REVIEW ARTICLE

A Review on the Comparison of Different Treatments for Carotid In-Stent Restenosis

Chizhong He, Shuo Wang, Xiaohong Zhou, Zhexian Yang

ABSTRACT: Different treatment options for carotid in-stent restenosis (ISR) have been reported with good outcome, including carotid endarterectomy (CEA), repeated carotid angioplasty stenting (CAS) and percutaneous transluminal angioplasty (PTA) with drug-coated balloons (DCBs). However, the optimal treatment option for ISR has not yet been determined. A systematic literature search was performed in the databases of Medline, Embase, Cochrane library, and unpublished data from clinicaltrials.gov from 1990 to March 1, 2019. Studies were enrolled if they reported treatment strategies for carotid ISR treatment and met the inclusion criteria. After study inclusions, data were extracted and summarized. Totally 25 cross-sectional studies were included, containing 5 comparative studies, 16 studies using repeated PTA, and 4 studies adopting CEA treatment. Our study summarized the current available data, showing that all the studies could effectively relieve the carotid ISR by significantly improving the angiographic stenosis and decreasing the peak systolic velocity values. Meanwhile, CEA treatment had the best long-term effects in relieving restenosis, while re-PTA with stenting/balloon angioplasty had a certain rate of restenosis, ranging from 33% to 83%. Furthermore, re-PTA/stenting and balloon angioplasty treatment had less complications compared with CEA. Also, we analyzed the risk factors that might affect the long-term prognosis of carotid ISR patients. The therapeutic measures for carotid ISR had their own features, with CEA had the highest efficacy while re-PTA/stenting and balloon angioplasty were with less complications. More large-scale comparative clinical studies are needed to further ascertain the best strategies.

RÉSUMÉ: Examen comparatif entre divers traitements de la resténose carotidienne sous-tendant la pose d'endoprothèses. Dans le cas de la resténose carotidienne, la littérature scientifique signale différentes possibilités de traitement sous-tendant la pose d'endoprothèses (*stents*). Ces traitements s'accompagnent de bons résultats et incluent l'endartériectomie carotidienne, l'angioplastie répétée et l'angioplastie percutanée transluminale au moyen de ballonnets actifs (*drug-coated balloons*). Cela dit, on n'est pas encore parvenus à déterminer une possibilité idéale de traitement. Nous avons effectué une recension systématique de la littérature scientifique au moyen des bases de données suivantes : MEDLINE, Embase et Cochrane Library. Nous avons également fait appel à des données jamais publiées tirées du site Internet *clinicaltrials.gov* et comprises entre l'année 1990 et le 1er mars 2019. Pour notre propos, nous avons retenu des études si elles satisfaisaient à nos critères d'inclusion et si elles faisaient état de stratégies de traitement destinées à la resténose carotidienne et sous-tendant la pose d'endoprothèses. Nous avons ensuite extrait de ces études des données et les avons résumées. Un total de 25 études transversales a été inclus : 5 d'entre elles étaient de nature comparative ; 16 portaient sur l'angioplastie répétée ; et 4 portaient sur l'endartériectomie carotidienne. Notre étude a résumé les données actuelles disponibles et a montré, en nous fondant sur ces études précédentes, qu'il était possible atténuer de manière efficace la resténose carotidienne en améliorant de manière notable la technique angiographique de la sténose et en diminuant les valeurs maximales de tension systolique. En parallèle, on a noté que l'endartériectomie carotidienne était le traitement procurant les meilleurs résultats à long terme en ce qui concerne la resténose tandis que l'angioplastie percutanée transluminale au moyen de ballonnets actifs comportait toujours un certain taux de resténose variant entre 33 et 83 %. Plus encore, il convient de préciser que l'angioplastie percutanée transluminale avec ou sans ballonnets actifs entraînait moins de complications en comparaison avec l'endartériectomie carotidienne. Enfin, nous avons analysé les facteurs de risque pouvant affecter le pronostic à long terme des patients atteints de resténose carotidienne. Les mesures thérapeutiques destinées à la resténose carotidienne comportaient toutes leurs propres caractéristiques, l'endartériectomie carotidienne étant la plus efficace alors que l'angioplastie percutanée transluminale avec ou sans ballonnets actifs entraînait moins de complications. Chose certaine, des études cliniques comparatives de plus grande envergure demeurent nécessaires afin de déterminer quelles sont les meilleures stratégies.

Keywords: Carotid in-stent restenosis, Percutaneous transluminal angioplasty, Balloon angioplasty, Carotid endarterectomy, Long-term prognosis

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Introduction

Vascular restenosis is the recurrent lumen narrowing phenomenon occurring in 30–50% of patients subjected to revascularization procedures, which is arbitrarily defined as a permanent narrowing of vessel diameter greater than 50% when compared with a reference artery.[1] With the increased use of non-invasive detection techniques, the morbidity of in-stent restenosis (ISR) becomes increasingly frequent. However, despite the innovative devices and procedures recently developed and the novel concomitant drug therapies administered to patients, it still represents a limiting factor in the long-term success of revascularization procedures.[2]

Currently, for the stenosis of carotid artery, carotid endarterectomy (CEA) is still the golden standard approach for the treatment of symptomatic patients.[3] Recently, it has been shown in the clinical trials that carotid artery stenting (CAS) had comparable efficacy compared with CEA.[4,5] CAS may still be considered for patients with high risk for complications because of different comorbidities or anatomical variations.[6] However, the benefits of CAS in preventing the future stroke may be hampered by the occurrence of ISR. It has been reported that the morbidities of ISR during CAS were between 1.8% and 20%, depending on the definition of restenosis used and the duration of follow-up, which are considered to be equivalent to restenosis rates after CEA (with the morbidity of restenosis between 1.8% and 22%, Table 1).[7,8]

Different treatment options are available when revascularization of ISR is warranted, but still no clear treatment algorithm on the optimal technique is available.[9] Previous reports have indicated that repeated stent placement, angioplasty with balloon techniques, and surgical treatments are the main treatments for ISR. Recently, drug-coated balloons (DCBs) or drug-eluting balloons (DEBs), with the features of homogenous distribution of antiproliferative drugs to the vessel wall,[10] have been advocated for treatment of ISR in the coronary and femoropopliteal areas in recent years, but an overview of this application in the carotid artery restenosis is still lacking.[11,12] It has been reported that DCB angioplasty showed satisfactory efficacy in carotid artery stenosis and in-stent restenosis in several studies.[13] However, little is known about the long-term effects of DCB angioplasty compared with cutting balloon or regular balloon angioplasty or operations such as CEA. Furthermore, although a small number of reviews and several reports have summarized the intervention strategies for ISR, no comprehensive review has been conducted to investigate the efficacy and long-term prognosis of CEA, DCBs, cutting balloon angioplasty, or repeated CAS on carotid ISR patients. In this review, we searched the main databases and enrolled all the clinical studies that investigating the therapeutic efficacy of different treatment strategies on carotid ISR, while comparing the efficacy and prognosis of these different types of treatments. Our study may provide more evidence for the treatment of carotid ISR.

