Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2022**; 23(4): 128
https://doi.org/10.31083/j.rcm2304128

Systematic Review

Drug-coated Balloons in the Neurovascular Setting: A Comprehensive, Systematic Review of Current Use and Indications

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Academic Editors: Massimo Volpe, Filippos Triposkiadis, Grigorios Korosoglou and Matteo Cameli
Submitted: 10 December 2021 Revised: 13 January 2022 Accepted: 21 January 2022 Published: 2 April 2022

Abstract

Background: Drug-coated balloons (DCB) are an established tool in the prevention and treatment of coronary and peripheral artery restenosis. The underlying effects of restenosis resemble those in the neurovascular field, yet data on the use of DCB in cervical and intracranial arteries is rare. **Methods**: Medline, and international and major national guidelines and recommendations were systematically searched for data addressing the use of DCB in the neurovascular setting. **Results**: Of the 1448 relevant records found in Medline, 166 publications were considered for this review. **Conclusions**: Data on the use of DCB in the neurovascular setting show a possible benefit over preceding alternatives, such as self-expanding stents, and balloon-mounted or drug-eluting stents. Nonetheless, the role of DCB remains under-researched, and publications remain lacking.

Keywords: drug-coated balloons; percutaneous transluminal angioplasty; neurovascular; neurointerventional; arterial stenosis; carotid artery stenosis; intracranial atherosclerotic stenosis; stroke; paclitaxel

1. Introduction

Materials and devices for neurovascular interventions traditionally have a close connection to cardiovascular devices, and many include or are inspired by precursors with a long history of testing. Over the past 15 years, general advances in the fields of neurointervention and neuroimaging, supported by crucial international study results, as well as technical advances in device manufacturing, have led to a surge in neurointerventional procedures and indications. Consequently, the need for more specific interventional instruments and materials increased and stand-alone neurovascular devices, e.g., stent retrievers or certain blood flow modulating implants, have had their breakthrough or had even been newly developed as a result.

But also, devices with long-term proven reliability in the cardiovascular setting were now deployed in the neurovascular setting, particularly angioplasty devices and principles, such as stents and balloons.

However, despite the increase in treatment options for neurovascular atherosclerotic stenosis, neurointerventionalists have not observed the same treatment outcomes as their colleagues in interventional cardiology and have not been able to establish the full range of possible interventional options. Major trials comparing carotid artery stenting (CAS) vs. transluminal endarterectomy (TEA) have been unable to demonstrate the inferiority of the long-established surgical procedure to the newer micro-invasive procedure [1–4]. Because CAS and TEA have comparable long-term results and different indications, the debate regarding CAS vs. TEA resembles the longstanding debate regarding percutaneous coronary intervention vs. coronary artery bypass grafting [5–9]. Additionally, the success of coronary artery stenting, particularly small coronary vessel transluminal angioplasty [10–12], has not been replicated in intracranial atherosclerotic stenosis in major trials: The SAMMPRIS trial has indicated the superiority of aggressive medical treatment to intracranial stent-assisted angioplasty in new arteriosclerotic lesions [13]. In the VISSIT trial, stenting has been found to result in more stroke and death than medical therapy [14]. Since then, research on the interventional treatment of arterial stenosis in the neurovascular setting, particularly the treatment of intracranial arteries, has declined.

However, new techniques and devices have emerged in the meantime, and developments in the field of cardiology have again advanced the development of neurointervention. Thus, drug-coated balloons (DCB) and drug-eluting stents (DES) have become a focus of neurointerventionalists. Although initial, limited data have shown promising results, the potential applications and indications for these devices remain to be elucidated.

This review provides a systematic overview of the literature and guidelines on DCB use and indications in the neurovascular setting.

2. Materials and Methods

This systematic review was performed according to the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* [15] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement [16].

Medline was searched through the PubMed interface with no restrictions in language and publication period. Publications suitable for answering the questions of this review were identified on the basis of combinations of the following:

- Article type: no restriction.
- Vascular setting: neurovascular.
- Intervention: DCB, DES.
- Device type: DCB, DES.
- Drugs: drugs applicable to DCB: paclitaxel; "limus-based" drugs, i.e., everolimus, sirolimus, or zotarolimus.

Additionally, current guidelines of the American Heart Association, American Stroke Association, European Society of Cardiology, European Society for Vascular Surgery, and European Stroke Organisation were evaluated for the above items [17,18].

Among the 1448 records in Medline meeting the search criteria, 241 were selected for screening on the basis of greatest relevance to the covered topics. Among these, 166 publications were identified as eligible for this review.

3. Results

3.1 Drug-coated Balloons

3.1.1 History

Since the first percutaneous transluminal coronary angioplasty in 1977, performed by Grüntzig [19], the materials and methods used have evolved from bare-balloon angioplasty to coronary stents, drug-eluting stents and balloons, DCB, and bioresorbable scaffolds [20,21]. The principle of PTA was rapidly introduced in many vascular areas, in which surgical stenosis treatment was typically used, because it had already been demonstrated to be beneficial in the supraaortic, neurovascular area at the time when PTA was introduced [22,23].

In 1983, PTA of the extracranial internal carotid artery (ICA) was first described in the literature [24], and 7 years later, suspected cerebral embolization through plaque damaging was addressed to in a groundbreaking way by the first cerebral protection device in a triaxial setup [25]. Despite these developments, major trials, such as SPACE (2004) and Crest (2010), did not demonstrate the superiority of the endovascular method to open surgery [2,26].

