degree of luminal narrowing caused by the intimal hyperplasia was calculated on non-subtracted DSA images using the method applied in the ECST trial [17], as the extent of in-stent intimal hyperplasia can be precisely determined using the stent wall as a reference, corresponding to the ECST method of stenosis calculation.

The site of vascular access and the type of anti-aggregation medication was also recorded. The registered technical success and outcome parameters were the following: rate of successful re-PTA, defined as less than 50% residual stenosis, procedural complications (ischemic stroke from distal emboli), postprocedural adverse events (access site complications) the length of the follow-up period, modified Rankin scale (mRS) at the last follow-up and the occurrence of any stroke during follow-up. Due to the COVID-19 pandemic, most of the last follow-up visits were performed by telephone interview. If a patient died during the follow-up, the cause of death was recorded when possible.

Ethical approval for retrospective patient data retrieval was granted by the Institutional Review Board (IG/02169-000/2020). Written informed consent was waived due to the retrospective nature of the study. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Between March 2013 and March 2021, endovascular treatment of 46 high-grade (>50%) in-stent restenosis (ISR) lesions at the origin of the ICA by angioplasty using a drug-eluting balloon (DEB) was performed in our institution in 45 patients (median age 64.9 years; age range 46.9–75.8 years; male/female ratio 3.2/1), with 1 patient developing bilateral ISR. During the same period, altogether 950 ICA stent-PTA procedures were performed in the same center, giving an estimated ISR rate of around 5%, although the exact rate of ISR cannot be specified as detailed analysis of the non-ISR cases was not performed.

Patient demographics, ISR lesions characteristics and risk factors are listed in Table 1.

Overall, 16 lesions (35%) developed in a Roadsaver and 30 lesions (65%) in a Wallstent.

Although 52% (24/46) of the original ICA lesions were symptomatic at the time of stent implantation, only 1 of the 46 ISR lesions (2%) was symptomatic with mild hemiparesis, homonymous hemianopsia and central facial palsy, the remaining asymptomatic lesions were detected during regular DUS follow-up. The imaging work-up in cases of a suspected ISR on DUS always included a CTA in order to exclude false positive DUS readings, before performing invasive imaging (DSA). A CTA positive for ISR could be confirmed by the DSA series in all the cases.

The median time between the stent-PTA and the detection of the ISR lesions was 8.2 months (range 1.4–186.2 months) and 24% (11/46) of the ISR lesions developed more than 1 year following the CAS procedure. The frequency of ISR lesion development is shown in Fig. 3.

The average luminal narrowing caused by ISR measured on the DSA images was 70±2% (standard error of mean), ranging from 50% to 90%. Technical success, defined by a residual stenosis less than 50% was reached in all cases, with an average residual stenosis rate of 27±2%, ranging from 5% to 49%. Intraprocedural and postprocedural complications were not encountered. An exemplary case is presented in Fig. 2.

Clinical follow-up data could be obtained in all the 45 patients (100%), either by direct communication at personal or telemedical follow-up visits, telemedicine interviews of relatives or the general practitioner or by looking up follow-up data through the National eHealth Infrastructure (EESZT) database, with an average follow-up time of 31.7 months (range 1–96 months). There were no recurrent strokes in the territory of the treated ICA in any of the patients. Of the 45 patients 9 (20%) died during the follow-up period. The cause of death was a neoplasm in 6 cases (4 pulmonary, 1 renal, 1 head and neck cancer), consequences of anterior spinal artery syndrome in 1 case and unknown in 2 cases. Of the 6 fatal neoplasms 3 (50%) were already diagnosed at the time of the DEB re-PTA procedure. The 2 patients with unknown cause of death were lost to follow-up 3 and 24 months after the re-PTA procedure, death was confirmed by relatives via telephone interview but the exact cause could not be retrieved in these cases.

Follow-up DUS imaging results after the initial DEB re-PTA were available in all the 46 lesions with a median follow-up time of 24 months (range 1–96 months) and revealed an asymptomatic, high-grade (>50%) recurrent ISR lesion in 4 cases (8.7%), which was additionally verified by CTA. All the recurrent lesions developed in male patients and were treated by a second DEB re-PTA, as described earlier, with subsequent clinical and imaging follow-up. There were no symptoms of ischemia in the affected hemisphere throughout the follow-up period. A third high-grade asymptomatic recurrence of neointimal hyperplasia was detected in a single case (2%) 12 months after the second DEB re-PTA. This lesion was again treated with a third DEB re-PTA, with a most recent follow-up after 36 months showing no signs of a fourth recurrent ISR.

Discussion

In this retrospective cohort of 45 patients, the safety and efficacy of a paclitaxel-eluting balloon has been shown for the treatment of in-stent restenosis of the extracranial carotid artery. None of the primary endpoint events of vascular death, TIA and stroke in the territory of the treated ICA occurred. A recurrent ISR lesion following DEB re-PTA, as secondary endpoint occurred in 8.7% of the lesions and was successfully treated with a second and in one case with a third re-PTA procedure, without further recurrent ISR lesions during the follow-up period. To our awareness, the study presents the largest case series to date on the treatment of ICA ISR using a DEB device, showing significantly better results in the prevention of recurrent stenotic lesions compared to other methods published in the literature.

