Image in intervention

Endovascular therapy of symptomatic high-grade stenosis of left internal carotid artery in C6 segment using Elutax "3" Neuro pDEB

Paweł Latacz[1], Tadeusz Popiela[2], Paweł Brzegowy[2], Borys Kwinta[3], Maciej Chwała[4], Marian Simka[5]

[1]Department of Neurology, Jagiellonian University Medical College, University Hospital, Krakow, Poland
[2]Chair of Radiology, Jagiellonian University Medical College, Krakow, Poland
[3]Department of Neurosurgery and Neurotraumatology, Jagiellonian University Medical College, Krakow, Poland
[4]Department of Surgery, Faculty of Health Sciences, Jagiellonian University Medical College, Krakow, Poland
[5]Department of Anatomy, University of Opole, Opole, Poland

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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

Corresponding author:
Paweł Latacz MD, PhD, Department of Neurology, Jagiellonian University Medical College, University Hospital, 2 Jakubowskiego St, 30-688 Krakow, Poland, phone: +48 12 400 25 51, e-mail: pawlat@me.com
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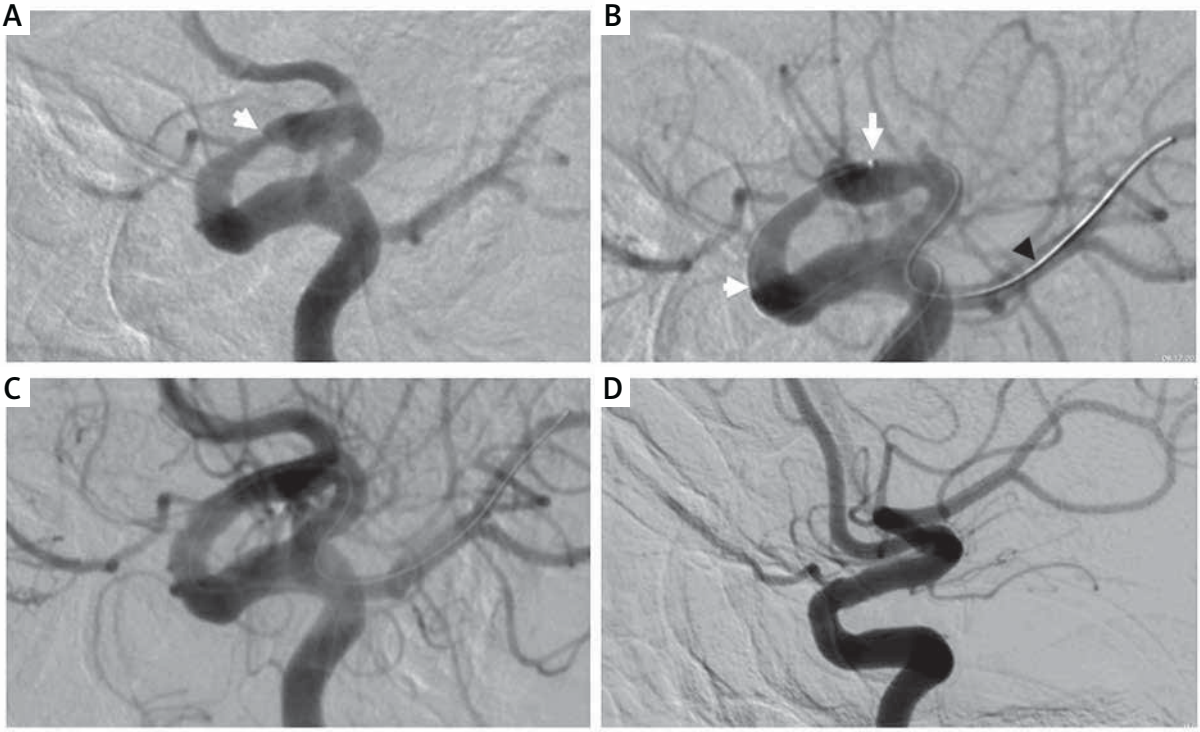

Figure 1. A – Critical stenosis of the left internal carotid artery in the C5/C6 segments (arrow), **B** – Elutax "3" Neuro drug coated balloon angioplasty at the site of the stenosis (balloon between white arrows, black arrow – guidewire in the middle cerebral artery), **C** – final result of angioplasty, **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

Guoming Li [a], Hanzi Qiao [a], Hao Lin [a], Rongfei Wang [a], Fajun Chen [a], Shaoxue Li [a], Weilin Yang [a], Lei Yin [a], Xuecheng Cen [a], Yingguang Zhang [a], Xiao Cheng [a,b,c], Alvin Yi-Chou Wang [a,*]

[a] Neurology Department, The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Dade Road No.111, Guangzhou, Guangdong 510120, China
[b] Guangdong Provincial Chinese Emergency Key Laboratory, Guangzhou 510120, China
[c] Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou 510006, China

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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

* Corresponding author.
E-mail addresses: 116974430@qq.com (G. Li), qiaohz122@163.com (H. Qiao), neurovascular@139.com (H. Lin), wangrongfei30@126.com (R. Wang), 89623538@qq.com (F. Chen), siuhoklai@live.com (S. Li), 584656401@qq.com (W. Yang), 15626048582@163.com (L. Yin), 329677946@qq.com (X. Cen), 1439467124@qq.com (Y. Zhang), chengxiaolucky@126.com (X. Cheng), alvinfree@sohu.com (A.Y.-C. Wang).