However, it's a meanwhile frequently performed procedure that's not only carried out in surgically non-accessible anatomy but is regarded equally to surgical treatment in regard of different risk factors and conditions of both methods. But both methods stimulate neointimal proliferation, a mechanism that is believed to be primarily responsible for restenosis and instant restenosis in the neurovascular setting [27] increasing the risk of new ischemic events and death after successful treatment.

In intracranial arteries, owing to the high risk of complications, endovascular treatment of intracranial atherosclerotic stenosis (ICAS) has rarely been reported after an initial two-case report on PTA of high-grade basilary artery stenosis in 1980 [28]. Stents for intracranial use were first described in emergency or ultima ratio settings of SAH [29,30] and surgically inaccessible major aneurysms rather than ICAS treatment. Stent-assisted treatment of ICAS was later incorporated into neurovascular interventions [31–35]. However, concerns regarding the mid- to long-term benefits of endovascular treatment of ICAS arose early [36]. Ultimately, no randomized multicenter trials to date have demonstrated an advantage of stent assisted ICAS treatment over the best medical treatment (SAMMPRIS [13], VISSIT [14]).

A major reason for the devastatingly poor outcomes of stent-treated ICAS is the high incidence of in-stent restenosis, which is again probably caused by neointimal proliferation [37–39].

The issue of neointimal proliferation and its negative effects on long-term outcomes have also been observed in the field of cardiology and were addressed in the early 2000s already after a retarding effect on neointimal proliferation after short-term exposure to taxane in a porcine model was described [40,41]. Consequently, the development of DCB began.

DCB are now a part of cardiovascular guidelines [18, 42] and international consensus statements [43,44], with the caveat that a class effect of DCB should not be presumed, because the results varied among different types of DCB [42,45].

In the neurovascular setting, the problem of neointimal proliferation leading to in-stent restenosis and restenosis after angioplasty was initially countered by DES, too. However, the effects of DCB observed in non-neurovascular fields led to the introduction of DCB in the neurovascular setting in due course [44].

The primary use of DCB was the prevention and treatment of in-stent restenosis and restenosis of extracranial carotid artery arteriosclerotic stenosis (ECAS) and ICAS, and reported results indicated advantages over bare-balloon angioplasty as well as re-angioplasty, resembling findings in the field of cardiology. This method was pioneered in 2011 and 2012 by Vajda *et al.* [46,47] with promising results and was only revisited in 2018 [48–56]. However, despite good results and reviews continuing to advocate

Table 1. Commercially available DCB with CE mark, intended for use or usable off-label in the neurovascular field.

Device name, producer	Drug, dosage ($\mu g/mm^2$)	Excipient	Diameter, length (mm)	Guide wire lumen
Agent™, Boston Scientific	PCX, 2	ATBC	2–4, 12–30	0.014′′
AngioSculptX, Cardiva	PCX, 3	Antioxidant, NDGA	2/2.5, 15/10	0.014′′
ELUTAX “3”, AR Baltic Medical	PCX, 2.2	Dextran	1.5–6, 10–40	0.014′′
ELUTAX-SV, Aachen Scientific	PCX, 2.2	Dextran	2-4/10-40	0.014′′
Danubio, Minvasys	PCX, 2.5	BTHC	1.5–4, 10–40	0.014′′
SeQuent® Please NEO, B. Braun	PCX, 3	Iopromide	2–4/10–40	0.014′′
Pantera® Lux™, Biotronik	PCX, 3	BTHC	2–4/10–30	0.014′′
Restore DEB®, Cardionovum	PCX, 3	Shelloic acid	2–4/15–30	0.014′′
Chocolate Touch®, QT Vascular	PCX, 3	N. N., hydrophilic spacer	2.5–6/40–120	0.014′′, 0.018′′
Dior® II, BioStream/BioPath	PCX, 3	Shellac	Stream 2–4/15–30 BioPath 4–8/20–150	0.014′′ /0.035′′
Essential Pro, iVascular	PCX, 3	N. N.	1.5–4.5/10–40	0.014′′
IN.PACT™ Admiral AV DCB, Medtronic	PCX, 3.5	Urea	4–12, 40–120	0.035′′
Selution SLR™, MedAlliance	SRO, 1	Poly (lactic-co-glycolic acid) (PLGA) + phospholipids [60]	1.5–5/10–40	0.014′′, 0.018′′
Virtue® SAB, Orchestra BioMed	SRO, N. N.	Phospholipid., perforated balloon	N. N.	0.014′′
Magic Touch, Concept Medical	SRO, 1.27	Phospholipid carrier	1.5–12/10–200	0.014′′, 0.018′′, 0.035′′
Protégé/Protégé NC, Wellinq	PCX/3	N. N., hydrophilic coating	2–4.5/10–30	0.014′′
Extender PTCA, Invamed	PCX/1	Iopromide	2–5/10–30	0.014′′

ATBC, acetyl-tributyl citrate; BTHC, n-butyryl tri-n-hexyl citrate; NDGA, nordihydroguaiaretic acid; PCX, paclitaxel; SRO, sirolimus.

for the evaluation of DCB in the treatment and prevention of ECAS and ICAS in in-stent restenosis [57–59] and restenosis, data addressing the use of DCB and the evaluation of its possible benefits in the neurovascular setting remain rare; consequently, we believe that this field is underinvestigated, and publications are lacking.