Methods

Data Sources and Searching Strategies

An electronic literature search was conducted to identify candidate articles published until March 2019, based on the published articles in Pubmed (MEDLINE), EMBASE, Cochrane Library, and unpublished data through clinical trials website (www.clinicaltrials.gov). MESH terms and other terms were used for literature search using different combinations. The terms used included "in-stent re-stenosis," "in-stent restenosis," "re-restenosis," "in-stent stenosis," "recurrent stent stenosis," "carotid artery," "treatment," "therapy," "PTA" or "percutaneous transluminal angioplasty," "angioplasty," "drug eluting balloon" or "drug coated balloon," "drug-eluting stents" or "drug-coated stents," "paclitaxel-coated" or "paclitaxel," with no language restrictions. Two authors (C. He and X. Zhou) conducted that literature search independently, whereas a third investigator (S. Wang) solved any discrepancies.

Eligibility Criteria

The clinical trials would be included in this review if they met the following criteria: (i) Participants: adults older than 18 and have been diagnosed as in-stent restenosis after PTA. Since that carotid stent induces artifactually higher peak systolic velocities, the velocity criterion was not used to evaluate carotid artery stenosis. Luminal reductions by ultrasonography on gray-scale images and color flow disturbances were evaluated.[14] Clinically significant stenosis was defined as luminal reduction of 80% or higher. High-grade in-stent stenosis, identified by ultrasonography, was further verified by biplanar carotid angiography, and the stenosis was measured geometrically on the basis of the North American Symptomatic Carotid Endarterectomy Trial criteria;[14] (ii) Intervention: the treatment strategies of the studies contained CEA, PTA (repeated CAS, regular balloon angioplasty, cutting balloon angioplasty, or drug-coated balloon angioplasty); (iii) Outcomes: treatment efficacy (e.g., angiographic stenosis ratio and peak systolic velocity changes) and treatment complications; (iv) Study design: clinical studies with the publication types such as retrospective studies and cross-sectional studies were included.

Studies were excluded if (i) they were published in the forms of case reports, reviews, editorials, conference abstracts; (ii) they were not written in English; (iii) they did not focus on carotid in-stent restenosis; and (iv) they did not report the key results concerning the treatment efficacy or complications.

Data Extractions

The data extracted from the included studies contained the following aspects: (1) Study characteristics: study design, year, publication, and study region; (2) Studies' outcomes: diagnosis, treatment, treating results, devices used, and complications; (3) Patients characteristics: number of patients, gender ratio, mean age, symptoms, target vessels, diameter stenosis, previous treatments, time to first ISR, risk factors, and drugs used.

Results

Literature Search Results

After searching the literature, totally 545 studies were identified after removing the duplicates. Furthermore, 306 full-text eligible studies were further assessed after removing the studies that did not meet the inclusion criteria. Then 25 studies were finally included for further review, and no unpublished data were obtained. The studies finally enrolled included 5 comparative studies, 4 studies with operative treatment, and 19 studies using PTA with balloon or stent angioplasty. A flow diagram outlining the literature search strategies and results is presented (Figure 1), with the study

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Table 1: The morbidity of stroke after different interventions for asymptomatic and symptomatic patients

Author, year, and publication	Disease model	Interventions	**Stroke rates after interventions**	**Asymptomatic**	**symptomatic**
Carballo 1996 *J Vasc Surg*	Recurrent carotid stenosis	CEA	7.8% during a mean follow-up interval of 34 months	5.6%	19%
Gagne 1993 *J Vasc Surg*	Recurrent carotid artery disease	CEA	1.8%	–	–
O'Donnell 1996 *J Vasc Surg*	Recurrent carotid artery stenosis	CEA vs. percutaneous intervention	–	2.1%	7.5%
Eckstein 2008 *Lancet Neurol*	Symptomatic, severe (≥70%) carotid artery stenosis	CAS or CEA	–	10.7% for CAS and 4.6% for CEA	–
Levy 2005 *J Neurosurg*	Recurrent stenosis after CAS	CAS	4%	–	–
Setacci 2003 *J Endovasc Ther*	In-stent restenosis after CAS	In-stent restenosis after CAS	5.2%	–	–
Setacci 2005 *Eur J Vasc Endovasc Surg*	In-stent restenosis after CAS	CAS	3.4%	–	–
Zhou 2006 *J Vasc Surg*	In-sent restenosis after CAS	CAS	3.4% for high-grade and 15.9% for moderate-grade	–	–
Chakhtoura 2001 *J Vasc Surg*	In-sent restenosis after CAS	CAS	8%	–	–
Lal 2003*J Vasc Surg*	In-sent restenosis after CAS	CAS	–	–	5% (6.4% for 5 years)
Willfort-Ehringer 2002 *J Endovasc Ther*	Carotid stent restenosis	Wallstent placement	3.0%	–	–
Borst 2003 *Eur J Vasc Endovasc Surg*	In-stent restenosis after CAS	CAS	1.8%	0.9%	0.9%
Wholey 2000 *Catheter Cardiovasc Interv*	Restenosis after CAS	CAS	3.46%	–	–
Lal 2012 *Lancet Neurol*	Restenosis	CAS or CEA	6.0% for CAS and 6.3% for CEA	–	–
Montorsi 2012 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	–	–	1.2%
Chakhtoura 2011 *J Vasc Surg*	In-stent restenosis after CAS	CAS	8%	–	–
Bartlett 1987 *J Vasc Surg*	Recurrent carotid stenosis	–	6.0%	–	–
Das 1985*Ann Surg*	Recurrent carotid stenosis	CEA	4.6%	–	–
Koebbe 2005 *Neurosurg Focus*	In-stent restenosis after CAS	CAS	4%	–	–
Frericks 1998 *Stroke*	Carotid recurrent stenosis	CEA	4–22%	–	–
Radak 2014 *J Vasc Surg*	Carotid recurrent stenosis	CEA	–	0.6–3.6%	8.8–19%
Tekieli 2012 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	1.2%	–	–
Gandini 2014 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	4.8%	–	–
AbuRahma 2011 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	3–20%	–	–
Donas 2011 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	3.3%	–	–
Reimers 2006 *J Endovasc Ther*	In-stent restenosis after CAS	CAS	–	–	3.1%
Summary			1.8–20% for CAS1.8–22% for CEA	0.9–10.7% for CAS0. 6–5.6% for CEA	0.9–5% for CAS7.5–19% for CEA

CEA = carotid Endarterectomy; CAS = carotid artery stenting.