The reported rates of ISR following CAS vary widely between 3% and 31%, depending on the extent of luminal narrowing used as threshold, the Doppler criteria applied during follow-up and the length of the follow-up period [14, 18, 19, 22]. The present study does not attempt to analyze the parameters responsible for the development of ISR in the investigated patient cohort, we can only estimate the primary ISR rate in our center to be around 5%, based on the total number of CAS procedures and the detected ISR lesions during follow-up in the same time period. While this is a rough estimate, as a detailed analysis of the follow-up data from all the CAS patients has not been performed, our result is similar to the 5.7% ISR rate (>50%) reported in a recent meta-analysis considering more than 16,000 stented carotid arteries [20].

> The average luminal narrowing was 70% (i.e., severe) in the present cohort, yet only 1 lesion (2%) was symptomatic, which might raise questions regarding the indication for a preventive invasive treatment. The ISR was first identified as a relevant problem in the coronary arteries, resulting in the development of drug-eluting coronary stents (DES) [24]. To our knowledge, there is currently no medical treatment available to stop or reverse the development of neointimal hyperplasia. The risk of stroke associated with ISR was assessed in a secondary analysis of the International Carotid Stenting Study (ICSS). The analysis found a 40.7% cumulative 5-year risk of at least moderate (50%) ISR and those patients had a significantly higher risk of ipsilateral stroke compared to individuals without ISR [25]. Our personal experience, which confirms this finding, is that ISR is a progressive condition with a potential risk of stent occlusion when left untreated and DEB angioplasty provides a repeatable, low-risk treatment option. It should be noted however that randomized studies need to be conducted in order to clarify the indication of a preventive invasive treatment.

Recent reviews on the treatment of ICA ISR emphasize the lack of evidence and randomized controlled trials (RCTs) for guidance in the indications and the selection of treatment methods [10, 21]. Huang et al. recently reviewed 35 studies on the treatment of carotid ISR, covering 1374 procedures [10] and reported repeat CAS (66.3%), PTA with conventional balloons (17.5%) and endarterectomy (CEA) (14.3%)

among the most favored treatment options. The results of the three methods were similar in the rates of stroke and TIA in the postoperative period (PTA 1.1%, rCAS 1.1%, CEA 1.5%). CEA was associated with postoperative death rate of 2.5%, whereas the rate of long-term stroke and TIA in the PTA group was 5.7%. The rate of ISR recurrence was 27.8%, 8.2% and 1.6% after PTA, repeat CAS and CEA, respectively.

The largest single center cohort on ICA ISR re-PTA using conventional balloons has been published recently by Mihály et al. with 46 lesions treated by re-PTA using conventional and in 3 cases using a paclitaxel-eluting balloon [22]. The authors reported a 21.7% ISR recurrence and 6.5% stent occlusion rate after a median follow-up period of 29.5 months, giving a combined recurrence rate of 28.2%, which is similar to the 27.8% recurrence rate reported in the review by Huang et al. [10].

The literature on DEB re-PTA treatment of carotid ISR has been analyzed recently by Bhatia et al. [14]. They found data from DEB treatment of altogether 33 ICA ISR lesions, including their 2 own cases, of which 11 (33%) ISR lesions were symptomatic. Technical success rates, procedural safety and follow-up results were promising, with three asymptomatic and one symptomatic recurrent ISR lesions (4/33, 12%) occurring in the follow-up period.

In the present study, all ICA ISR lesions were treated exclusively by DEB re-PTA. This was based on the encouraging results of an earlier study with the participation of 1 of the authors comparing the efficacy of DEB versus conventional balloons in the re-PTA of 63 intracranial ISR lesions and showing a markedly reduced recurrence ISR rate of 9% with DEB versus 50%, with conventional balloons [13]. Our ICA ISR recurrence rate of 8.7% in the present study is very similar to these earlier intracranial DEB re-PTA results (9%) [13] and is around one third of the 27–28% recurrence rate reported with conventional balloons in other studies [10, 22]. Our ISR recurrence rate after DEB re-PTA is also very similar to the 8.2% result following repeat CAS [10]. It should be, however, noted that sequential recurrent lesions can effectively be managed by repeated DEB re-PTA procedures but that might not be straightforward with repeat CAS interventions, as the implantation of a third or even a fourth co-axial stent in the same vessel segment can be problematic.

Our study has several limitations: the observational and nonrandomized design is subject to methodological and selection biases inherent in this form of study. The imaging results were not verified by a core laboratory. There may be bias due to patients lost to follow-up and missing data in the retrospective dataset. A detailed analysis of the primary stent-PTA procedures was not performed. Only one type of DEB was used in the present cohort and it is conceivable to assume that differences in drug type, concentration and the method of fixation on the balloon could significantly influence the efficacy of different DEBs [23].

Conclusion

The DEB re-PTA using a paclitaxel-eluting balloon is a safe and effective alternative to other treatment options for extracranial carotid ISR. The primary recurrence rates are at around one third of those reported in the literature for re-PTA with conventional balloons. The recurrent lesions could again be safely managed by additional DEB re-PTA procedures, finally resulting in complete prevention of ISR. Although data on the usefulness of DEB technology in the field of carotid ISR management are accumulating from retrospective cases series, larger scale prospective, controlled studied are much needed for the establishment of this technology in the toolbox of neurovascular interventionists.

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Author Contribution All authors made a significant contribution to the study and to manuscript preparation. AM, EB, FN and ZV contributed to study conception and design, AM, EB, GB, IG, SN, GL, MF and GBK contributed to data acquisition and MM and IR contributed to data interpretation and analysis. AM and ZV drafted the manuscript, GL, MF, GBK, MM, IR and FN critically revised the paper, and IR contributed significantly to the intellectual content. CN, MM, IR, FN and ZV approved the final version of the manuscript.