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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].

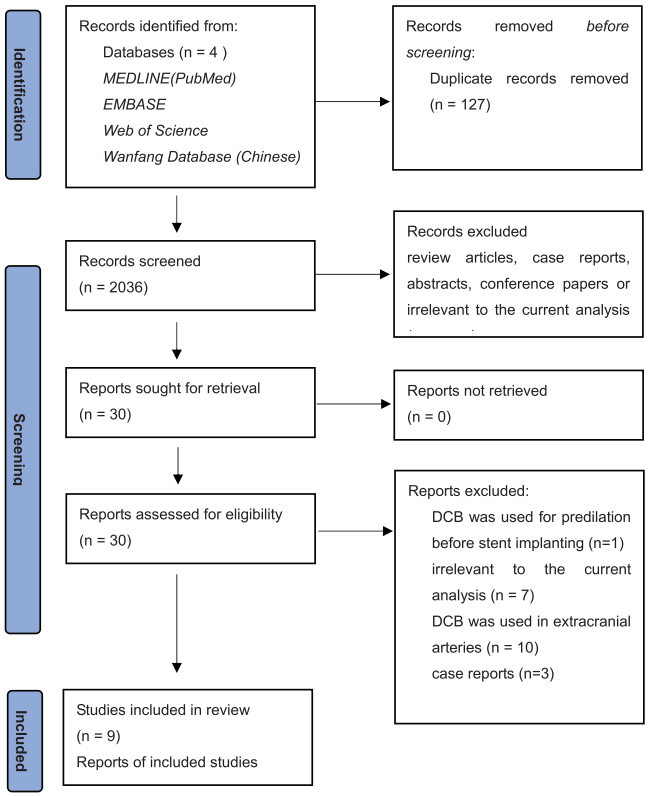

Fig. 1. Flowchart for study screening and selection.

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

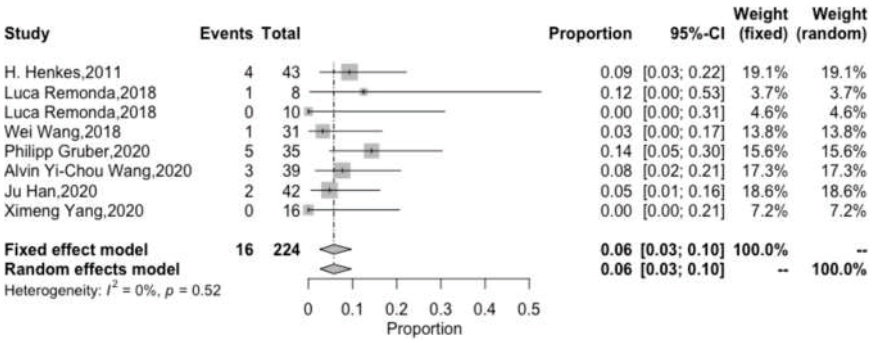

Fig. 2. Forest plot summarizing the proportion of restenosis in ICAD patients treated with DCB during follow-up.

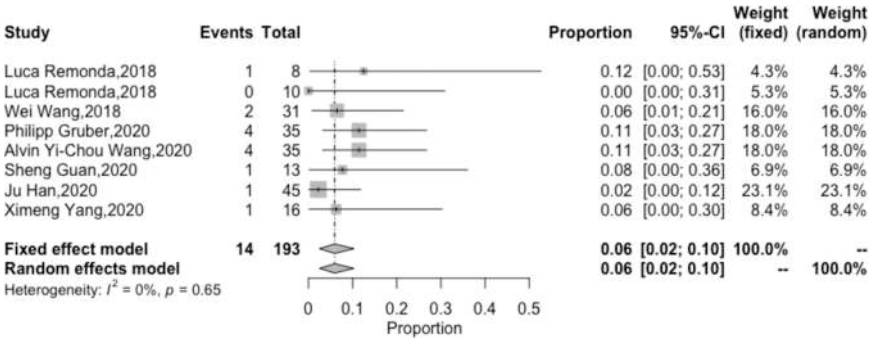

Fig. 3. Forest plot summarizing the proportion of periprocedural complications in ICAD patients treated with DCB during follow-up.

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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ORIGINAL ARTICLE

Treatment of In-stent Restenosis of the Internal Carotid Artery Using Drug-eluting Balloons

Annamária Marton[1] · Eszter Blényesi[1] · Katalin Török[1] · Gábor Balogh[2] · István Gubucz[3] · Sándor Nardai[3] · Gábor Lenzsér[3] · Csaba Nagy[3] · Gábor Bajzik[3] · József Tollár[1] · Imre Repa[3] · Ferenc Nagy[1] · Zsolt Vajda[3]

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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.

✉ Zsolt Vajda
vajdus@gmail.com

[1] Department of Neurology, Somogy County Moritz Kaposi Teaching Hospital, Kaposvár, Hungary

[2] Department of Surgery, Somogy County Moritz Kaposi Teaching Hospital, Kaposvár, Hungary

[3] Neurovascular and Interventional Unit, Somogy County Moritz Kaposi Teaching Hospital, Kaposvár, Hungary

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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.