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Table 2: Basic information and main results of included studies

Study	Publication	Study region	Diagnosis	Treatment	Follow-up period (months)	Efficacy	Devices and key procedure	Complications
Comparative studies								
Aburahma 2001	*J Vasc Surg*	USA	Recurrent carotid artery stenosis	CEA vs. PTA	22.1 vs. 18.1	PTA/stenting has a higher incidence of restenosis than reoperation, which is associated with a percentage of cranial nerve injuries.	The target lesion was crossed with a soft-tipped 0.018-inch wire and dilated with a 4-mm balloon catheter. Finally, the stent was deployed in the internal carotid artery, which may extend into the common carotid artery, if needed.	PTA/stenting treatment had more ipsilateral stroke but with less cranial nerve injuries.
Chung 2017	*J Vasc Surg*	USA	Carotid in-stent restenosis	Balloon angioplasty vs. Balloon plus stent	31.6	Interventions fail to improve long-term stroke/death/MI or patency rates relative to nonintervention.	The lesions were crossed with a 0.014-inch wire. At the operator's discretion, the lesions were dilated to the desired diameter with a high-pressure, cutting, or drug eluting balloon. Stents were placed if there was significant recoil or prior stent fracture or kinking.	One stroke and subsequent death at 30 days. The stroke occurred 8 h after intervention, with acute stent thrombosis. No acute MIs occurred within the first 30 days.
Levy 2005	*J Neurosurg*	USA	Recurrent carotid artery (CA) stenosis after stent-assisted angioplasty	Stenting vs. Cutting balloon angioplasty	16.42 ± 10.58	Decreased In-stent PSV after procedure. Angioplasty with balloon technique is more effective.	Not reported	No neurological complication during the periprocedural period or experienced symptoms during the follow-up period.
Satecci 2005	*Eur J Vasc Endovasc Surg*	Italy	In-stent restenosis after carotid angioplasty	Balloon angioplasty vs. cutting balloon angioplasty	12.4	1. Restenosis area decreased.2. All patients remained asymptomatic and without recurrent restenosis greater than 30%.	CAS procedures were carried out using self-expandable stents. Cutting balloon angioplasty was carried out using CB coronary device 0.014 inch.	No procedure-related complication occurred within 30 days after any treatment for ISR.
Zhou 2006	*J Vasc Surg*	USA	In-stent restenosis after CAS	Balloon angioplasty vs. cutting balloon angioplasty	12	Technical success was achieved in all patients, and no periprocedural complications occurred. Cutting balloon exerted better efficacy compared with regular balloon angioplasty.	A self-expanding monorail carotid stent (Wallstent [Boston Scientific, Natick, MA, USA] or Acculink [Guidant, Santa Clara, CA, USA]) was deployed across the internal carotid stenosis. Post-stenting balloon angioplasty was performed with either a 5- or 6-mm-diameter angioplasty balloon.	No periprocedural complications occurred.

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Table 2. *Continued*

Study	Publication	Study region	Diagnosis	Treatment	Follow-up period (months)	Efficacy	Devices and key procedure	Complications
PTA treatments								
Chakhtoura 2011	*J Vasc Surg*	USA	In-stent restenosis after CAS	balloon angioplasty or angioplasty and re-stenting	10 ± 6	Angiography confirmed these high-grade (≥80%) in-stent restenoses, which were successfully treated with balloon angioplasty or angioplasty and re-stenting.	The stenosis was crossed with a 0.018-in Roadrunner extra support guidewire (Cook), and pre-stent dilatation was performed with low-profile 4 × 30-mm balloon catheters inflated to 8 atm, followed by stent deployment. Poststent dilatation was performed with 5- or 6-mm high-pressure balloons inflated to 12 atm.	No periprocedural complications occurred, and these patients remained asymptomatic and without recurrent restenosis over a mean follow-up time of 10 ± 6 months.
Koebbe 2005	*Neurosurg Focus*	USA	Recurrent carotid artery stenosis	Balloon angioplasty and stent placement	36	No further ischemic events occurred in this series of patients.	A 0.35–0.38–in Terumo guidewire (Boston Scientific, Fremont, CA, USA) was passed through the stenosis. The Savvy angioplasty balloon catheter system (Cordis Endovascular, Johnson and Johnson Corp.) was then passed over the wire, across the stenosis, and the balloon was inflated up to 8–10 atm.	No neurological or cardiac complications were reported in this series in the perioperative period.
Lal 2003	*J Vasc Surg*	USA	In-stent recurrent stenosis after CAS	Repeat PTA	18.8	The ISR was relieved after treatment.	Stenoses were crossed with 0.018-inch Roadrunner extra-support guide wires for the WallStents, and 0.014-inch guide wires for the Acculink carotid stents. An antiembolic filter device (Accunet; Guidant) was used in all cases in which the Acculink stent was delivered.	No complication was reported.
Lanzino 1999	*J Neurosurg*	USA	Recurrent carotid artery stenosis	PTA and stent placement	27	Endovascular PTA and stenting of recurrent carotid artery stenosis are both technically feasible and safe and has a satisfactory midterm patency.	Not reported	No major periprocedural deficits (neurological or cardiac complications) or death occurred.
Radak 2014	*J Vasc Surg*	Switzerland	Recurrent stenosis after CEA	PTA	49.8 ± 22.8	All but one procedure ended with a technical success (99.69%), which was defined as the deployment of the carotid stent or balloon angioplasty alone.	The type of embolic protection device used depended on anatomical characteristics, plaque embolic potentials, and localization and degree of the stenosis. If very tight stenosis was to be treated, coronary balloons were used for predilation; otherwise, direct stenting was done with self-expanding stents, followed by balloon angioplasty of the appropriate size.	In the early postoperative period, TIA occurred in 2.8% of the patients and stroke in 1.6%, followed by one death of a neurologic cause. No TIAs or strokes were verified during the follow-up, and non-neurologic mortality was 3.13%.