Declarations

Conflict of interest A. Marton, E. Blényesi, K. Török, G. Balogh, I. Gubucz, S. Nardai, G. Lenzsér, C. Nagy, G. Bajzik, J. Tollár, I. Repa, F. Nagy and Z. Vajda declare that they have no competing interests.

Ethical standards This retrospective analysis was conducted with approval of the Moritz Kaposi Teaching Hospital Institutional Review Board (IG/02169-000/2020). Consent to participate: informed consent for the study was waived due to the retrospective nature of the study; however, patients or a family member gave informed consent for the endovascular procedure. Consent for publication: publication has been approved by all co-authors.

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Cardiovascular Revascularization Medicine 35 (2022) 76–82

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Outcomes With Drug-Coated Balloons vs. Drug-Eluting Stents in Small-Vessel Coronary Artery Disease

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DCB
Small-vessel disease coronary disease

ABSTRACT

Background: The use of drug-coated balloons (DCBs) in small-vessel coronary artery disease (SVD) remains controversial.
Methods: We performed a meta-analysis of all randomized controlled trials (RCTs) reporting the outcomes of DCB vs. DES in de-novo SVD. We included a total of 5 RCTs (1459 patients), with (DCB $n = 734$ and DES $n = 725$).
Results: Over a median follow-up duration of 6 months, DCB was associated with smaller late lumen loss (LLL) compared with DES (mean difference −0.12 mm) (95% confidence intervals (CI) [−0.21, −0.03 mm], $p = 0.01$). Over a median follow-up of 12 months, both modalities had similar risk of major adverse cardiovascular events (MACE) (8.7% vs. 10.2%; odds ratio (OR): 0.94, 95% CI [0.49–1.79], $p = 084$), all-cause mortality (1.17% vs. 2.38%; OR: 0.53, 95% CI [0.16–1.75], $p = 0.30$), target lesion revascularization (TLR) (7.9% vs. 3.9%; OR: 1.26, 95% CI [0.51–3.14], $p = 0.62$), and target vessel revascularization (TVR) (8.2% vs. 7.8%; OR: 1.06, 95% CI [0.40–2.82], $p = 0.91$). DCBs were associated with lower risk of myocardial infarction (MI) compared with DES (1.55% vs. 3.31%; OR: 0.48, 95% CI [0.23–1.00], $p = 0.05$, I2 = 0%).
Conclusion: PCI of SVD with DCBs is associated with smaller LLL, lower risk of MI, and similar risk of MACE, death, TLR, and TVR compared with DES over one year. DCB appears as an attractive alternative to DES in patients with de-novo SVD, but long-term clinical data are still needed.

1. Introduction

Small vessel coronary artery disease (SVD) is often treated with percutaneous coronary intervention (PCI) [1], but is a complex lesion subset and is associated with high risk of major adverse cardiovascular events (MACE). Current treatment options for SVD include standard balloon angioplasty, drug-eluting stents (DES), and drug-coated balloons (DCBs). Balloon angioplasty is associated with high restenosis rates due to elastic recoil and adverse remodeling [2]. DES have been associated with worse outcomes in smaller compared with larger vessels [3–5] likely due to the small vessel caliber with little room to accommodate neointimal tissue growth.

Drug-coated balloon (DCB)-only PCI has emerged as an alternative treatment option to de-novo coronary artery disease and in-stent restenosis (ISR). [6–8] However, the outcomes with DCB in SVD have been controversial [9–15]. We performed a systematic review and meta-analysis to compare the angiographic and clinical outcomes of DCB vs. DES in SVD.

2. Methods

The current meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) [16]. We performed a systematic computerized search limited to the English language through Medline, Embase, and Cochrane databases from January 2000 to January 2021 using the following search

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terms separately and in combination; "Drug-eluting balloon," "DEB," "drug-coated balloon," "DCB," "paclitaxel-coated balloon," "PCB," "small-vessel coronary artery disease," and "small-vessel disease." We screened the retrieved studies' bibliographies, previous reviews, and ClinicalTrials.gov for any relevant studies not found through the initial search.

2.1. Study selection and data collection

We included randomized controlled trials (RCTs) that compared outcomes with DCB vs. DES in the treatment of de-novo SVD (reference vessel diameter ≤ 3 mm) (Fig. S1). In the DCB arm, stenting was allowed only as a bailout strategy in case of suboptimal results, defined as persistent residual stenosis, vessel recoil, or flow-limiting dissection.

The data were extracted by two independent investigators (KB, MM) and confirmed by a third investigator (MS). The data included baseline study characteristics, baseline clinical and angiographic characteristics of the included patients and lesions, and the outcomes of interest. Discrepancies among investigators were settled by consensus. The included studies' bias risk was assessed using the Cochrane risk assessment tool for RCTs (Table S2) [17]. Potential publication bias was assessed using the Egger test by visually examining the funnel plots (Fig. S2).

2.2. Study outcomes

The clinical outcomes of the current study included periprocedural myocardial infarction (MI) and long-term outcomes, including MACE, target lesion revascularisation (TLR), target vessel revascularisation (TVR), MI, all-cause mortality, and angiographic late lumen loss (LLL) measured by quantitative coronary angiography. Definitions of outcomes by each study included are shown in Table S1. Results were reported at the longest follow-up time available and according to the intention-to-treat analysis.