Table 1 (Ref. [60]) displays commercially available DCB with a CE mark, intended for intracranial use or usable off-label in the neurovascular setting.

3.1.2 Drugs

After testing of several drugs for the prevention of neointimal proliferation in stents and balloons [61–65], paclitaxel followed by sirolimus have become established in DCB and are currently the main drugs used.

3.1.2.1 Paclitaxel

Paclitaxel is an antimicrotubular drug that stabilizes microtubule polymerization during mitosis, thus inducing cell death [66,67]. It effectively inhibits coronary neointimal proliferation *in vitro* and *in vivo* [68]. Paclitaxel is highly lipophilic and therefore virtually insoluble in water [69], thus decreasing drug loss during application and drug downstream—i.e., the effect of leaching of paclitaxel distal to the treated stenosis. However, the amount of paclitaxel effectively reaching the vessel wall during DCB angioplasty, is estimated to be only 10% (5–20%):

- 5–30% of loss en route to the destination.

- 40–70% loss during or directly after balloon inflation and deflation through washout.

- 0–30% of the drug may remain unapplied and may be recovered with the balloon after the intervention [70].

This proportion of lost paclitaxel led to suspicions of tissue harm and consequently to investigations of downstream effects, which culminated in a highly regarded, yet methodically and statistically limited meta-analysis connecting the application of paclitaxel-eluting devices to higher mortality in selected studies [71]. The results of this meta-analysis are controversial. Soon after, several contradictory meta-analyses and trials concerning this issue were published [72–77]. Studies investigating the direct effects of drugs downstream from paclitaxel-coated devices nevertheless did not find relevant harm to (coronary) tissue distal to the point of application in the vessel [70,78–81]. Today, the effect of paclitaxel from paclitaxel-containing implants on tissue away from the site of application is considered irrelevant and is no longer directly related to increased mortality [82,83].

3.1.2.2 Sirolimus

Sirolimus is another name of rapamycin, which is derived from Streptomyces hygroscopius. Its immunosuppressive and antiproliferative effects stem from blocking the cell-cycle specific kinase Target of Rapamycin (TOR) and subsequently halting cell mitosis and inducing cytostasis [84,85]. The antiproliferative effect of sirolimus discov-

ered in early work [86] has been demonstrated to be highly effective in the treatment of coronary neointimal proliferation and in-stent restenosis and restenosis through DES [87,88].

Further developments in coating led to the development of sirolimus-coated balloons (SCB), which can be applied in the same manner as paclitaxel-coated balloons (PCB) with sufficient sirolimus transfer to the vessel wall [89]. The advantages of sirolimus over paclitaxel are mainly seen in sirolimus having a broader therapeutic range, larger safety margin, greater success in restenosis treatment than other anti-restenosis drugs, and that it is cytostatic instead of cytotoxic [90–92].

Several trials have demonstrated that SCB, which emerged in the mid-2010s, are effective in the treatment of coronary neointimal proliferation [93–95]. The range of commercially available SCB remains narrow, and randomized trials are scant. Currently, no published data are available on the use of SCB in ECAS or ICAS. However, because SCBs are available in the cardiovascular setting, they may one day be used in the neurovascular setting as well.

3.1.3 Different Coating Techniques and Excipients

In the current state of the art of DCB, the coatings contain a drug (e.g., paclitaxel) and a transfer enhancing excipient or spacer, because bare drug-coated devices achieve less transfer of the anti-proliferative drug [70,96,97]. The drug on the balloon is dosed in μg/mm^2 balloon surface, and the amount of drug transferred to the vessel wall tissue is directly correlated with the inhibition of neointimal proliferation; however, the magnitude of drug transfer varies significantly [44].

The most common excipients in DCB are derived from modified plant and bacterial substances (e.g., n-butyryl tri-n-hexyl citrate, dextran, nordihydroguaiaretic acid, resveratrol, shellac, and urea), organic plasticizers (e.g., acetyltributylcitrate), magnesium stearate, and the iodine-containing contrast agent iopromide. Urea- and magnesium stearate-containing coatings have been found to strongly inhibit neointimal proliferation in a porcine model [98] and in patients. However, estimating the applied dose *in vivo* (i.e., in atherosclerotic human vessels) remains a challenge. The optimal technique and excipient may be yet unidentified, given that new coating techniques and excipients continue to be developed, and existing ones are being improved.

3.2 Use and Current Indications of DCB in the Neurovascular Setting

The primary use of DCB in the neurovascular setting is to treat or prevent vessel stenosis and restenosis, as reflected by the data in the literature.

To date, no official guidelines or recommendations exist regarding the primary use of DCB in the neurovascular setting. However, guidelines consider intracranial angioplasty in emergency situations and bail-out maneuvers [99,100].

Therefore, interventionalists are dependent on focused, extensive clinical and imaging diagnostics.

3.2.1 Extracranial

3.2.1.1 Internal Carotid Artery. Although *in vivo* experiments with temporal occlusion of the ICA have found that as much as 15% of mean cerebral perfusion is supplied by the ipsilateral external carotid artery [101], to date, no relevant advantage of sole external carotid artery-stenosis treatment—both endovascular and surgical—has been reported [102], apart from case reports focused on rare symptoms and constellations of external carotid artery stenosis. Treatment of the extracranial carotid artery is mainly focused on treatment of the proximal ICA; therefore, this section focuses on ECAS treatment of the ICA.