Raithel 2005	*J Cardiovasc Surg*	Germany	Recurrent stenosis after CAS	PTA alone or PTA plus CAS	12	Twenty-two patients with recurrent ISR were treated by re-PTA.	Not reported	Not reported
Willfort-Ehringer 2002	*J Endovasc Ther*	Austria	Carotid stent restenoses	PTA with Wallstent stent placement	12	ISR ($n = 6$) were detected and treated with stent placement. Lasting success (patency > 12 months after retreatment) was achieved in four patients.	The catheter was exchanged, and 1 mg of atropine was given intravenously before deployment of a Wallstent (Boston Scientific), which was further dilated with a 5- to 6-mm-diameter balloon at 8–10 atmospheres for 5–10 s.	Interventions for carotid stent restenosis were completed without any procedure-related complications or neurological sequelae documented by neurological examination at 30 days.
				Drug-coated balloon angioplasty				
Gandini 2014	*J Endovasc Ther*	Italy	Recurrent carotid in-stent restenosis	Paclitaxel-eluting balloon angioplasty	36.6 ± 2.7	1. Angiographic stenosis decreased from 87 ± 4% to 6 ± 4%.2. Peak systolic velocity decreased (4.7 ± 1.5 to 0.6 ± 0.3 m/s).3. Revascularization rate was 33.3% at 36 months.	4 × 20-mm second-generation drug-eluting balloon (DIOR II; Eurocor, Bonn, Germany) inflated for 60 s to deliver 5 μg/mm^2 of paclitaxel.	No neurological or myocardial events were recorded during follow-up. One patient died at 3 months.
Montorsi 2012	*J Endovasc Ther*	Italy	Carotid artery in-stent restenosis	Drug-eluting balloons	13.7 ± 1.5	1. Final angiography showed stenosis reduction from 84.5 ± 4.9% to 19 ± 4.9%.2. The minimal lumen area increased from 3.19 ± 1.73 to 12.78 ± 1.97 mm^2.3. The average PSV decreased from 4.0 ± 1.0 to 0.9 ± 0.1 m/s.	An over-the-wire paclitaxel-eluting balloon (In. Pact Admiral; Medtronic-Invatec, Roncadelle, Italy) compatible with 0.035-inch guidewires. The total drug load depends on both size and length of the balloon (up to 8 mg for a 6 × 120-mm balloon).	One patient had a left hemispheric stroke 2 months after the procedure.
Piccoli 2015	*J Endovasc Ther*	Italy	Restenosis after carotid endarterectomy	Paclitaxel-coated DCB	18	1. All procedures achieved angiographic success (<30% residual stenosis).2. During follow-up, 14 patients were without restenosis and 4 patients were with mild (<30%) stenosis.	After predilating the lesion with a 3.5 × 20-mm semicompliant balloon, a 4.0- to 5.0-mm paclitaxel-coated DCB with a length adequate to minimize geographical miss (either 40 or 80 mm) was inflated for 70 or 80 s.	One patient who had a TIA during prolonged DCB inflation
Pohlmann 2017	*Neuroradiology*	Germany	Carotid artery in-stent restenosis	Drug-eluting balloons	9	1. Restenosis area decreased from 85 ± 8% to 16 ± 7%.2. The 1-year EFS was 100%, and the 2-year/3-year/5-year EFS was 83%.	DEB dilation was performed in an identical setting using second-generation drug-eluting balloons: in six procedures, we used a SeQuent Please® (Braun Melsungen AG, Vascular Systems, 12,359 Berlin, Germany) and in five procedures, the IN.PACT Amphirion ® balloon (Medtronic, Minneapolis, MN, USA)	No interventional complications leading to new or aggravated neurological deficits in the patients

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Table 2. *Continued*

Study	Publication	Study region	Diagnosis	Treatment	Follow-up period (months)	Efficacy	Devices and key procedure	Complications
Tekieli 2012	*J Endovas Ther*	Poland	Recurrent carotid in-stent stenosis	A balloon-mounted drug-eluting stent	17	1. Angiographic stenosis was reduced from 84.6 ± 7.5% to 10.7 ± 3.6%.2. Minimal lumen diameter increased from 1.19±0.39 to 4.03±0.15 mm.	Post-dilation with a 4.5-mm balloon was performed if indicated by intravascular ultrasound (IVUS)13 scans obtained with a rapid-exchange, phased-array, 3.5-F catheter (1.17-mm maximal diameter of the scanner; Eagle Eye Gold, Volcano Corporation, Rancho Cordova, CA, USA)	No major periprocedural complication or TIA
Regular and cutting balloon angioplasty								
Donas 2011	*J Endovasc Ther*	Germany	In-stent stenosis after carotidartery stenting	Balloon angioplasty	36.5 ± 21.6	1. The primary and assisted primary patency rates were 68.8%.2. The freedom of new neurological events during follow-up was 75%.	Not mentioned	Not mentioned
Heck 2009	*J NeuroInterv Surg*	USA	Carotid in-stent restenosis after carotid artery stenting	Cutting balloon angioplasty	24	1. Angiographic result of 20% stenosis was achieved in all patients.2. The 1-month patency without restenosis after cutting balloon angioplasty is 5/6 (83%), and the patency without restenosis at 20 or more months is 4/5 (80%).	The cutting balloon (Boston Scientific) is a non-compliant balloon with three or four (depending on the size of the balloon) microsurgical blades.	1. No procedural complications2. No ischemic events during the follow-up period in any of the six patients
Reimers 2006	*J Endovasc Ther*	Italy	In-stent restenosis after CAS	Regular and cutting balloon angioplasty	17 ± 5	Procedural success was achieved in all patients.	In 22 procedures, regular angioplasty balloons with a diameter ranging from 5.5 to 7.0 mm (mean 5.9 ± 1.7 mm) and a length varying from 10–40 mm were used.	At 30 days and during follow-up, no deaths, transient ischemic attacks, or strokes were observed.
Satecci 2009	*J Cardiovasc Surg*	Italy	Carotid highly calcified de novo stenosis	CAS with/without cutting-balloon angioplasty	1	Haemodynamic depression occurred in 18/50 in CAS group and 3/52 in CAS plus CBA group.	Not mentioned	No major intraprocedural complications were observed. One TIA was registered.
CEA								
Borst 2003	*Eur J Vasc Endovasc Surg*	The Netherlands	ISR after CAS	Standard CEA with removal of the stent	13	All four surgically treated patients remained asymptomatic and without recurrent restenosis over a mean follow-up time of 13 months.	Not reported	No major complications occurred.

Marcucci 2012	*J Cardiovasc Surg*	Italy	ISR after CAS	Standard CEA with complete removal of stent and the entire atherosclerotic plaque	18	The mean follow-up of 18 months showed a normal patency of the surgical correction without recurrent restenosis using ultrasound examination.	In all cases an early distal clamping of the ICA was carried out and then a long arteriotomy was made on the anterior wall of the vessel extending from below the stent in the CCA to normal intima above the plaque in the ICA. The stent bare was knitted by means of Potts scissor without particular difficulty.	No death or major complications occurred.
Reichmann 2011	*J Vasc Surg*	The Netherlands	ISR after CAS	Standard CEA with stent removal	21	All 15 patients remained asymptomatic and without recurrent restenosis (>50%) on duplex ultrasound imaging.	An average 5 cm length arteriotomy was performed over the stent. The length of the arteriotomy depended on the length of the implanted stent device. The stent was removed in all cases, including intimal endarterectomy until proximal and distal resection planes were free from atherosclerotic debris.	One patient sustained an intraoperative minor ischemic stroke. No neurologic complications occurred in the other 14 patients.
Yu 2017	*Stroke Vasc Neurol*	China	Carotid in-stent restenosis	Standard CEA with stent removal	25	One patient died of rectal cancer without ischemic attack and restenosis 4 years post-operation. In one patient occurred recurrent symptomatic restenosis (90%) 1 year later; all other patients remained asymptomatic and without recurrent restenosis (>50%) by follow-up carotid ultrasound or CT angiography.	A 3–10 cm length arteriotomy was performed over the stent. The length of the arteriotomy depended on the length and the location of the implanted stent. In all cases, the stent was removed as one single complex with intimal hyperplasia; endarterectomy was done in the usual way without much difficulty. The artery was stitched up in a routine way without patch angioplasty.	A total of three complications happened in three patients (30%).