2.3. Statistical analysis

Statistical analysis was conducted using Review Manager software (Version 5.3.5. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Descriptive analyses were conducted using frequencies for categorical variables and means with standard deviations (SD) for continuous variables. Categorical variables were compared using Fisher's exact or chi-square tests, while continuous variables were analysed using the two-sample *t*-test. Tests were two-tailed, and a *p*-value of ≤0.05 was considered statistically significant.

Odds ratios (ORs) or mean differences (MD) with 95% confidence intervals (CIs) were presented as summary statistics. Statistical heterogeneity across trials was assessed by I^2 statistics, with I^2 statistic values <25%, 25% to 50%, and >50% considered as low, moderate, and a high degree of heterogeneity, respectively. The DerSimonian and Laird random-effects model and inverse variance model were used to calculate OR and MD, respectively. We performed a sensitivity analysis excluding the study by Cortese et al. given use of a first-generation DCB and lack of adequate lesion preparation (25%) [11]. We performed another sensitivity analysis comparing DCBs vs. second-generation DES [10,12,14].

3. Results

We included a total of 5 RCTs (1459 patients), with (DCB $n = 734$ and DES $n = 725$). The characteristics of the included studies are described in Table 1. Only three studies compared the outcomes with DCB vs. second-generation DES [10,12,14]. We used both the 6 months (for angiographic outcomes) and 3 years (for clinical outcomes) publications for the BELLO study [13,18]. Bailout stenting in the DCB-only group occurred in 10% of patients ranging between 5.1% to 35.7%, with recent studies reporting fewer bailout stenting events. The baseline clinical and angiographic characteristics of the included patients and lesions are summarized in Table 2.

3.1. Outcomes

Both technical (98.8 vs. 99.2%, $p = 0.96$) and procedural (97.1% vs. 98.1%, $p = 0.26$) success was similar between both groups. There was no difference in the risk of periprocedural MI with DCB compared with DES (2.2% vs. 3.9%; OR: 0.56, 95% CI [0.21, 1.48], $p = 0.25$, $I^2 = 0\%$) (Figs. 1 and 2).

During a median follow-up duration of 6 months (range 6–9 months), DCBs were associated with smaller LLL compared with DES (MD: −0.12 mm (95% CI [−0.21, −0.03 mm], $p = 0.01$, $I^2 = 56\%$)). Over a median follow-up of 12 months (range 9–36 months), both arms had similar risk of MACE (8.7% vs. 10.2%; OR: 0.94, 95% CI [0.49, 1.79], $p = 0.84$, $I^2 = 59\%$), all-cause mortality (1.17% vs. 2.38%; OR: 0.53, 95% CI [0.16, 1.75], $p = 0.30$, $I^2 = 0\%$), TLR (7.9% vs. 3.9%; OR:

Table 1
Characteristics of the included studies.

Study	Trial/registry	Study type	Number of patients with DCB/DES	Balloon/stent type	Country (# of centers)	Follow-up time (months)	Enrolment dates	Vessel size	Bailout stenting %	Primary endpoint
Cortese et al. 2020	PICCOLETO II	RCT	118/114	Elutax DCB (AR Baltic Medical, Vilnius, Lithuania)/Xience DES (Boston Scientific, USA)	Europe (5)	12	May 2015 – May 2018	2.00–2.75 mm	6.8%	In-lesion LLL at 6 months
Tian et al. 2020	RESTORE-SVD	RCT	116/114	RESTORE DCB (Cardionovum, Germany)/RESOLUTE DES (Medtronic, USA)	China (12)	24	August 2016 – June 2017	2.25–2.75 mm	5.2%	Percentage diameter stenosis at 9 months
Jeger et al. 2018	BASKET-SMALL 2	RCT	382/376	SeQuent Please DCB (B. Braun, Germany)/Xience (Abbott Vascular, USA) or Taxus or Promus DES (Boston Scientific, USA)	Europe (14)	12	April 2012 – February 2017	<3 mm in diameter	5.1%	MACE at 12 months
Latib et al. 2012	BELLO	RCT	90/92	IN.PACT Falcon DCB (Medtronic, USA)/Taxus Liberte DES (Boston Scientific, USA)	Italy (15)	6–36 months	Not discussed	<2.8 mm	20.2%	In-segment LLL ta 6 months
Cortese et al. 2010	PICCOLETO	RCT	28/29	Dior DCB (Eurocor, Germany)/Taxus DES (Boston Scientific, USA)	Italy (1)	9	August 2007 and August 2008	≤2.75 mm	35.7%	Percentage diameter stenosis at 6 months

DCB: drug-coated balloon; DES: drug-eluting stent; LLL: late lumen loss; MACE: major adverse cardiovascular events; RCT: arandomized controlled trial.

Table 2
Baseline characteristics of the included patients and lesions.