Use of PTA vs. TEA for the treatment of ECAS has been investigated intensively, yet the clear superiority of either remains unproven. Although TEA appears to raise the risk of a myocardial infarction, the risk of ipsilateral stroke is higher in PTA [103]. However, long-term outcomes may be similar [104]. The advantages and particularly the disadvantages of both treatment types are subject to an ongoing discussion and must be considered for each patient individually.

The use of DCB as an index treatment of external carotid artery stenosis is not common. To our knowledge, no trial or major case study has investigated the effects of using DCB in the PTA treatment of de novo ECAS.

The primary use of DCB is therefore the treatment of ECAS restenosis after TEA and PTA, which is a common issue: in the 2018 ICSS trial, the 5-year cumulative risk of restenosis after TEA and in-stent restenosis after PTA has been reported to be approximately 30% for TEA and 40% for PTA, thus raising the overall risk of ipsilateral stroke in the studied population of 1530 individuals [105].

Challenging ECAS in-stent restenosis (ISRS), the use of DCB was first reported in 2012 in two case series (IN.PACT™ Amphirion, Medtronic, Dublin, Ireland [106] and IN.PACT™ Admiral, Medtronic-Invatec, Dublin, Ireland [48]) describing the application of paclitaxel DCB in an ISRS after standard balloon predilation. At a median follow-up of 15 months, a total of ten treated patients showed not only arrested neointimal hyperplasia in the dilated vessel lumen but also a subsequent decrease in flow peaks on Doppler sonography.

This phenomenon was also reported in a case series of nine patients in 2014 with ISRS refractory to several preceding endovascular maneuvers (DIOR II; Eurocor) [107].

Piccoli *et al.* [108] have published a case series of 18 patients in 2015 with high-grade stenosis after TEA, who were treated with DCB before stent-PTA of the carotid artery. At a mean follow-up of 18 months, no restenosis

Table 2. Studies addressing the use of DCB for restenosis treatment of the extracranial carotid artery.

Author, year	DCB treatment N	Target	Follow-up	Reported outcome	Periprocedural stroke/death
Liistro *et al.* [106], 2012	3	In-stent restenosis	36 months for symptoms, 24 months for stent patency	100% asymptomatic, 100% stent patency	-
Montorsi *et al.* [48], 2012	7	In-stent restenosis	21 ± 19 months, mean 12 months	Significant decrease in in-stent peak systolic velocity	-
Piccoli *et al.* [108], 2015	18	Stenosis after TEA	13–22 months, mean 18 months	Stent patency >50% in 100% of cases	-
Pohlmann *et al.* [49], 2017	9, 11 procedures	In-stent restenosis	5 years	Event-free rate 83%	-
Tekieli *et al.* [109], 2019	27	In-stent restenosis	26 months	Earlier 2nd ISRS after DCB treatment than bare balloon, but at a lower rate in total	2% in total (DCB and bare balloon PTA)
Haupert *et al.* [110], 2020	18	Stenosis after TEA	12 months	Comparable results for DCB vs. CAS vs. bare balloon PTA vs. open surgery/14% restenosis	3% in total (DCB, CAS, and bare balloon PTA)
Mihály *et al.* [52], 2021	2	In-stent restenosis	9–53 months, mean 30 months	No restenosis in DCB-treated patients	Not reported

over 50% of the vessel lumen occurred (IN.PACT™ Pacific balloon, Medtronic Vascular, Dublin, Ireland; Lutonix Balloon, Becton Dickinson, Franklin Lakes, USA).

In a retrospective single-center study, Pohlmann *et al.* [49] (SeQuent® Please, Braun Melsungen, Vascular Systems, Melsungen, Germany; IN.PACT™ Amphirion balloon, Medtronic, Dublin, Ireland) studied nine patients treated with DCB for ISRS (11 procedures in total due to bilateral ISRS in one patient and repeated DCB treatment due to restenosis after 19 months in another patient). In that study, the event-free rate was 100% after the first year and 83% after 5 years of follow-up. No periprocedural strokes or deaths were observed.

The first direct comparison of DCB angioplasty vs. bare balloon angioplasty in ISRS treatment was a single-center prospective registry evaluation, in a study published in 2019 by Tekieli *et al.* [109]. The DCB-group (n = 27) showed a second ISRS after DCB treatment earlier (mean 23 months) than the bare-balloon group (n = 19; mean 26 months). However, the rate of second ISRS was smaller in the DCB-treated group (23%) than in the group with bare balloon treatment (32%). The rate of periprocedural stroke or death was reported to be <2% for the bare-balloon (n = 19), DCB (n = 27) and stent-supported (n = 6) arms and is considered a DCB complication in this review.

Another retrospective single-center study comparing different techniques of endovascular treatment vs. open surgery for ICA restenosis after TEA has not shown significant differences in a 1-year follow-up in terms of overall survival, survival without recurrent restenosis, and survival without reintervention for DCB (n = 18), bare balloon (n = 7), and CAS (n = 9) vs. open surgery (Lutonix, Becton Dickinson) [110]. Moreover, no significant differences among the three endovascular techniques were observed; however, because of the small number of cases, this result has limited validity.