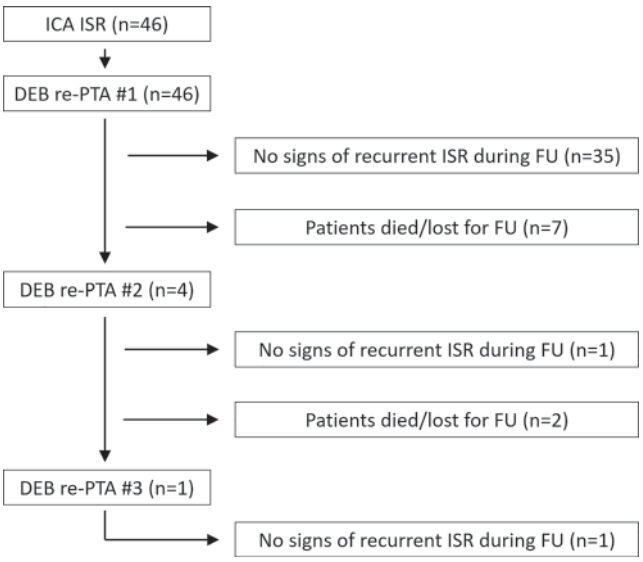

Fig. 1 Schematic drawing illustrating the treatment and follow-up algorithm of recurrent stenotic lesions following carotid artery stenting. *ICA* internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *PTA* percutaneous transluminal angioplasty, *FU* follow-up

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

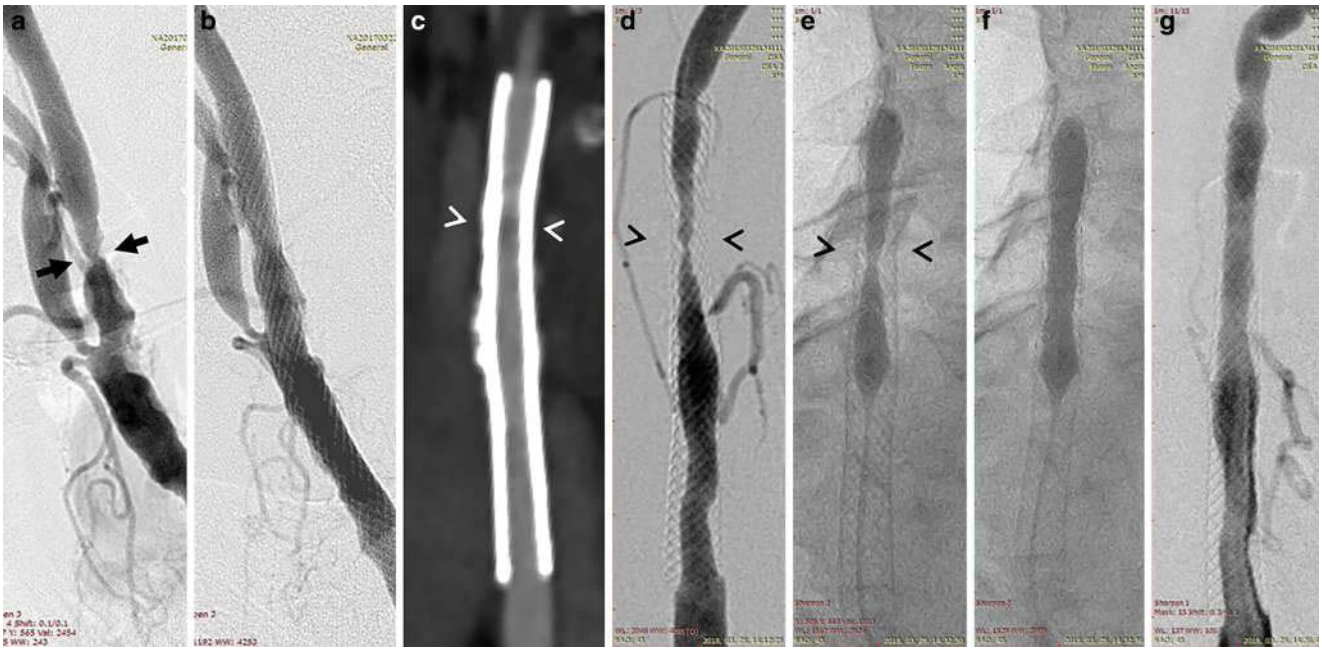

Fig. 2 Illustrative case demonstrating the DEB re-PTA procedure of an ISR lesion of the right-sided ICA in a 63-year-old female patient. A high-grade stenotic lesion in the proximal portion of the right ICA (*arrows* in **a**) was treated with stent implantation, followed by angioplasty with good result (**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