	DCB (n = 734)	DES (n = 725)	p-value
Age mean ± SD	65.30 ± 10.23	66.47 ± 10.40	0.030
Men %	74.68	73.37	0.609
Multivessel Disease %	70.96 [588]	66.46 [582]	0.110
Hypertension %	78.01	81.75	0.086
Dyslipidemia %	66.02	64.76	0.652
Diabetes %	35.79	37.02	0.664
Current smoking %	22.11	20.16	0.396
Previous MI %	38.46	32.12	0.013
Family history of CAD %	36.78	30.73	0.017
Prior CABG	7.37	7.56	0.969
Prior PCI	53.93	52.69	0.673
Vessel involved			
LAD	28.83	27.12	0.503
LCx	40.47	39.28	0.681
RCA	17.44	19.20	0.423
Diagonal	14.24 [206]	10.97 [206]	0.395
OM/Ramus Intermedius	13.54 [206]	17.22 [206]	0.369
PDA/PL	21.31 [206]	22.26 [206]	0.909
LVEF Baseline mean ± SD	58.18 ± 4.77	59.60 ± 4.219	$p < 0.001$
Lesion/procedural characteristics			
Bifurcation lesion	8.31 [528]	9.84 [519]	0.451
AHA B2/C Lesion	44.47 [234]	46.67 [235]	0.700
Minimal luminal diameter (mm)	0.61 ± 0.25	0.61 ± 0.26	1.000
Reference vessel diameter (mm)	2.42 ± 0.25	2.41 ± 0.29	0.480
Lesion length (mm)	12.91 ± 6.46	12.81 ± 6.27	0.764
Predilation	80.21 [738]	78.93 [731]	0.587
Bailout stenting	10.04 [328]	0.9 [228]	p < 0.001
Procedural success	97.11 [738]	98.13 [731]	0.267
Lesion success	98.85 [262]	99.20 [257]	0.967

CABG: Coronary artery bypass graft; CAD: coronary artery disease; DCB: drug-coated balloon; DES: drug-eluting stent; LAD: left anterior descending; LCx: left circumflex; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; OM: obtuse marginal; PCI: Percutaneous coronary intervention; PDA: posterior descending artery; PL: posterolateral; RCA: right coronary artery.
Numbers between square brackets represent the number of subjects with a reported variable when different from the baseline.

1.26, 95% CI [0.51, 3.14], $p = 0.62$, $I^2 = 54\%$), and TVR (8.2% vs. 7.8%; OR: 1.06, 95% CI [0.40, 2.82], $p = 0.91$, $I^2 = 46\%$) (Figs. 2 and 3). DCB was associated with lower risk of MI compared with DES (1.55% vs. 3.31%; OR: 0.48, 95% CI [0.23, 1.00], $p = 0.05$, $I^2 = 0\%$).

On sensitivity analysis and exclusion of the study by Cortese et al. 2010, both modalities had similar risk of MACE (OR: 0.74, 95% CI [0.43, 1.27], $p = 0.28$, $I^2 = 39\%$), all-cause mortality (OR: 0.46, 95% CI [0.13, 1.71], $p = 0.25$, $I^2 = 0\%$), TLR (OR: 0.87, 95% CI [0.40, 1.89], $p = 0.72$, $I^2 = 23\%$), and TVR (OR: 0.68, 95% CI [0.29, 1.59], $p = 0.38$, $I^2 = 0\%$). DCBs remained associated with lower risk of MI compared with DES (OR: 0.43, 95% CI [0.20, 0.92], $p = 0.03$, $I^2 = 0\%$). This sensitivity analysis yielded similar results with much reduction in heterogeneity (Fig. S3).

DCB had similar risk of MACE (OR: 0.97, 95% CI [0.61, 1.53], $p = 0.89$, $I^2 = 0\%$), all-cause mortality (OR: 0.60, 95% CI [0.07, 4.90], $p = 0.63$, $I^2 = 0\%$), TLR (OR: 1.29, 95% CI [0.53, 3.18], $p = 0.57$, $I^2 = 0\%$), TVR (OR: 0.76, 95% CI [0.42,1.39], $p = 0.37$, $I^2 = 0\%$), and MI (OR: 0.48, 95% CI [0.21, 1.08], $p = 0.08$, $I^2 = 0\%$) compared with second-generation DES (Fig. S4). A summary of the study results is shown in Fig. 4.

4. Discussion

The main findings of our study can be summarized as follows: 1) the use of DCB in SVD PCI is associated with smaller late lumen loss over 6 months and a lower incidence of MI during a median follow-up of 12 months, 2) both DCBs and DES are associated with a similar risk of MACE, death, TLR, and TVR when used in PCI of SVD, 3) When comparing DCBs and second-generation DES, both modalities were comparable with a similar risk of clinical events at a median follow-up of 12 months.

In our analysis, DCBs were associated with lower risk of MI compared with DES during a median follow-up of 1 year. DES are currently commonly used in SVD PCI. Other options include regular balloon angioplasty or medical therapy, which might not be adequate in severely symptomatic patients or when the goal is to achieve complete revascularization. However, DES may have limitations in SVD, as suggested by the higher MI risk with DES in our study. DES are associated with neointimal hyperplasia and late occurrence of neoatherosclerosis and stent thrombosis, which can be exaggerated in small vessels with little room to accommodate the neointima [19]. DES had more LLL in our study. The risk of ISR is higher in smaller caliber vessels, longer lesions, and patients with diabetes mellitus, that are commonly associated with SVD [20]. Previous studies have demonstrated that the risk of MACE, including MI, was almost double in small vessels as compared with large vessels treated with DES [4,5]. It is possible that with further follow-up, the gap favoring DCB will widen given that the current-generation DES have a perpetual 2% yearly risk of stent-related adverse events [21], but longer-term studies are required.