Mihály *et al.* [52] published a comparison of ISRS treatment and re-ISRS treatments in a group of 46 patients with CAS (n = 7) vs. bare balloon (n = 37) vs. DCB (IN.PACT™ Falcon; Medtronic, Dublin, Ireland; Ranger™, Boston Scientific Corp., Marlborough, USA) angioplasty (n = 2) and found no restenosis in the DCB group in a mean follow-up of 30 months. The authors have concluded that DCB is superior to CAS and bare balloon angioplasty in the prevention of ISRS; however, owing to the small number of cases, this result has limited validity.

Table 2 (Ref. [48,49,52,106,108–110]) shows the study data in detail.

3.2.1.2 Vertebral Artery. Vertebral artery atherosclerotic stenosis (VAOS) may account for up to 25% of cerebral ischemia cases [111,112] causing a high rate of mortality due to manifestation in the posterior circulation. The CAVEATS [113], VAST [114], and VIST [115] trials have investigated stent-assisted PTA of the vertebral arteries, and the results have suggested medical treatment as the first line of therapy. However, the ongoing debate about which treatment is better resembles that with ICAS.

Limited data are available regarding the use of DCB as primary treatment for VAOS. Wang *et al.* [116] reported the first case of DCB PTA in a patient with high-grade stenosis originating at a dominant vertebral artery, who did not qualify for stent-assisted PTA. The treatment was uneventful, as was the follow-up at 6 months, and no restenosis was observed on computed tomography angiography after that period.

In 2020, Gruber *et al.* [117] published a retrospective single-center study on 12 patients treated with DCB only

Table 3. Results of studies investigating DCB as a primary treatment for VAOS.

Number of studies; *period*	Patients n	Follow-up	Restenosis rate	Periprocedural complication rate
4; 2018, 2020, 2021	88	7.5 months (IQR 6–12)	5% (IQR 0–10)	0.5% (IQR 0–2)

for VAOS. No technical failures or instances of restenosis were found after a mean follow-up of 6.1 months, and no periprocedural major adverse events were recorded.

Wang *et al.* [118] have reported a restenosis rate of 10% at 6 months after DCB treatment (Orchid, Acotec Scientific, Beijing, China; Dhalia, Acotec Scientific, Beijing, China) of VAOS in 26 patients. No periprocedural strokes/deaths were reported. The trial was a pilot for a larger, prospective randomized single-center trial comparing VAOS treatment through DCB (PCB, Acotec Scientific, Beijing, China) with distal embolic protection (n = 49) vs. bare metal stenting without embolic protection (n = 46), which was published in 2021 [119]. The technical success rate was comparable in both groups (94% for DBC vs. 96%), and fewer embolic DWI lesions were observed in the DCB group. The restenosis rate was comparable in both groups after the mean follow-up of 12 months (10% DCB vs. 13% bare metal stent). The reported rate of periprocedural major adverse events was 2% in total, with one case in each group.

Table 3 summarizes the results of the described studies.

Of note, the role of DCB in the treatment of subclavian artery stenosis is unknown. In the current literature, only a few case reports have addressed this topic, including one case report of successful treatment of ISRS in the subclavian artery [120–122].

3.2.2 Intracranial

SAMMPRIS (2011/12) and VISSIT (2015) put the use of intracranial bare-metal stents for ICAS treatment on the second line. High-intensity statin and dual- to mono-platelet inhibition [13] has since then been considered first-line. Endovascular treatment is considered in cases of a second stroke in the same vessel territory under medical therapy. However, as devices and strategies have evolved, the idea of "leaving nothing behind" that originated in cardiology has prompted the investigation of the use of DCB as a primary treatment approach for atherosclerotic stenotic vessel disease in the neurovascular setting, too.

In 2018, Gruber *et al.* [50] were the first to publish a comparative retrospective cohort study, investigating the effect of ICAS treatment with a DCB (Neuro Elutax sV, Elutax, Aachen scientific, Aachen, Germany) vs. a bare-metal stent for intracranial stenosis treatment (Wingspan® Stent system, Boston Scientific, Marlborough, USA). In eight patients treated with DCB and 11 patients treated with the stent system, a significantly lower rate of the endpoint combination of ischemic re-event and/or restenosis was observed in the DCB-group (n = 1 DCB vs. n = 7 stent system). The follow-up time was 9.5 months in the DCB group and 10 months in the stent group. No peri- or intraprocedural complications were reported for the DCB-group, but one intraprocedural in-stent thrombosis and one case of temporary hyperperfusion syndrome were reported in the stent group.

In addition, in 2018, Han *et al.* [51] published a retrospective single-center analysis of 30 patients with 31 vessel segments treated for symptomatic high-grade ICAS with DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany). Two patients with periprocedural stroke were reported, and after a mean follow up of 10 $\pm$ 3 months, no new ischemic symptoms were observed. Angiographic follow-up revealed one case of asymptomatic restenosis (3%).

Also in 2018, Gruber *et al.* [53] described the primary DCB treatment (SeQuent® Please Neo, B. Braun Melsungen, Melsungen, Germany) of ten patients with high-grade, symptomatic ICAS. They received a median stenosis reduction grade of 28% (IQR 75–80% to IQR 45–53%) without restenosis during the follow-up period of 3 months. No periprocedural adverse events were recorded, and no new ischemic events or deaths were recorded in the follow-up.