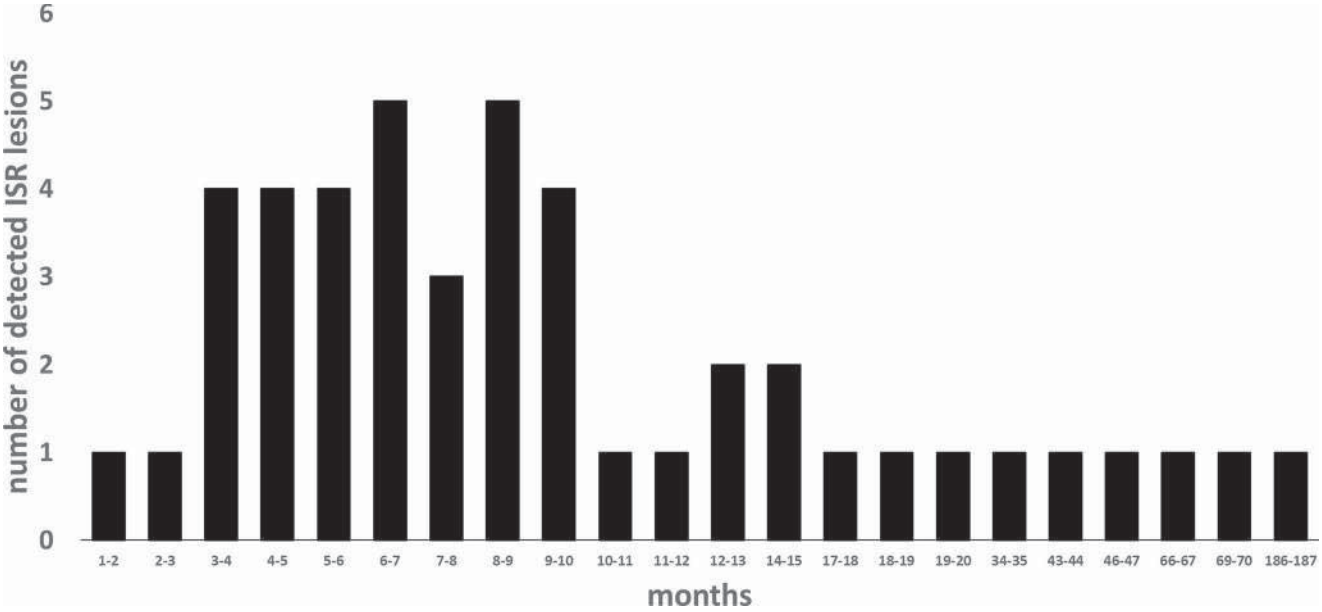

Fig. 3 Diagram showing the frequency of newly detected ISR lesions in the follow-up period following CAS. *ISR* in-stent restenosis

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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Drug-Coated Balloons for Treatment of Internal Carotid Artery Restenosis After Stenting: A Single-Center Mid-Term Outcome Study

Kamran Hajiyev[1] · Hans Henkes[1,2] · Ali Khanafer[1] · Philipp Bücke[3] · Florian Hennersdorf[4] · Hansjörg Bäzner[5] · Philipp von Gottberg[1]

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Abstract

Purpose Endovascular and surgical treatments of stenosis of the extracranial internal carotid artery (ICA) are common procedures, yet both introduce a risk of restenosis due to endothelial hyperplasia. Drug-coated balloons (DCBs) are designed to decrease neointimal hyperplasia, however rarely used in the neurovascular setting. This study retrospectively analyzes mid-term results of DCB-treated in-stent restenosis (ISR) of the ICA.

Materials and Methods The medical history, comorbidities, and periprocedural data of patients receiving DCB treatment for > 50% ISR of the ICA after carotid artery stenting were analyzed. Follow-up after DCB treatment was performed with Doppler ultrasound. Suspicious cases were checked with CT- or MR-angiography and—if there was agreement between the modalities—validated with digital subtraction angiography. Potential risk factors for restenosis and differences in outcomes after PTA with three types of DCB balloons were evaluated.

Results DCB treatment was performed in 109 cases, 0.9% of which involved in-hospital major stroke; no minor strokes occurred. A total of 17 patients (15.6%) had recurrent ISR after DCB treatment, after a mean time of 30.2 months (7–85 months). Tobacco use was significantly associated with a higher incidence of recurrent ISR.

Conclusion DCB angioplasty for ISR is an effective treatment that may delay and decrease restenosis. Treating comorbidities and adopting lifestyle changes may additionally help prevent ISR.