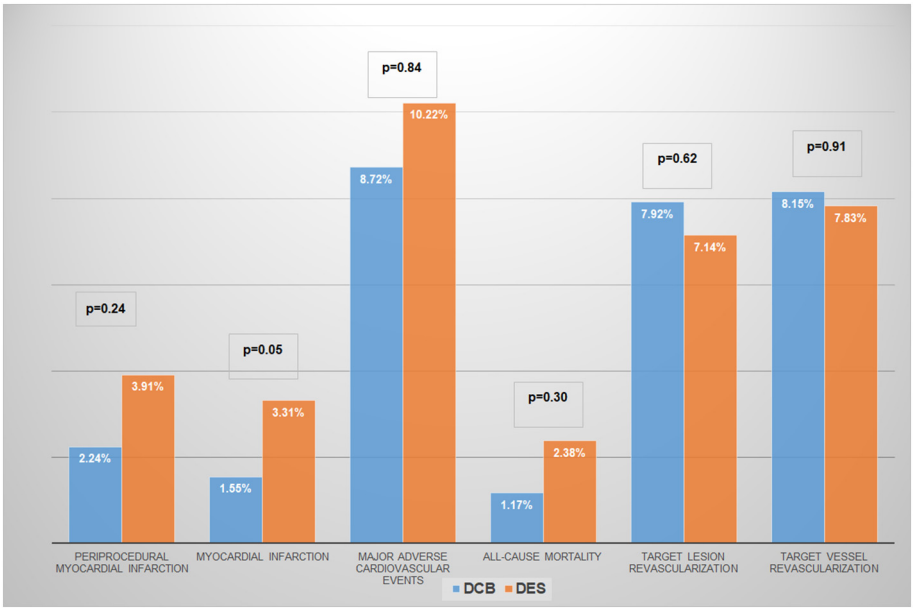

Fig. 1. Outcomes with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease. DCB: drug-coated balloon; DES: drug-eluting stent.

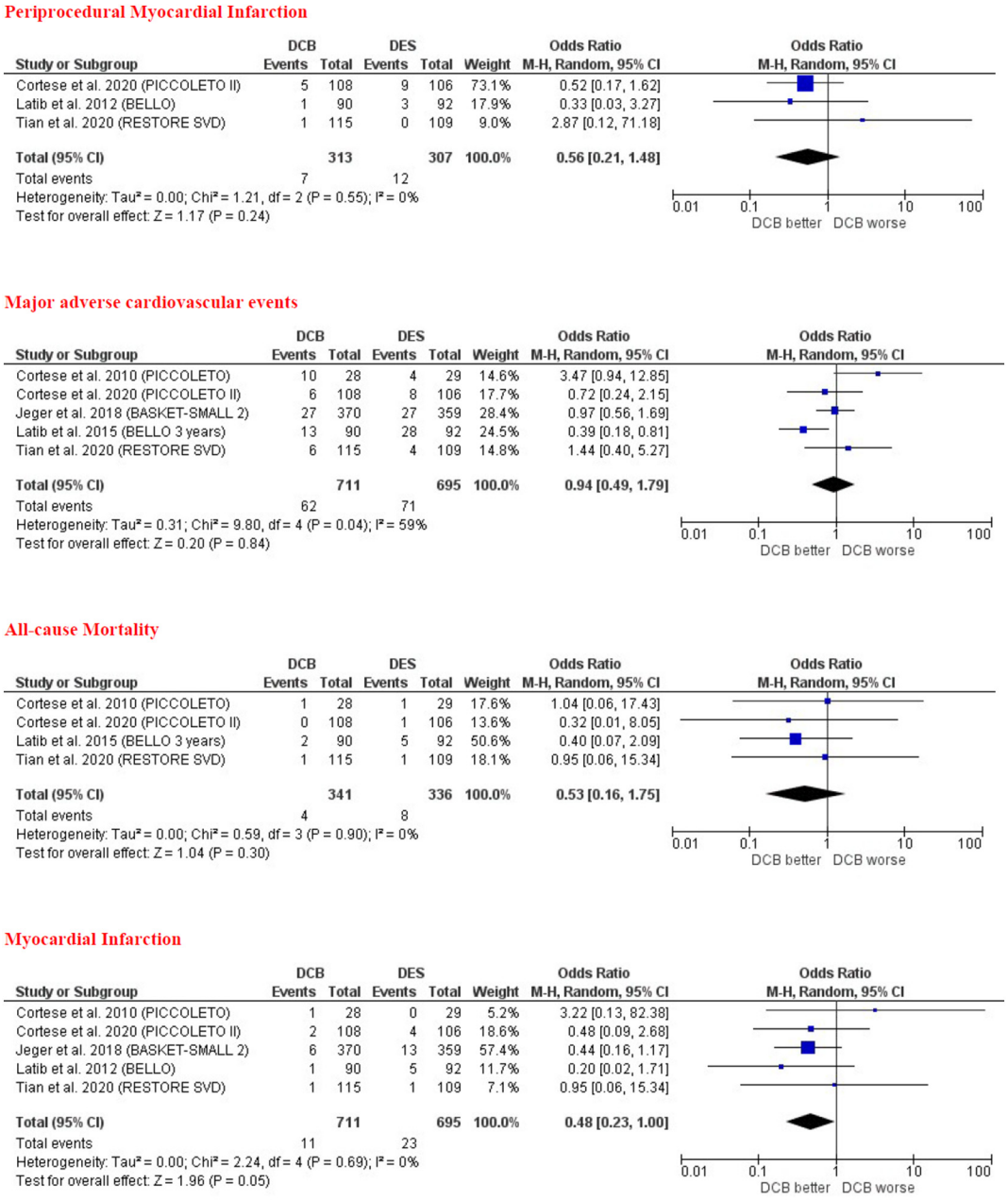

Fig. 2. Pooled analysis of the odds of periprocedural myocardial infarction, major adverse cardiovascular events, all-cause mortality, and myocardial infarction with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease; the summary statistic is the odds ratios and mean differences calculated according to the Mantel-Haenszel method with random effects, respectively; marker size is proportional to the study weight. DCB: drug-coated balloon; DES: drug-eluting stent.