Zhang *et al.* [54], in 2020, reported a retrospective study comparing the treatment of high-grade, symptomatic intracranial stenosis with bare-balloon PTA (n = 73) and DCB PTA (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany; n = 42). Both groups achieved favorable outcomes; however, the restenosis rate in the DCB group was significantly lower than that in the bare-balloon group in a 6-month follow-up (DCB restenosis rate 5% vs. 34%). The rate of periprocedural complications was 3% in the DCB-group and 11% in the bare balloon–group.

A Chinese single-center retrospective cohort study published in 2020 [56] described DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany) for the primary treatment of ICAS with bare balloon predilation. A total of 39 vessel segments in 35 patients were treated, and the angiographic follow-up was 11 $\pm$ 4 months. The authors reported a restenosis rate of 8%, with a disproportionately high incidence in intracranial ICA, thus suggesting that the risk of restenosis varies among vascular segments. The reported rate of periprocedural complications was 6% for two major complications.

Remonda *et al.* [123] have described two types of DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany; ELUTAX-SV, Aachen Scientific, Aachen, Germany) for the treatment of high-grade ICAS in a 2021 study with a total of 33 patients and 35 vessel segments treated. In a mean follow-up of 9 months (IQR 3–22 months), resteno-

Table 4. Results of the studies published to date addressing primary treatment of ICAS with DCB.

Number of studies; *period*	Treated vessel segments N	Follow-up	Restenosis rate	Periprocedural complication rate
7; *2018–2020*	181	7.8 months (IQR 3–11)	6% (IQR 0–13)	3.9% (IQR 0–6.5)

Table 5. Results of studies addressing intracranial ISRS treatment with DCB.

Number of studies; *period*	DCB maneuvers N	Follow-up	Restenosis rate	Periprocedural complication rate
2; 2011, 2020	51	5.3 months (3; 7.5)	4.5% (0; 9)	1.5% (0; 3)

sis occurred at a rate of 12%. The authors reported a 6% rate of periprocedural complications. The results were not reported according to the balloons used.

In 2020, Yang *et al.* [124] investigated the safety and short-term efficacy of DCB for symptomatic intracranial vertebrobasilar artery stenosis exclusively. A total of 16 treated patients showed good to very good results (0–20% residual stenosis), and no restenosis and new symptoms were observed in the 6-month angiographic and clinical follow-up. The rate of periprocedural complication was 6%.

Table 4 summarizes the results of the described studies.

DCB for the treatment of ICAS restenosis and ICAS ISRS is another field of DCB use in the neurovascular setting. However, data on this topic are scarce. The need for this treatment is based on the frequent rate of restenosis of ICAS after balloon and stent treatment. A current review from China on risk factors and the incidence of intracranial ISRS has pooled 5043 patients from 51 studies on the subject and reported a 12–18% rate of relevant restenosis in intracranial stents after the first ICAS treatment at a mean follow-up time of 18 months [125]. Among the patients with ISRS, 29% were symptomatic.

As in cardiology, neointimal proliferation is suspected to be a main factor influencing intracranial ISRS [27], among other factors including thrombus reorganization, elastic return, vascular remodeling, or platelet aggregation [126]. Regarding this pathophysiology, data published in 2011 and 2012 by Vajda *et al.* [46,47] on the treatment and prevention of intracranial ISRS were promising. In the 2011 study, among 51 patients with intracranial ISRS, 63 maneuvers of restenosis treatment were performed, 41 using a DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany) vs. 20 using a bare balloon. After a mean follow up of 7.5 months with a maximum of 17 months, a restenosis rate of 9% was reported for DCB vs. 50% for bare balloons. The rate of major periprocedural events was 3%.

The data published in 2012 addressed the prevention of ISRS by investigating the effects of using a DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany) before applying a self-expanding stent in symptomatic ICAS. This maneuver, performed in 51 patients, resulted in a restenosis rate of 3% after a mean follow-up of 9 months and a maximum of 16 months. The rate of major adverse events was 5%.

However, both studies have described technical problems with the applied DCB relating to the stiffness of the device, which complicated control and led to technical failure in a minority of cases.

Since then, only Xu *et al.* [55] further investigated the use of DCB (SeQuent® Please, B. Braun Melsungen, Melsungen, Germany) of intracranial ISRS treatment in a study of 11 patients with symptomatic ISRS with DCB. No symptomatic strokes or deaths were reported for the supplied territory of the treated vessel in a 3-month follow-up in this preliminary study.

Table 5 summarizes the results of both studies addressing ISRS treatment with DCB.

To date, there have been no investigations or recommendations on the use of DCB in cervical or intracranial dissected vessels, nor for occluded vessels (via embolus) or comparable intracranial artery diseases with limited indications for revascularization.

4. Discussion

This review addressed the broad range of applications of DCB in the neurovascular setting. The alternatives to DES and DCB in the neurovascular setting were the prior methods of bare-balloon angioplasty, balloon-mounted stents, and self-expandable stents.

Although self-expanding stents, such as the Wingspan® stent system (Stryker), have been discredited by SAMMPRIS and VISSIT, careful patient selection and a focus on findings from medical centers with extensive experience in endovascular treatment have revealed much better results in ICAS treatment than VISSIT/SAMMPRIS [127–129]. Two large randomized multicenter studies are currently underway and aim to address the safety and effectiveness of self-expanding stent PTA in ICAS treatment. A reassessment of self-expanding stents in ICAS treatment is likely to be imminent. However, these stent systems remain expensive, and, with a two-step deployment technique (after predilation), they may be associated with a higher intrinsic risk of periprocedural complications [130]. The reported rates of periprocedural complication and restenosis are also higher with self-expanding stents than DCB for ICAS treatment, although the comparability is limited. Furthermore, the recent approach of “leaving nothing behind” in stenosis treatment in cardiology is not

adhered to with any type of stent treatment. While this alone is not a rationale for the superiority of sole DCB treatment, especially in considering re-stenosis treatment approaches, treatment options for surgically non-accessible vessels of the brain may be reduced after repeated stent treatment.