CAS = carotid artery stenting; DCB = drug-coated balloon; DEB = drug-eluting balloon; PTA = percutaneous transluminal angioplasty; CEA = carotid Endarterectomy; PSV = peak systolic velocity; ICA = internal carotid artery; EFS = event-free survival; MI = myocardial infarction; TIA = transient ischemic attack; CB = cutting balloon.

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characteristics and main results presented in Table 2. It was presented that studies conducted in USA and Italy accounted for the majority of the enrolled studies. In detail, among the five comparative studies, two studies compared the efficacy between regular with cutting balloon angioplasty and the other three studies compared CEA with PTA, balloon angioplasty with balloon plus stent implantation, stenting with cutting balloon angioplasty, respectively. Four studies reported the treatment of ISR with CEA. Meanwhile, among the 16 studies with PTA treatment, 7 studies reported re-PTA with stent placement,[15–21] 5 studies reported DCB angioplasty,[22–26] the other 4 studies reported the efficacy of ISR treatment with regular or cutting balloon angioplasty.[27–30]

Outcomes of Treatment Efficacy

Comparative Studies

Among the five comparative studies, Aburahma et al. compared the efficacy of operative treatment with PTA/stenting for the treatment of carotid restenosis, demonstrating that PTA/stenting has a higher incidence of restenosis than reoperation, but with less perioperative and neurological complications.[31] Meanwhile, Chung et al. indicated that treatment using balloon angioplasty did not improve the long-term outcomes of patients with carotid ISR.[32] However, Levy et al. reported angioplasty with balloon technique decreased carotid restenosis more efficiently.[3] Furthermore, Setacci et al.[33] reported that cutting balloon angioplasty had better long-term outcomes [14 ± 5% restenosis, peak systolic velocity (PSV) of internal carotid artery (ICA) 95 ± 11 cm/s] compared with repeated balloon angioplasty (17 ± 8% restenosis, ICA PSV 105 ± 15 cm/s) or repeated CAS (22 ± 7% restenosis, ICA PSV 122 ± 13 cm/s). Also, Zhou et al. reported that cutting balloon angioplasty improved the ISR by decreasing the ISR rate from 88.6% to 15%, whereas PTA decreased the ISR rate from 82.5% to 20%.[14] These results indicated that CEA might provide better effects in improving the ISR compared with PTA, while among the balloon angioplasty techniques, cutting balloon angioplasty could exert better long-term prognosis.

Angioplasty Efficacy

To evaluate the efficacy of those types of therapeutics, three parameters were used, the angiographic stenosis rate, the PSV changes, and the long-term prognosis. For the angiographic stenosis rate, the studies adopting the PTA interventions, few studies reported about the angiographic stenosis rate, but most of the studies reported that through endovascular PTA treatment, angiographic stenosis decreased significantly and ISR was successfully treated. On the other hand, most of the studies adopting DCB angioplasty reported the angiographic stenosis changes. In detail, it showed that the study of Gandini et al. showed that DCB treatment decreased the angiographic stenosis from 87% to 6%,[22] while the study of Montorsi et al. showed that the final angiography stenosis reduced from 84.5% to 19% after intervention.[23] Also, the study of Pohlmann et al. showed the restenosis area decreased from 85% to 16%[25] and the study of Tekieli et al. exhibited the stenosis reduced from 84.6% to 10.7% upon DCB treatments.[26] For the treatment of regular balloon angioplasty, the stenosis rates decreased to 16% in Zhou et al.'s study after intervention.[14] For the treatment of common or cutting balloon angioplasty, the study of Donas et al. showed that the primary and assisted primary patency rates were 68.8%,[27] while the angiography stenosis rates also decreased to 20% after treatment (Heck's study[28]). At last, the therapeutic of CEA could also significantly solve the problem of carotid ISR.

The second parameter is the PSV changes before and after the angioplasty intervention. It showed that the PSV values decreased from 4.7 to 0.6 m/s in Gandini et al.'s study,[22] from 4.0 to 0.9 m/s in Montorsi et al.'s study after DCB treatment.[23] The studies covering other types of therapeutics did not report the changes of PSV values.

The third parameter is the long-term follow-up results, which is the most important outcome in choosing the appropriated treatment modalities. As to the PTA with stenting treatment, Koebbe et al. showed that among the 19 carotid ISR patients, 1 patient exhibited restenosis after re-PTA for 14 months of follow-up.[21] Lal et al. reported the long-term results of PTA relieved carotid ISR in three out of five patients after 1-year follow-up.[16] In the study of Lanzino et al., it showed that PTA combined with stent placement effectively treated the carotid ISR for at least 6 months.[17] Meanwhile, in the study of Willfort-Ehringer et al., it was demonstrated that the six patients with carotid ISR were all treated with PTA with stenting, with only four patients remained patent for >1 year. As to the treatment with DCB, it was shown that the revascularization rate was 33.3% after DCB treatment in Gandini et al.'s study.[22] In the study of Piccoli et al., 14 of 18 patients were without restenosis, and the other 4 patients with mild (<30%) restenosis during follow-up.[24] In Pohlmann et al.'s study, the 1-year event-free survival (EFS) was 100%, with the rates of 2-year/3-year/5-year EFS were 83%.[25] Furthermore, for the treatment of other balloon angioplasty, all patients remained asymptomatic and without recurrent restenosis greater than 30% during 18 months of follow-up using regular balloon angioplasty. Also, the 1-month patency without restenosis after cutting balloon angioplasty was 5/6 (83%), and the patency without restenosis was 4/5 (80%) after 20 months follow-up adopting the cutting balloon angioplasty.[28] For the patients using CEA for carotid ISR, Borst et al. reported that all four surgically treated patients remained asymptomatic and without recurrent restenosis over a mean follow-up time of 13 months.[34] Marcucci et al. and Reichmann et al. all described that patients with a normal patency of the surgical correction were without recurrent restenosis during the follow-up period,[35,36] while Yu et al. reported that one patient occurred recurrent symptomatic restenosis (90%) 1 year later and all other patients remained asymptomatic and without recurrent restenosis.[37]

Complications

As to complications, most of the studies reported the 30-day peri-operative or peri-procedure complications. Aburahma et al. compared the 30-day perioperative complications between CEA and PTA/stenting, indicating that patients with CEA had less ipsilateral strokes but more cranial nerve injuries.[31] The study of Chung et al. showed that one stroke and subsequent death occurred at 30 days,[32] other comparative studies all reported that no procedure-related complications occurred within 30 days.