The use of DCBs in SVD offers many advantages, mainly due to avoiding permanent prosthesis implantation. Having a smaller profile, they are more deliverable in smaller vessels compared with DES. They are more attractive to use in patients at higher bleeding risk, as the recommended duration of dual antiplatelet therapy is only four weeks [12,22]. Most importantly, DCBs are associated with vascular healing and positive remodeling, particularly in small coronary lumens [23,24]. In our analysis, late lumen loss was lower with DCBs compared with DES at six months, an effect that is expected to be more pronounced with more extended angiographic follow-up.

The use of DCBs in SVD has limitations. DCBs require adequate lesion preparation, which sometimes can be difficult and carries the risk of suboptimal results (e.g., persistent residual stenosis and dissections), necessitating bailout stenting. Iatrogenic dissections have a higher chance of healing with DCBs [25]. The risk of restenosis is higher type for C or greater dissections, hence such lesions should be treated with bailout stenting. In contrast, types A and B dissections can be treated with a DCB-only strategy. Our study found that the rate of bailout stenting in more recent studies did not exceed 7%, which appears acceptable. The acceptance of this strategy, especially by less experienced operators, might be a challenge as the default response to most dissections is stenting. Another limitation of DCBs is that, unlike DES, the class effect of DCBs cannot be established. The notion that "not all DCBs are created equal" is crucial in understanding clinical outcomes and choosing the right tool. There is heterogeneity in the excipient, drug mounting technology, and drug transfer rate, leading to mixed clinical trial results. The lack of a "class effect" was also shown in the SCAAR "Swedish Coronary Angiography and Angioplasty Registry" [26] and emphasized in the European revascularization guidelines [27]. There are emerging promising data on the use of sirolimus-coated balloons but direct comparison with the currently available paclitaxel-coated balloons is still required [28].

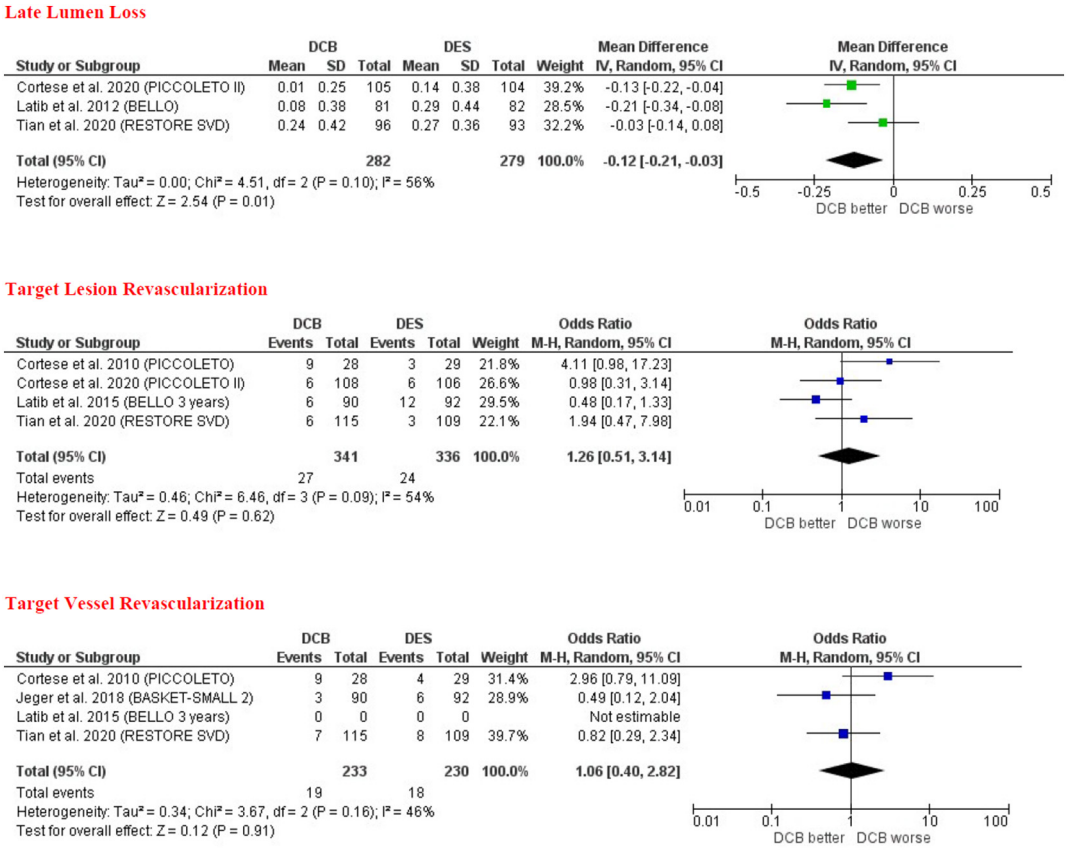

Fig. 3. Pooled analysis of the odds of target lesion revascularization and target vessel revascularization and mean difference in late lumen loss with drug-coated balloons vs. drug-eluting stents in small vessel coronary artery disease; the summary statistic is the odds ratios and mean differences calculated according to the Mantel-Haenszel method and inverse variance method with random effects, respectively; marker size is proportional to the study weight. DCB: drug-coated balloon; DES: drug-eluting stent.