Balloon-mounted stents use a one-step deployment technique but have not been demonstrated to be superior to self-expanding stents for ICAS treatment in a study of 409 patients with 407 symptomatic ICAS treatments, in terms of complication rates [131]. In a prior evaluation of the same study group focusing on in-hospital complications, a 7% rate of disabling strokes or death was reported in both study arms [132]. Like self-expanding stents, balloon-mounted stents have been reported to be difficult to navigate in the neurovascular setting, which often contains more tortuous vessels than the cardiology and peripheral angioplasty settings [46,47].

DES for ICAS PTA were initially described in 2005 by Abou-Cheb [133] and Boulos [134]. To date, 15 studies in 480 patients treated for ICAS with DES have been published [135–147]. Periprocedural complications occurred in an average of 5.3% of cases, and at an imaging follow-up of 4–55 months, the rates of stroke within and after 30 days were reported to be 8% and 2%, respectively, at an ISRS rate of 4% [148]. Despite not being directly comparable, these values surpass the results in SAMMPRIS and VISSIT.

A network meta-analysis of ISRS treatments found the usage of DES and DCB in treatment of coronary ISRS superior to bare-metal-stent-in-stent and bare-balloon-in-stent revascularization in terms of target lesion restenosis reduction [149]. However, many interventionalists view the presence of several metal layers as a limitation of the DES-/bare-metal-stent-in-stent principle, whereas after DCB therapy, further interventional options exist [150].

Nonetheless, DES remain expensive devices, and the long-term effects of their eluted drugs on the brain tissue remain unclear; moreover, they do not adhere to the approach of "leaving nothing behind". The published data on DES have shown promising results in terms of low restenosis rates, although the periprocedural complication rates may be above those of DCB. However, the recent BASKET SMALL 2 trial [151] in the field of cardiology comparing DCB vs. DES in the treatment of small diameter coronary artery stenosis has indicated the superiority of DCB treatment. This setting may be comparable to the neurovascular setting, thus again favoring DCB.

Bare-balloon angioplasty with consideration of neurovascular features, e.g., submaximal inflation [152], achieved better results than the medical and stent PTA arms in SAMMPRIS in two studies, with 1-year ischemic event-free survival rates of 91% [153] in 2012 and 94.5% [154] in 2016. In a total of 65 patients, the rate of periprocedural complications was also significantly lower than that with stent PTA in SAMMPRIS. Although bare-balloon angioplasty inherits the same procedural steps as DCB angioplasty, the reported rate of periprocedural complications is lower. A reason for this may be that, as in cardiology, the main approach when using a DCB is a DBC-only approach, resulting in careful patient selection and possibly a more careful preparation and application of the procedure and device. Additionally, in the treatment of de novo stenosis without the presence of a stent, the mechanism of late lumen enlargement plays an important additional role. Analogous to the Glagov phenomena, there is a compensatory enlargement of the total vessel cross-section with enlargement of the vessel lumen, which can be seen in paclitaxel-coated DCB when applied in the cardiovascular setting in approximately 2/3 of all cases [155–157]. If this effect is also active in the neurovascular setting, it may also contribute to a lower rate of complications.

Notably, bare-balloon PTA of ICAS appears to remain a safe and more efficient alternative to bare-metal stent PTA. However, the moderate- to long-term rates of restenosis are unclear. Because bare-balloon PTA devices are inexpensive and relatively easy to navigate in the neurovascular setting, further research on their mid- to long-term benefits is necessary to estimate their value vis-à-vis DCB. The stimulus for neointimal proliferation should be much less than in stent-assisted angioplasty; thus, bare-balloon angioplasty as an initial treatment may achieve comparable results to DCB treatment. However, at least in the prevention and treatment of ISRS, the mid- to long-term results of bare-balloons may be inferior to those of DCB-treatment as bare-balloons do not include protection from neointimal proliferation.

Also, a major concern of the intracranial use of DCB is embolism through particle coating downstream, leading to embolic stroke. Bare-balloon catheters do not have this issue, raising the question of whether DCB-angioplasty may carry a higher risk of stroke. A study by Colleran *et al*. [81] with n = 343 patients checked for signs of cardiac infarction following bare-balloon angioplasty (n = 116), DCB angioplasty (n = 115) and DES-angioplasty (n = 112). It showed no difference in the three study arms in terms of periprocedural or early postprocedural signs of cardiac infarction [81]. There are no data comparing the rate of embolic infarction following intracranial bare-balloon angioplasty vs. DCB angioplasty; however, when comparing the mass of debris collected distal to the saphenous vein, as well as cardiac and carotid arteries after angioplasty [158,159], the amount of collected debris with a mean of 16 mm^3 is far above the volume/amount of coated material on a DCB in total, which can be estimated to be approximately 1 mm^3 or 9 mg, respectively [70]. The burden from plaque debris would therefore play a major role in downstream infarction, despite not being connected to the kind of balloon.