✉ Philipp von Gottberg
p.vongottberg@klinikum-stuttgart.de

Kamran Hajiyev
k.hajiyev@klinikum-stuttgart.de

Hans Henkes
h.henkes@klinikum-stuttgart.de

Ali Khanafer
a.khanafer@klinikum-stuttgart.de

Philipp Bücke
philipp.buecke@insel.ch

Florian Hennersdorf
florian.hennersdorf@med.uni-tuebingen.de

Hansjörg Bäzner
h.baezner@klinikum-stuttgart.de

[1] Neuroradiologische Klinik, Klinikum Stuttgart, Stuttgart, Germany

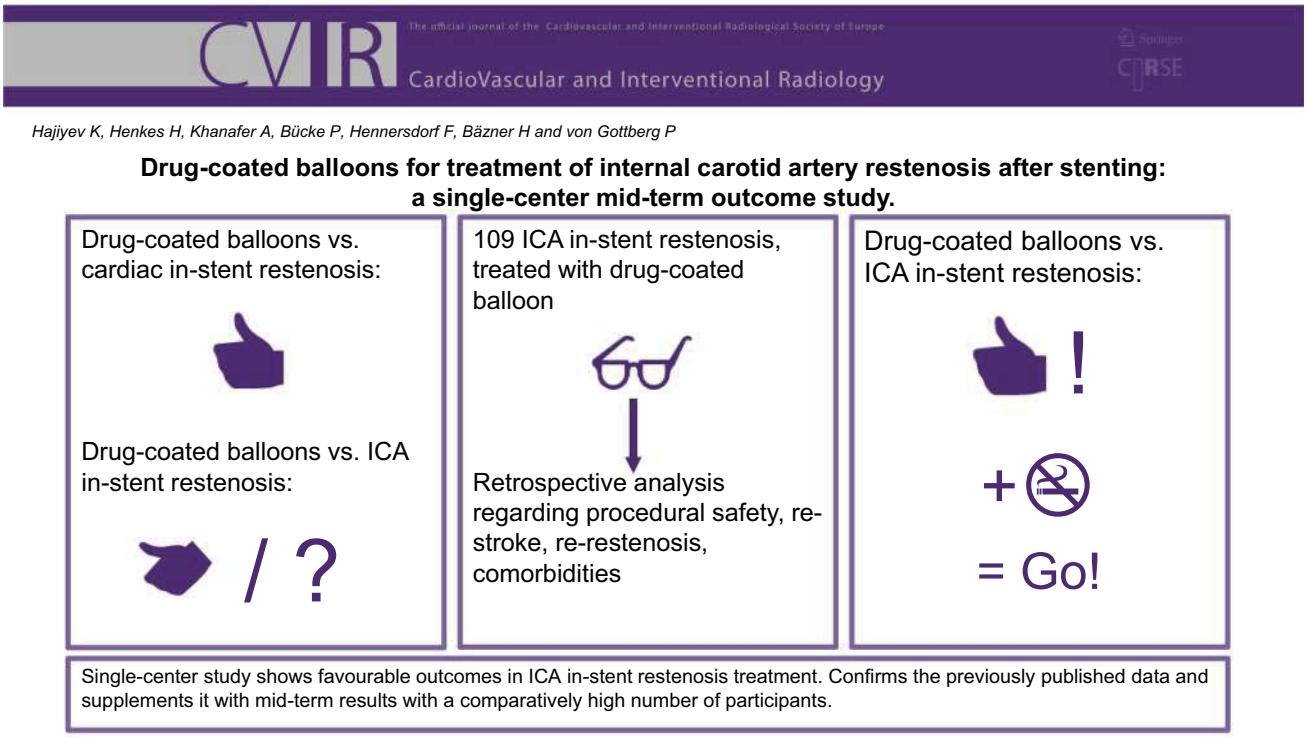
[2] Medizinische Fakultät, Universität Duisburg-Essen, Essen, Germany

[3] Universitätsklinik für Neurologie, Bern University Hospital, Inselspital, Bern, Switzerland

[4] Abteilung Diagnostische und Interventionelle Neuroradiologie, Radiologische Universitätsklinik Tübingen, Tübingen, Germany

[5] Neurologische Klinik, Klinikum Stuttgart, Stuttgart, Germany

Graphical Abstract



Keywords Stroke · Carotid artery stenting · In-stent restenosis · Drug-coated balloons · Carotid artery atherosclerotic disease

Introduction

In the treatment of moderate- to high-grade stenoses of the ostium of the internal carotid artery (ICA), carotid artery stenting (CAS) is a common and established procedure with long-term results that are comparable to surgical options [1–3].

CAS may lead to proliferation to the vessel's endothelium, and neointimal hyperplasia is believed to be a major factor influencing in-stent restenosis (ISR) [4]. In the CREST study, in which end points of death/stroke/myocardial infarction were analyzed in patients with ICA stenosis who were randomly assigned to receive CEA or CAS, patients with rather than without ICA ISR had a higher risk of recurrent stroke [5].

In a 2019 meta-analysis of more than 16,000 carotid interventions, the cumulative risk of > 70% restenosis has been found to be 5.2% at 12 months after CAS [6]. The 2018 International Carotid Stenting Study (ICSS) has reported a 40% five-year cumulative risk of restenosis after CAS. Again, restenosis significantly influenced the incidence of ipsilateral recurrent stroke in the study population [7].

Drug-coated balloons (DCBs) are devices specifically designed to challenge neointimal hyperplasia [8, 9].

In the neurovascular setting, after pioneering works by Vajda et al. in 2009 [10] and 2011 [11], and despite promising additional data in 2012 [12] and 2014 [13], further reports on DCB treatment of ISR have been sparse but remain promising [14–16].

To further elucidate the role of DCBs in the treatment of ISR, we analyzed mid-term results of ICA ISR treated with DCB.

Methods

This single-center retrospective analysis was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee. All patients were informed in detail about the specific use and off-label indications for DCBs in ISR, and written informed consent was obtained from all patients before the procedure.

Patient Selection and Evaluation

Both symptomatic and asymptomatic patients with extracranial carotid artery stenosis (NASCET > 50%)

confirmed by digital subtraction angiography and treated with CAS in an elective or acute setting between 2009 and 2023 were retrospectively analyzed.

Patients with suspected ISR > 50%, concordant on Doppler and CT-/MR-angiography imaging, after confirmation by digital subtraction angiography, were treated with conventional balloons or DCBs, with or without additional stent implantation. The appropriate treatment method (bare balloon vs. DCB vs. balloon angioplasty and re-stenting) was carefully considered by our neurovascular team, on the basis of the morphology and length of the ISR. Only patients with confirmed ISR > 50% and exclusive DCB treatment were included.