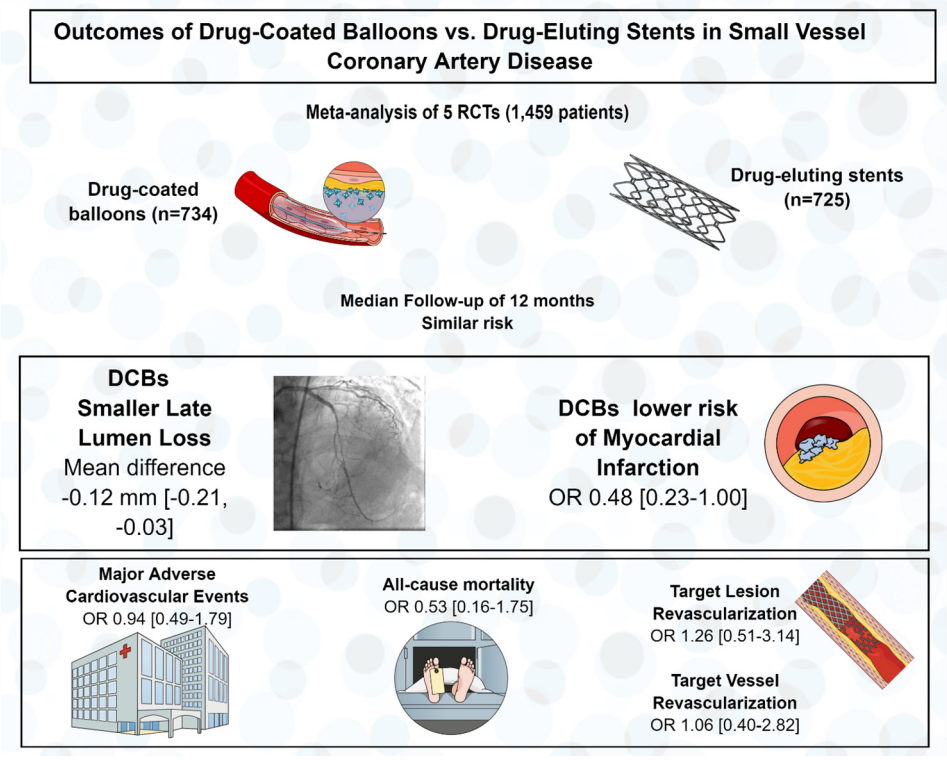

Fig. 4. Summary of the study results.

In our analysis, both DES and DCBs were comparable in MACE, TLR, TVR, and all-cause mortality risk. This equivalency was also demonstrated in our sensitivity analysis comparing DCBs vs. second-generation DES. Our findings, especially with the lower incidence of MI with DCBs, support using DCBs in SVD. Using DCBs fulfils the concept of adequate treatment of atherosclerotic lesions and delivery of anti-restenotic drugs without leaving anything behind. Larger randomized trials with longer follow-up are needed to confirm our findings, and ensure the durability of DCBs in SVD. Our results are generally similar to the study by Sanchez et al. in the overall outcomes [29]. We did not, however, perform metaregression given the low number of included studies. Moreover, we performed a pre-specified sensitivity analysis that showed equivalency of DCBs and second-generation DES.

4.1. Limitations

Our study has several limitations. First, there is significant heterogeneity, given the differences in the type of DCB and the frequency of adequate lesion preparation. We attempted to overcome this limitation using random-effect models and by performing further sensitivity analyses. Second, the study was performed using published data not patient-level data. Third, bleeding outcomes were not consistently reported and could not be analysed. Fourth, our results are reported at a median follow-up time of 12 months, and more extended follow-up data are needed. Finally, the number of trials is still limited and a beta-error still possible for many outcomes assessed.

5. Conclusions

PCI of SVD with DCBs is associated with smaller LLL, a lower risk of MI, and, with the limited data available so far, and similar risk of MACE, death, TLR, and TVR compared with DES over one year. DCB appears as an attractive alternative to DES in patients with de-novo SVD, but long-term clinical data are still needed.

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CRediT authorship contribution statement

Michael Megaly: conceptualization, Development or design of methodology, statistical analysis, writing the initial draft.

Kevin Buda: data curation, development or design of methodology.

Marwan Saad: data curation.

Mariam Tawadros: data curation.

Ayman Elbadawi: data curation.

Mir Basir: critical review, commentary, and revision.

J Dawn Abbott: critical review, commentary, and revision.

Stephane Rinfret: critical review, commentary, and revision.

Khaldoon Alaswad: critical review, commentary, and revision.

Emmanouil Brilakis: Conceptualization oversight and leadership responsibility for the research activity planning and execution. Critical review, commentary, and revision.

Declaration of competing interest

Emmanouil Brilakis: consulting/speaker honoraria from Abbott Vascular, American Heart Association (associate editor Circulation), Amgen, Biotronik, Boston Scientific, Cardiovascular Innovations Foundation (Board of Directors), ControlRad, CSI, Ebix, Elsevier, GE Healthcare, InfraRedx, Medtronic, Siemens, and Teleflex; research support from Regeneron and Siemens. Shareholder: MHI Ventures.

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All other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.03.008.

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