As to the PTA/stenting treatment, most studies reported that no periprocedural complication occurred, indicating that PTA/stenting is a safe treatment that could be widely used for carotid ISR. For DCB treatment, three studies described that no

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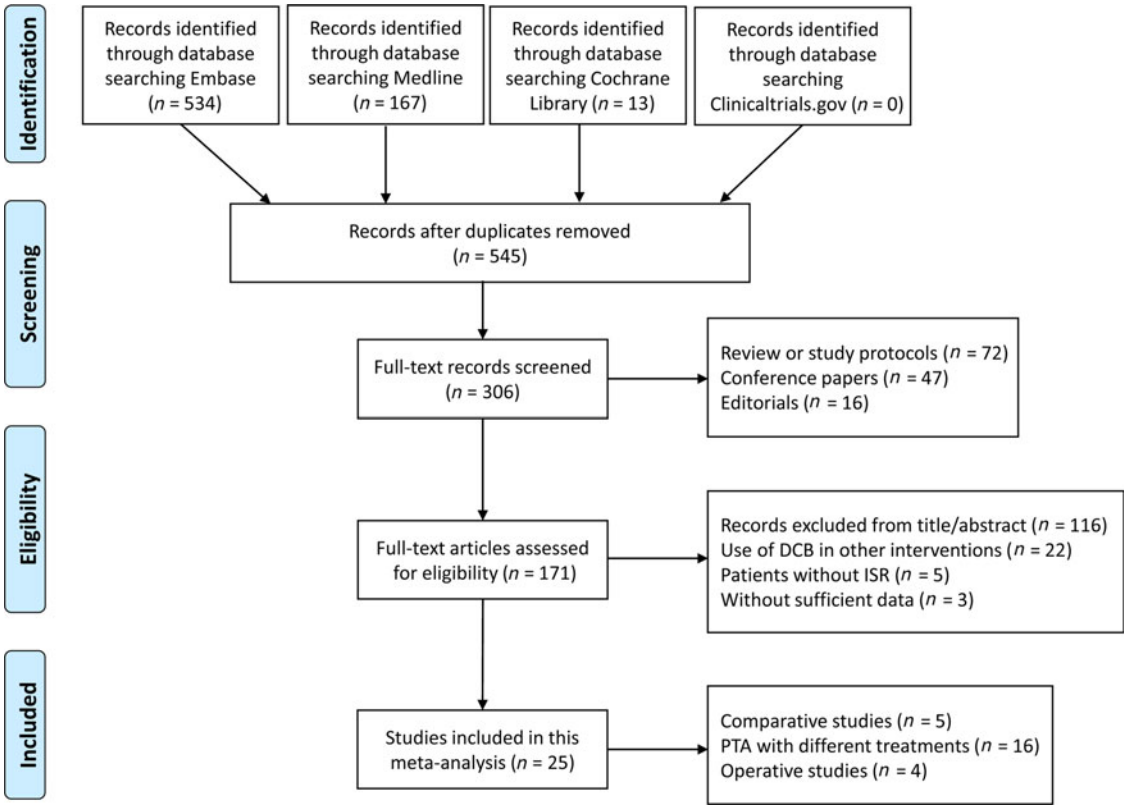

Figure 1: *The flow diagram of literature search and selection of studies.*

interventional complications leading to new or aggravated neurological deficits in the patients,[22,25,26] whereas Montorsi et al. reported that one patient had a left hemispheric stroke 2 months after procedure and Piccoli et al. reported that one patient had a transient ischemic attack (TIA) during prolonged DCB inflation.[23,24] For the studies that intervened with the cutting balloon angioplasty, Heck reported no procedural complications or ischemic events during the follow-up period,[28] while the study of Satecci et al. showed no major intraprocedural complications.[30] As to the operation treatment, two out of four studies reported that no major complications occurred. Reichmann et al. reported that 1 patient sustained an intraoperative minor ischemic stroke, while no neurologic complications occurred in the other 14 patients.[36] Also, Yu et al. reported that a total of three complications happened in three patients (30%).[37]

As to the long-term complications, it was shown that patients with PTA remained asymptomatic and without recurrent restenosis over a mean follow-up time of 10 ± 6 months.[15] Also, Radak et al. reported that no TIAs or strokes were verified during the follow-up, and non-neurologic mortality was 3.13%.[18] No ischemic events were observed during the follow-up period in any of the six patients reported by Heck.[28] Other studies did not provide long-term risk of treatments. Therefore, we might conclude that PTA/stenting and balloon angioplasty treatment had less complications compared with CEA.

Factors Affecting the Prognosis

In order to further analyze the factors that might affect the efficacy and long-term prognosis of patients with carotid in-stent restenosis, we summarized the main commodities and other risk factors in Table 3.

As to the baseline characteristics, it showed that mean age of patients in the enrolled studies ranged from 61.3 to 78.1 years. For the features of the diseases, most of the patients in these studies were asymptomatic. As to the target vessels, most of the studies did not provide the detailed information, while it was reported that patients in the DCB group had both the left and the right carotid lesions. Furthermore, as to the diameter stenosis of the lesion vessels, most of the studies reported that a larger than 80% restenosis existed. However, Chung et al. reported a >50% restenosis,[32] Radak et al. reported that the stenosis was >50% for symptomatic patients and >80% for asymptomatic patients.[18] In the balloon angioplasty and CEA groups, the diameter stenosis was larger than 70%.

As to the previous treatments before the restenosis, three out of seven studies adopting re-PTA/stenting had previous CEA treatment while the other four studies had CAS history. For balloon angioplasty group, only one study had previous CEA treatment, with other studies had CAS interventions. For the CEA subgroup, all the studies had previous CAS interventions. The time to first ISR after treatments was also reported in the included studies. For patients with previous CEA treatment, the time to first ISR after treatments was 16–57 months, whereas for CAS interventions, this time interval ranged from 6 to 21 months.

For the comorbidities of patients in these studies, most of the studies reported that patients were complicated with hypertension, diabetes, dyslipidemia, and smoking. However, the percentage of these commodities were similar in different subgroups, which did not affect the long-term effects of the treatment

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Table 3: Basic characteristic of patients in the included studies