The pre-procedural evaluation included a neurological and degree –of –stenosis assessment and platelet function test (Multiplate®, Roche Diagnostics/VerifyNow®, Werfen). ISR was considered symptomatic if a patient experienced transient ischemic attacks (TIAs), amaurosis fugax or cerebral infarction of the corresponding ICA territory in the preceding six months, or acute cerebral ischemia in the preceding seven days.

Patients were considered asymptomatic if they had neither stroke nor TIA within the preceding six months. The NASCET method [17] was used to determine the degree –of –stenosis.

Baseline demographics; risk factors; and clinical and periprocedural data were retrospectively collected from our hospital's database.

Procedure and Technical Data

Patients received dual antiplatelet therapy for at least three days before the procedure, and general anesthesia (GA) was preferred. The aforementioned platelet function tests were performed on the day of the procedure to ensure adequate platelet inhibition. A 6 F guiding catheter was used for selective catheterization of the common carotid artery. Diagnostic angiography was performed to confirm the degree and morphology of the ISR. Unfractionated heparin was infused as a bolus of 3000–5000 IU. A 0.014-inch microguidewire was then navigated beyond the ISR. A DCB of the proper size, preferably a 4/20-mm balloon, was used to cover the whole length of the ISR. Oversizing was deliberately avoided. The DCB was kept inflated for 60–90 s, then deflated and withdrawn. A final angiogram was obtained in all cases. Technical success was defined as restoration of blood flow within the stent, with residual stenosis below 30%. The balloon catheters used were Emperor® (AR Baltic Medical, Vilnius, Lithuania; $n = 7$), SeQuent® Please (B. Braun SE, Melsungen, Germany; $n = 50$), and SeQuent® Please NEO (B. Braun SE, Melsungen, Germany; $n = 52$).

Post-procedural Period

Arterial blood pressure should be maintained at a systolic level of 120–130 mmHg for at least 24 h. A neurological assessment and, in most cases, post-procedural computed tomography or magnetic resonance imaging (MRI) were performed before hospital discharge. Periprocedural neurological events were documented and categorized as follows:

- TIA: reversible focal neurological deficit < 3 h.
- Cerebral hyperperfusion syndrome: symptoms associated with brain edema and intracerebral/subarachnoid hemorrhage.
- Stroke: acute, persistent focal neurological deficit with cerebral ischemia; categorized as:
  - Major stroke – an increase on the mRS of ≥ 3 points.
  - Minor stroke – an increase on the mRS of ≤ 2 points from pre-stroke status.

All patients were scheduled for ISR checkup through Doppler sonographic imaging at 3, 6, 9, and 12 months after CAS, and then every six months thereafter. The occurrence of recurrent stenosis after DCB therapy was defined as the primary outcome.

Statistical Analysis

Continuous data are described as the mean, median, minimum, and maximum. Hazard ratios with 95% confidence intervals (CIs) were estimated with Cox regression to analyze the influence of continuous data on survival time. Numbers and percentages were used to describe categorical data. The incidence rates of ISR were calculated as events per 100 years. Incidence rate ratios (IRRs) were calculated to compare the incidence rates between groups. For incidence rates and IRRs, 95% CIs are given. Equality of survivor functions was compared with log-rank tests. All statistical tests were two-sided and had a significance level of 0.05. Stata/IC 16.1 for Unix was used for the statistical analysis.

Results

Among 3489 patients who underwent CAS in the mentioned period, 190 patients received treatment for ISR at our hospital. Exclusive treatment with DCB angioplasty was performed in 109 patients, all of which were technically successful and are reported herein.

This patient cohort included 38 women and 71 men, and the median age was 68 years (range: 32–86 years). The

Table 1 Baseline demographics and risk factors

	Total (n = 109)
Sex	
Female	38 (34.9%)
Male	71 (65.1%)
Age (years)	
Median	68
Range	32–86
Atrial fibrillation	10 (9.2%)
Diabetes mellitus	44 (40.4%)
History of tobacco use	49 (45%)
Arterial hypertension	87 (79.8%)
Peripheral artery disease	24 (22%)
Coronary artery disease	29 (26.6%)
Dyslipidemia	54 (49.5%)

Table 2 ICA-stenosis details at presentation for initial angioplasty

	Total (n = 109)
Location of ISR	
Right	51 (46.8%)
Left	58 (43.2%)
NASCET (%)	
50–75%	74 (67.9%)
> 75%	35 (32.1%)
Previous neck radiation	8 (7.3%)

distribution of symptomatic vs. asymptomatic stenosis was n = 5 vs. n = 104 (95.4%).

The most common comorbidities were arterial hypertension (79.8%), dyslipidemia (49.5%), tobacco use (45%), and diabetes mellitus (40.4%; Table 1).

Hundred-seven procedures (98.2%) were performed under GA. Thirty-five patients (32.1%) had an ISR exceeding 75%, and eight patients (7.3%) had a history of radiotherapy to the neck (Table 2).

One patient (0.9%) suffered a major stroke due to intraprocedural embolic M1 occlusion after ipsilateral DCB angioplasty, although the thrombus was immediately removed by mechanical thrombectomy.

No other neurological event and no myocardial infarction was observed in the in-hospital phase. A total of 68 patients underwent MRI after treatment, which revealed clinically inapparent microlesions on diffusion-weighted imaging (DWI) in 23 patients (33.8%). Three (2.8%) patients had minor complications at the femoral access site.