When considering the pharmacological effect of Paclitaxel, there is concern for brain cells being exposed to this

Table 6. Data published in the described studies and trials on different devices for the treatment of intra- and extracranial atherosclerotic stenotic disease.

Periprocedural complication rate %	DCB	DES	Bare-metal stent	Bare-balloon PTA	Surgery
Extracranial carotid artery	0.7	n/a	5.3 [104]	6 [154]	5.1 [163]
Extracranial vertebral artery	0.5	4	5	1.1	n/a
Intracranial	3.9 in de novo 1.5 in restenosis	5.3	9, 6.2 without SAMMPRIS	n/a	n/a
Restenosis % in mean follow-up months	DCB	DES	Bare-metal stent	Bare-balloon PTA	Surgery
Extracranial carotid artery	9% in 26 months	n/a	8% in 17.4 months	28% in 17.4 months	12% in 20 months [165,166]
Extracranial vertebral artery	5% in 7.5 months	10% in 8.4 months [161–163]	29% in 8.8 months [161,162]	n/a	n/a
Intracranial	6% in 7.8 months de novo 4.5% in 5.3 months restenosis	4.8% in 27 months [147,148]	21% in 12 months, 16% in 12 months without VISSIT	n/a	n/a

toxin. Currently, there are no data on the toxicity of Paclitaxel on neurons after ICAS treatment through DCB. The toxic effect as well as the dose applied to neurons downstream after DCB can only be estimated: The whole dose on one DCB suitable for intracranial use is approximately 9 mg of Paclitaxel. Systemic doses used in oncology are approximately 300 mg while a single systemic Paclitaxel dose capable of causing peripheral neuropathy may be 70 mg/m^2 or higher [160]. An estimated 80–95% of the DCB Paclitaxel is not being transferred to the vessel wall. Thus, in in a worst-case scenario, approximately 8.6 mg of Paclitaxel would be available for downstream effects. There have been no reports of adverse events that could be related to the pharmacological effect of Paclitaxel on neurons, however, and they may be clinically inapparent, negligible or simply covered by overlaying and dominating symptoms following debris embolism.

In the treatment of extracranial arteries of the neurovascular setting, repeated CAS and bare-balloon-PTA are common. In a 2021 review [161] of results from 35 studies with a total of 1374 cases of ECAS ISRS, the reported rate of in-hospital adverse events was 1.1% for CAS as well as for bare balloon PTA, whereas the long-term rate of stroke and TIA was significantly higher with bare-balloon PTA than repeated CAS (6% vs. 2%). The mean rate of restenosis was 28% with bare-balloon PTA and 8% with CAS, both of which exceeded the published rates of restenosis in DCB.

In VAOS treatment, the use of bare-metal stents and DES has rarely been reported in the literature, yet endovascular treatment remains the only alternative to best medical treatment, because open surgery has been abandoned, owing to anatomic difficulties. In reviews and meta-analyses, the rate of DES restenosis has been found to be 12%, in contrast to 29% with bare-metal stents [162,163], after a mean follow-up of 8 months. The periprocedural complication rate was 2% for DES and 5% for bare-metal stents, with a total death rate at the end of follow-up of 7% with DES and 10% with bare-metal stents.

Another retrospective single-center study [164] of 32 DES in 30 patients in 2019 has reported a major periprocedural complication rate of 6.3% (n = 2) and a restenosis rate of 8% (n = 4) after a mean imaging follow-up of 8.8 months. DCB, in comparison, may yield better results in terms of mid-term patency and the periprocedural complication rate.

Table 6 (Ref. [104,147,148,154,161–163,165,166]) compares the data on alternative devices and techniques to DCB.

5. Conclusions

Based on the pathophysiological and technical background of atherosclerotic disease in the neurovascular setting, the issues currently faced by neurointerventionalists resemble those encountered by cardiologists years ago.

Whereas restenosis treatment and prevention have been successfully counteracted with DES and DCB in cardiology, in the neurovascular field, since the publication of data from large randomized multicenter trials more than 10 years ago, further research on endovascular techniques and devices for the treatment of stenotic/restenotic disease as well as possible benefits of DES and DCB has declined sharply or has not yet begun.

A comparison of the scant data in the literature regarding the use of DCB in the neurovascular setting suggests possible benefits but also highlights the continued lack of research and publications in this area.

To attempt a reconsideration of the treatment of extra- and intracranial stenosis after CREST, SAMMPRIS and VISSIT, we therefore strongly advocate intensified research on DCBs neurovascular use.

Abbreviations

CAS, carotid artery stenting; DCB, drug-coated balloon; DES, drug-eluting stent; ECAS, extracranial carotid artery stenosis; ICAS, intracranial artery stenosis; IQR, interquartile range; ISRS, instant restenosis; PCB, paclitaxel-coated balloons; PTA, percutaneous transluminal angioplasty; SCB, sirolimus-coated balloons; TEA, transluminal endarterectomy; VAOS, vertebral artery atherosclerotic stenosis.

Author Contributions

PVG and HH designed and performed the research; PVG and AC managed the data; HH, PVG, and CW analyzed the data; US provided help and advice on the technical aspects of DCB; PVG, US, JC, and HH wrote and revised the manuscript. All authors contributed to editorial changes to the manuscript. All authors red and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The authors express their gratitude to C. Knispel for source acquisition. The authors also thank all the peer reviewers for their opinions and suggestions.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

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