Studies included	Number of patients	Gender	Mean age (years)	Asymptomatic	Target vessel	Diameter stenosis (%)	Previous treatments	Time to first ISR (months)	Risk factors (%)	Drugs
Comparative studies										
Aburahma 2001	58 reoperations and 25 PTA/stenting	53% vs. 52% female	70 vs. 71	79% vs. 72%	–	–	CEA	41 vs. 43	SMK (63), DM (24), HTN (77), CAD (54)	Aspirin and ticlopodine or clopidogrel bisulfate
Chung 2017	59	67.5	–	84%	Internal carotid artery	>50	Bare-metal carotid stent	–	HTN (95), CAD (58), DM (36), COPD (12)	Aspirin, clopidogrel, warfarin
Levy 2005	8	–	–	50%	–	>80	Carotid Angioplasty and Stenting	–	–	–
Satecci 2005	407 CAS patients with 14 restenosis patients	2 females and 12 males	61.3 (50.3, 72.7)	Asymptomatic (9) and symptomatic (5)	–	>80	Carotid angioplasty and stenting	–	SMK (50), HTN (100), DM (42), Dyslipidemia (57), CAD (21)	Pre-CAS antiplatelet therapy (100%)
Zhou 2006	188 CAS patients with 7 ISR patients	One female with six males	68	Asymptomatic (6) and symptomatic (1)	–	87.6 ± 6.4%	CEA ($n = 4$), radiation-induced stenosis ($n = 1$), and high-cardiac-risk criteria ($n = 2$)	7.5	CAD (71), SMK (57), HTN (71), DM (43), dyslipidemia (43)	The patient was given clopidogrel (75 mg/day) and aspirin (81 mg/day) beginning 3 days before the intervention. After the stenting procedure, clopidogrel was continued for 3 months, and aspirin was continued for life.
PTA										
Chakhtoura 2011	50 CAS patients with 4 ISR	One man and three women	–	100%	–	>80%	CAS	13 ± 7	DM (25), HTN (50), SMK (50)	–
Koebbe 2005	22 recurrent stenosis patients after CEA	–	71	–	Not mentioned	>80	CEA	28	Not mentioned	All patients were pretreated with aspirin and clopidogrel for at least 3 days before the procedure.
Lal 2003	118 CAS patients with 22 ISR	–	70 ± 9	100%	–	40–99%	CAS	18.8	CAD (72), DM (36), HTN (87), SMK (37)	Aspirin, 325 mg once a day, and clopidogrel, 75 mg twice a day, for 2 days before the procedure.
Lanzino 1999	21	15 men and 6 women	69	11 asymptomatic	–	–	CEA	57	–	–
Radak 2014	319	29% male and 71% female	65 ± 7.87	220 asymptomatic and 99 symptomatic	–	>50% for symptomatic and 85% for asymptomatic patients	CEA	–	CAD (35), DM (36), HTN (94), SMK (67)	–
Raithel 2005	171 patients with 22 ISR	65% male and 35% female	66.2	–	–	–	CAS	–	–	–

Willfort-Ehringer 2002	279 patients with 8 ISR	Seven male and one female	63 ± 7	–	–	>70%	CAS	–	HTN (88), SMK (63), DM (100)	–
DCB angioplasty										
Gandini 2014	856 CAS patients with 9 restenosis patients	Seven females and two males	78.1 ± 5.6	One symptomatic and others asymptomatic	Seven of the nine patients had LICA disease while other two had RICA lesions	>80	3.4 ± 0.9 previous endovascular procedures	6.2 ± 1.2	HTN (67), DM (67), CAD (33), SMK (44)	Aspirin (100 mg/day) and clopidogrel (75 mg/day)
Montorsi 2012	830 CAS patients with 7 stenosis patients	Four females and three males	71.1 ± 8.0	Asymptomatic	Five patients had LICA disease while other two had RICA lesions	83.6 ± 4.8	Carotid artery stenting	21 ± 19	Not mentioned	Patients were treated with double antiplatelet therapy (clopidogrel 75 mg/day and aspirin 100 mg/day) for at least 10 days before the DEB intervention.
Piccoli 2015	18 patients	Seven females and 11 males	75	Asymptomatic	Fourteen patients had LICA disease, while other 4 had RICA lesions.	84 (75, 89)	CEA	16 (13, 18)	HTN (94), DM (28), CAD (39), SMK (78)	Dual antiplatelet therapy (aspirin 100 mg/day and clopidogrel 75 mg/day) was begun at least 4 days before.
Pohlmann 2017	176 CAS patients with 9 restenosis cases	Five females and four males	66.3 ± 11.5	Asymptomatic	–	83 ± 8	Carotid artery stenting	9	HTN (89), DM (44), SMK (56), Dyslipidemia (100)	All patients received orally administered acetylsalicylic acid (100 mg/day) and clopidogrel (75 mg/day) at least 3 days before the procedure.
Tekieli 2012	1217 CAS patients with 7 restenosis	Two females and five males	63.6	Asymptomatic (3) and symptomatic (4)	Three patients had LICA disease, while other four had RICA lesions.	84.6 ± 7.5	Carotid artery stenting	8.3	HTN (100), dyslipidemia (71), SMK (57) DM (14), CAD (71)	Before the procedure, all patients were continuously on low-dose aspirin (75 mg/day); they were also pretreated with clopidogrel (75 mg/day) for at least 7–14 days.
Regular and cutting balloon angioplasty										
Donas 2011	485 CAS patients with 16 developed ISS	–	–	Six were symptomatic, and 10 were asymptomatic.	–	>80	CAS	7.8 ± 3.5	Not mentioned	All CAS patients received 300 mg of clopidogrel and 100 mg of aspirin before the procedure. After CAS, double antiplatelet therapy (clopidogrel 75 mg/day and aspirin 100 mg/day) was maintained for 2 months.

(Continued)

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Table 3. *Continued*

Studies included	Number of patients	Gender	Mean age (years)	Asymptomatic	Target vessel	Diameter stenosis (%)	Previous treatments	Time to first ISR (months)	Risk factors (%)	Drugs
Heck 2009	296 CAS patients with 6 restenosis patients	Four females and two males	70.5 ± 13.5	Asymptomatic	Not mentioned	>70	Carotid artery stenting	Within 6 months	Not mentioned	Clopidogrel for at least 5 days and aspirin 325 mg for at least 2 days
Reimers 2006	31 ISR patients	27 males and 4 females	63.7 ± 13	77% asymptomatic	–	83.7 ± 7.0	100% with CAS	–	–	All patients were on aspirin (100 mg/day) and received ticlopidine (250 mg BID) or clopidogrel (75 mg/day) at least 48 h before the procedure. Heparin was administered at a dose of 100 U/kg.
Satecci 2009	102 restenosis patients	36 females and 66 males	76.4 ± 7.5	–	–	Symptomatic CAS >70% or asymptomatic CAS >80%	CAS	–	HTN (73), SMK (56), DM (34), CAD (45), Dyslipidemia (28), Heart failure (23)	Aspirin (125 mg/day) associated with clopidogrel (75 mg/day)
CEA										
Borst 2003	217 patients with 4 ISR	–	70 ± 8.2	Two asymptomatic and two symptomatic	–	90–99%	CAS	–	–	All patients were started on clopidogrel 72 h before the procedure and aspirin for life-long.
Marcucci 2012	Seven ISR	Four men and three women	76 ± 2	Four asymptomatic	–	>80%	CAS	13.1	DM (57), HTN (86), CAD (71)	Dual antiplatelets treatments with clopidogrel (75 mg) and aspirin (100 mg) for 1 month
Reichmann 2011	15 patients	10 males	64.5	symptomatic (10) or hemodynamically significant (>80%) asymptomatic ISR (5)	–	>80%	CAS	18.3	DM (20), HTN (87), SMK (87)	–
Yu 2017	10 patients	Nine male and one female	67.3	Nine symptomatic and one asymptomatic ISR	–	>70%	CAS	17	HTN (90), DM (30), CAD (30)	Aspirin therapy (300 mg) was administrated per day in 1 week after surgery then long-term aspirin therapy (100 mg) after being discharged.