The primary outcome of recurrent ISR exceeding 50% occurred in 17 patients (15.6%) after a mean time of

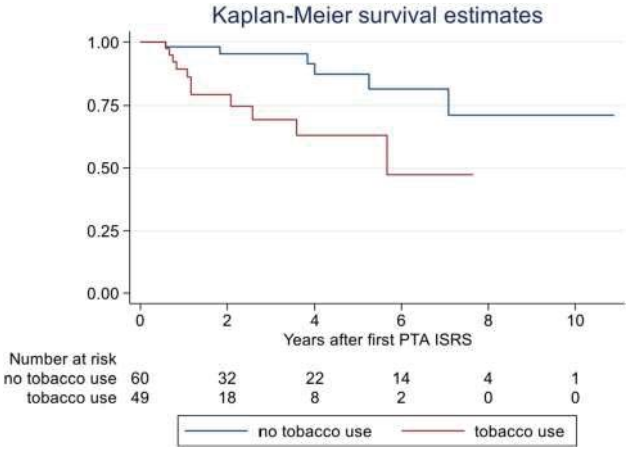


Fig. 1 Estimated rates of patients without recurrent ISRS in relation to tobacco use

30.2 months (7–85 months). All of these patients required follow-up treatment due to symptomatic ISRS (n = 12) or recurrent ISR > 75% (n = 5). Tobacco use (11/17, 64.7%) showed a statistically significant association with recurrent ISR (p = 0.005; Fig. 1). Five of the eight included patients with a history of neck radiation were represented in that group. Regarding the different balloon models, the mean time after re-intervention for the recurrent ISR was longer in patients treated with SeQuent® Please NEO, but the difference was not statistically significant. Furthermore, there were no significant differences in the results between the individual balloon models (Tables 3, 4).

Discussion

The aim of this study was to investigate the effect of DCB on ISR in patients after CAS with regard to time –to –restenosis after DCB angioplasty and safety/periprocedural aspects. Published data on ICA ISR treated with DCBs are sparse, and studies covering higher patient numbers have shorter mean follow-up times compared to the mean follow-up time of 30.2 months in this study [18–20]. However, with 15.6% recurrence of ISR > 50% at a mean time –to –restenosis after DCB angioplasty of 32.6 months, results from this study are comparable with data found in the literature (0–23% restenosis > 50%; mean time –to –restenosis 23 months).

The differences between the mean time –to –restenosis of the studies and our data can possibly be explained by the different numbers of cases and follow-up periods as well as the selection of patients.

Regarding patient selection, a report published by Wu et al. [16] shows promising results for DCB treatment of patients with post-radiation stenosis of the ICA. Radiation-induced atherosclerosis of the ICA is a fast-progressing,

Table 3 Characteristics and procedural data for patients with recurrent ISR

	Total (n = 17)
Sex	
Female	4 (23.5%)
Male	13 (76.5%)
Age (years)	
Median	68
Range	53–78
Atrial fibrillation	1 (5.9%)
Diabetes mellitus	10 (58.8%)
History of tobacco use	11 (64.7%)
Arterial hypertension	14 (82.4%)
Peripheral artery disease	1 (5.9%)
Coronary artery disease	5 (29.4%)
Dyslipidemia	8 (47.1%)
Time from DCB treatment to recurrent ISR (months)	
Mean	30.2
Range	7–85
Emperor®	
n	2
Mean	36.5
Range	25–48
SeQuent® Please	
n	9
Mean	24.1
Range	7–63
SeQuent® Please NEO	
n	6
Mean	37.2
Range	8–85

aggressive form of vessel disease compared with lifestyle-induced atherosclerosis [21]. We observed a remarkably high proportion of patients with neck irradiation with re-restenosis after DCB treatment of the ICA (62.5%). Yet, the mean time –to –re-restenosis was nearly twice the entire follow-up time reported by Wu et al.: 12 months of follow-up vs. 22.8 months until re-restenosis after DCB treatment in our data. The pathomechanism underlying this type of ICA stenosis might be more sensitive to drug-eluting devices than plain devices, because of the high proportion of neointimal hyperplasia; consequently, treating radiation-induced ICA restenosis with DCBs may be beneficial.

The statistical significance of the association between continuous tobacco use and the development of recurrent ISR suggests that past and/or current tobacco use and a history of radiotherapy to the neck increase the risk of ISR, but may also indicate that addressing neointimal hyperplasia through DCB treatment may be only part of the solution. Lifestyle modification and management of comorbidities may therefore influence the risk of ISR after DCB treatment [22]. However, particularly in smokers with a history of radiotherapy to the neck, short-term checks for ISR may be advisable.

All applied DCBs had a paclitaxel coating; however, the doses and excipients differed: 2.2 μg/mm^2 and dextran as excipient for the Emperor® DCB (as stated by the manufacturer) and 3 μg/mm^2 for the SeQuent® Please [23] and SeQuent® Please NEO DCB with iopromide as excipient (as stated by the manufacturer). Excipients enhance the amount of drug transferred to the vessel wall. However, the extent of drug transfer varies considerably among different excipients/models of DCBs [24]. Thus, the differing results for the applied devices might be explained by different degrees of drug transfer or different doses in the device coating.