CAS = carotid artery stenting; RICA = right internal carotid artery; LICA = left internal carotid artery; DCB = drug-coated balloon; DEB = drug-eluting balloon; HTN = hypertension; DM = diabetes mellitus; CAD = coronary artery disease; SMK = smoking; CEA = carotid Endarterectomy; ISR = in-stent restenosis.

modalities. Meanwhile, among the drugs used before and after the interventions, double antiplatelet therapy was commonly used in most of the studies.

Discussion

Despite various CAS procedures reported in the literature, the long-term incidence of ISR remains undefined, especially for carotid arteries. Choosing the best treatment strategy for stenosis and in-stent restenosis has been studied widely. Previous reports indicated that CEA and CAS had their own advantage and disadvantages for the treatment of carotid stenosis. However, for carotid ISR, little is known about the best treatment strategy. According to previous review, the most commonly used treatment option for ISR is re-PTA combined with the regular balloon angioplasty.[38] In this review of the literature, we showed that the treatment of CEA might be the best in achieving the best angioplasty efficiency, but with increased possibility of periprocedural complications, while for those patients with high-risk factors, re-PTA with balloon angioplasty might provide better protections.

Different reports have been published about the incidence for ISR.[38] For ISR after CAS, infrequent complication was reported by several authors, with an incidence of 3.5–4.9%,[39] which is still common for patients with CAS. Previously, the heterogeneity in the minimally required degree of ISR of studies limited the availability to compare the results. Some studies used the degree of lumen reduction, detected by ultrasound, whereas other studies adopted the PSV values. It has been reported that duplex velocities would increase with the presence of a stent and in absence of a stenotic lesion, while the type of stent used for previous CAS could also influence the ISR patent and the PSV values.[40–42] Therefore, the difference in these parameters in the treatment of ISR limited the summary of previous studies. Meanwhile, the diagnosis of ISR in the studies enrolled in this review was based mainly on the lumen stenosis by ultrasonography. However, due to the differences of patient selection, types of stents, and follow-up durations, a quantitative meta-analysis cannot be conducted. Furthermore, the degree of stenosis at which revascularization for symptomatic lesions is favored is also unclear. Because carotid ISR lesions appear less embologenic,[43] it is plausible that intervention may be reserved for only high-grade stenoses rather than for all lesions >50%.[32]

As to the treatment options of carotid ISR, still limited evidence was presented and the ideal therapeutics have not been identified, with the choice of re-PTA/stenting, repeated balloon angioplasty (regular, cutting or DCB), and surgical treatment (CEA with stent removal, carotid artery bypass, or interposition graft).[44] In our study, we showed that all the therapeutic measures for carotid ISR could effectively relieve the problem, whereas CEA might bring better long-term prognosis. Still, other studies indicated that the placement of a stent for carotid stenosis was associated with a 5.8% composite rate of stroke, death, and myocardial infarction compared with a rate of 12.6% for CEA at 30 days according to the SAPPHIRE trial. Nevertheless, an increased number of patients with recurrent stenosis in the subgroup of stenting compared with operation arm according to the CARESS trial.[3] Also, in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), severe (70–90%) recurrent stenosis was found in 14% of patients who had undergone angioplasty with or without stent placement compared with 4% of those who had undergone surgery.[45] Conducting CEA might provide better results with less occurrence of carotid ISR with the longest follow-up of 7 years for 0.1%.[46]

DCB angioplasty is a newly development technique that has the following advantages: immediate drug release without the use of a polymer that could trigger late thrombosis; no prolonged, direct drug contact with the arterial wall, allowing better reendothelization of the vessel; no foreign object left in the body, which is especially important in peripheral applications where stents may be used for suboptimal results; maintenance of original vessel anatomy and flexibility; and finally, lower restenosis rates in most indications.[47] However, it is worth keeping in mind that the concept of DCBs is still in development. This technology was hampered by a lack of solid preclinical data and long-term animal studies, non-standardized coating methods, and variances in the reproducibility of results. Currently, several kinds of DCBs are developed in market.[10] The mechanical action as the balloon crushes the plaque creates microchannels through which the paclitaxel can be absorbed by the vessel. Preliminary preparation of lesions using pre-dilation, atherectomy, or cutting balloon can optimize drug transfer during DCB inflation. Compared to long inflation durations, short inflations and nominal pressure cause less arterial injury, preserving the inhibitory effect. In our study, several studies reported that several patients might have TIA during prolonged DCB inflation. Therefore, in the setting of carotid ISR, utilization of distal or proximal protection devices is highly recommended. Furthermore, an enormous need for robust preclinical data is related to drug transfer capability, drug transfer amount in the vessel, residual drug concentration after inflation, and vessel tolerance to large drug amounts delivered in a short interval. Subsequently, this information must be translated to the clinical arena by randomized controlled clinical trials to confirm DCB efficacy in patients affected by atherosclerotic disease. Through the data from our review, we recommend using the paclitaxel-eluting technologies for carotid in-stent restenosis, which may provide better long-term results, but still more clinical trials are needed.

The major events occurring during or immediately after a revascularization procedure and triggering post-intervention vascular restenosis in patients include endothelial denudation, damage or rupture of elastic laminae in the vascular wall, oxidative stress, an imbalance in MMPs (matrix metalloproteinases) and their inhibitors, inflammation, apoptosis, cytokine and chemokine release, homing of circulating progenitor cells, and a phenotype switch of resident cells.[48] Restenosis is considered as an excessive wound healing reaction or as a maladaptive response of the artery to trauma induced during revascularization, resulting in neointimal hyperplasia and vascular remodeling. Currently, the available DCBs could release the drugs (paclitaxel, by inhibiting cell proliferation; trimetazidine, by protecting the endothelia) to the different targets in this pathological process. However, several other kinds of drugs, such as anti-inflammatory drugs, antioxidant drugs, drugs inhibiting cell proliferation and migration, have also been developed and tested in the restenosis models of animals. Therefore, considering these promising results, further efforts are warranted to develop DCB conjugated with novel drugs that are able to selectively affect smooth muscle cells, not just endothelial cells, both proliferation and migration.

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The limitations of this review are as follows. First, most of the included studies are cross-sectional studies and with heterogeneity in patients' characteristics, which cannot be quantitatively analyzed and synthesized. Meanwhile, the number of studies concentrating on the different interventions in treating carotid ISR is still very few, and more comparative studies are needed to further prove the long-term prognosis.

Conclusions

The therapeutic measures for carotid ISR had their own features, with CEA had the highest efficacy while re-PTA/stenting and balloon angioplasty were with less complications. More large-scale comparative clinical studies are needed to further ascertain the best strategies.

Statement of authorship

Study conception and design was contributed by SW and CH; literature search and data acquisition was conducted by CH and XZ; interpretation of the data was performed by XZ and ZY; CH drafted the manuscript; SW critically revised the manuscript; final approval was done by CH, SW, XZ, and ZY.

Disclosures

The authors have no conflicts of interest to declare.

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