Regarding periprocedural safety, the 0.9% incidence of major stroke and no death suggest that DCBs can be considered safe. The majority of procedures were performed in GA. In CAS, local anesthesia is believed to be responsible

Table 4 Analysis of the influence of risk profiles comprising specific comorbidities on the prevalence of recurrent ISR

	n	ATO* (y)	ISR (*n*)	Incidence per 100 years (95% CI)	*p* value** IRR (95% CI)
Sex					
Female	38	102.6	4	3.90 (1.46; 10.38)	0.436
Male	71	198.8	13	6.54 (3.80; 11.26)	1.68 (0.52; 7.06)
Atrial fibrillation					
No	99	274.6	16	5.83 (3.57; 9.51)	0.699
Yes	10	26.9	1	3.72 (0.52; 26.42)	0.64 (0.02; 4.11)
Diabetes mellitus					
No	65	152.3	7	4.60 (2.19; 9.64)	0.484
Yes	44	149.2	10	6.70 (3.61; 12.46)	1.46 (0.50; 4.51)
Tobacco use					
No	60	203.0	6	2.96 (1.33; 6.58)	0.005
Yes	49	98.5	11	11.17 (6.18; 20.16)	3.78 (1.28; 12.44)
Arterial hypertension					
No	22	56.6	3	5.30 (1.71; 16.44)	0.910
Yes	87	244.9	14	5.72 (3.39; 9.65)	1.08 (0.30; 5.85)
Peripheral artery disease					
No	85	239.8	16	6.67 (4.09; 10.89)	0.126
Yes	24	61.7	1	1.62 (0.23; 11.50)	0.24 (0.01; 1.56)
Coronary artery disease					
No	80	205.8	12	5.83 (3.31; 10.27)	0.773
Yes	29	95.7	5	5.23 (2.18; 12.56)	0.90 (0.25; 2.73)
Dyslipidemia					
No	55	145.2	9	6.20 (3.23; 11.92)	0.753
Yes	54	156.3	8	5.12 (2.56; 10.23)	0.83 (0.28; 2.41)
Balloon					
Emperor®	7	20.6	2	9.69 (2.42; 38.74)	–
SeQuent® Please	50	193.6	9	4.65 (2.42; 8.94)	0.509***
SeQuent® Please NEO	52	87.3	6	6.87 (3.09; 15.30)	1.48 (0.43; 4.65)**

*Accumulated time of observation

**Log-rank test for equality of survivor functions

***Comparison of SeQuent® Please vs. SeQuent® Please NEO

IRR incidence rate ratio

for the lower rate of myocardial infarction in comparison with patients receiving open surgery in GA [25]. However, for DCB treatment, we prefer GA to achieve better patient tolerance to longer balloon inflation times and higher precision in stenosis treatment through machine-assisted breath-holding. It is also easier in GA to handle sudden fluctuations in blood pressure and epileptic seizures caused by the inflation of the balloon.

Coating wash-off in the vascular system distal to the treated lesion has been reported [26]. Regarding paclitaxel doses, a systemic dose of approximately 300 mg is reported to cause peripheral neuropathy in oncology. This dose greatly exceeds the total amount of paclitaxel in the coating of a DCB; to date, there are no reports on pharmacological effects of paclitaxel after DCB treatment in the neurovascular setting [27]. Consistent with this, no patients in this study reported symptoms or effects that could be attributed to the use of DCBs in a vessel directly supplying the brain. A definitive answer to the question of whether and to what extent the brain is harmed by the use of a DCB in a vessel directly supplying it can therefore not yet be given.

The limitations of this study are the limited comparability with previously published studies on the treatment of ICA ISR by DCB and the paucity of data published on this topic to date. In addition, this study lacked a control group, thus decreasing the comparability of the results. Another limiting factor of the study is the fact that a small proportion of patients did not undergo imaging after the procedure; however, this was due to uneventful procedures in

which patients had no new symptoms and therefore probably only had minor impact on the results.

Conclusion

DCB is beneficial in the treatment of ICA ISR in terms of the time-to-restenosis and may therefore decrease the risk of stroke recurrence; the effect may vary between the different DCB models due to the different dosage of the drug and the excipients.

However, DCB treatment may be only part of strategies to prevent restenosis, and lifestyle changes, particularly tobacco cessation, may also play a role.

Author Contributions K. Hajiyev, H. Henkes, and P. von Gottberg conceived the manuscript. K. Hajiyev has collected the data. A. Khanafer, P. Bücke, F. Hennersdorf, and H. Bäzner evaluated the data. K. Hajiyev and P. von Gottberg wrote the manuscript. H. Henkes, F. Hennersdorf, and H. Bäzner advised on reference selection. H. Henkes, F. Hennersdorf, and H. Bäzner proofread the manuscript.

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Declarations

Conflict of interest H. Henkes: Consulting and proctoring for phenox GmbH, co-owner of CONTARA GmbH. The other authors declare that they have no further potential conflicts of interest.

Consent for Publication This work complies with all instructions to authors. Authorship requirements have been met and the final manuscript was approved by all authors. The manuscript was writing according to the STROBE checklist for cohort studies. This manuscript has not been published elsewhere and is not under consideration by another journal. Data and results described in this manuscript have not been presented elsewhere.

Ethical Approval This single-center retrospective analysis was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee.

Informed Consent All patients were informed in detail about the specific use and off-label indications for DCBs in ISR, and written informed consent was obtained from all patients before the procedure.

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