Critical analysis of the literature and standards of reporting on stroke after carotid revascularization

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ABSTRACT

Objective: Mechanisms of procedural stroke after carotid endarterectomy (CEA) or carotid artery stenting are surprisingly underresearched. However, understanding the underlying mechanism could (1) assist in balancing the choice for revascularization vs conservative therapy, (2) assist in choosing either open or endovascular techniques, and (3) assist in taking appropriate periprocedural measures to further decrease procedural stroke rate. The purpose of this study was to overview mechanisms of procedural stroke after carotid revascularization and establish reporting standards to facilitate more granular investigation and individual patient data meta-analysis in the future.

Methods: A systematic review was conducted according to the PRISMA statement.

Results: The limited evidence in the literature was heterogeneous and of low quality. Thus, no formal data meta-analysis could be performed. Procedural stroke was classified as hemorrhagic or ischemic; the latter was subclassified as hemodynamic, embolic (carotid embolic or cardioembolic) or carotid occlusion derived, using a combination of clinical inference and imaging data. Most events occurred in the first 24 hours after the procedure and were related to hypoperfusion (pooled incidence 10.2% [95% confidence interval (CI), 3.0-17.5] vs 13.9% [95% CI, 0.0-60.9] after CEA vs carotid artery stenting events, respectively) or atheroembolism (28.9% [95% CI, 10.9-47.0]) vs 34.3 [95% CI, 0.0-91.5]). After the first 24 hours, hemorrhagic stroke (11.6 [95% CI, 5.7-17.4] vs 9.0 [95% CI, 1.3-16.7]) or thrombotic occlusion (18.4 [95% CI, 0.9-35.8] vs 14.8 [95% CI, 0.0-30.5]) became more likely.

Conclusions: Although procedural stroke incidence and etiology may have changed over the last decades owing to technical improvements and improvements in perioperative monitoring and quality control, the lack of literature data limits further statements. To simplify and enhance future reporting, procedural stroke analysis and classification should be documented preemptively in research settings. We propose a standardized form enclosing reporting standards for procedural stroke with a systematic approach to inference of the most likely etiology, for prospective use in registries and randomized controlled trials on carotid revascularization. (J Vasc Surg 2022;75:363-71.)

Keywords: Stroke; Carotid Stenosis; Stent; Endarterectomy; Carotid; Embolic protection

Carotid artery revascularization is one of the best studied surgical procedures, with the focus of research classically centered on two primary outcomes: procedural (30-day) death and stroke. Accordingly, since the advent of carotid artery stenting (CAS), multiple randomized controlled trials (RCT) have compared CAS with carotid endarterectomy (CEA), consistently highlighting the importance of procedural stroke or a composite of procedural stroke, death, and myocardial infarction as the main outcome.[1] A recent meta-analysis of pooled data from RCTs on symptomatic and asymptomatic patients revealed a significantly higher risk of procedural stroke with CAS compared to CEA, mostly owing to a higher rate of minor strokes in the stenting arm.[2] Similarly, most contemporary administrative dataset registries still show that procedural stroke/death rates following CAS are significantly higher than these risks after CEA, particularly in "average risk for CEA" symptomatic patients. It is also noteworthy that a recent systematic review failed to demonstrate a decline in procedural risk after CAS over time, especially in symptomatic patients.[3]

In addition to studies comparing CEA and CAS, procedural adverse events including stroke, death, and myocardial infarction have also been used as the main end points in multiple other comparative analyses, including classical CEA vs eversion CEA, CEA under general vs locoregional anesthesia, and early carotid intervention after neurologic event in patients submitted to previous

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thrombolysis vs no thrombolysis. Surprisingly, little attention has been paid to the underlying mechanism of procedural stroke, either during CEA or during CAS.

The basic mechanisms underlying procedural stroke are heterogeneous but can be broadly classified in four categories: (1) atheroembolic debris, (2) internal carotid artery (ICA) occlusion, (3) hemodynamic (hypoperfusion or hyperperfusion) and (4) hemorrhagic.[4] Determination of the time of procedural stroke (especially discriminating between intraprocedural and postprocedural stroke), scrutiny of intraprocedural technical complications and hemodynamic disturbances, and the assessment of postprocedural carotid and brain imaging have been considered crucial parameters to determine the underlying cause.[5]

Neuroimaging studies, including diffusion-weighted (DW) and perfusion-weighted magnetic resonance imaging (MRI) can support the identification of subclinical events. Also, and most important, in either clinical or subclinical events, these imaging techniques support the characterization of the acute lesion and the delineation of the area of hemodynamic compromise improving the understanding of pathophysiologic mechanisms leading to cerebral ischemia in patients with ICA disease.[6] However, in contrast with primary ischemic index stroke events, poststroke cerebral MRI data are scarce.[7]

In this study, we aimed to provide a literature overview on the mechanisms involved in procedural stroke after carotid revascularization. Understanding the underlying mechanism could (1) assist in balancing the choice for revascularization vs conservative therapy, (2) assist in choosing either open or endovascular techniques, and, most important, (3) assist in taking appropriate periprocedural measures by appropriate neurologic and hemodynamic monitoring to assist in further decreasing procedural stroke rate. With these points in mind, we propose reporting standards for procedural stroke to facilitate future data comparison and individualized patient data meta-analysis.

METHODS

A systematic review was conducted according to the recommendations of the PRISMA statement.[8] The literature search was updated last on December 1, 2020. Using the PUBMED database and the following query (("Carotid Stenosis"[Mesh] AND "Stents"[Mesh]) OR (Carotid artery stenting)) OR (carotid endarterectomy [MeSH Terms])) AND ((procedural stroke mechanism) OR (periprocedural stroke)), a total of 797 results were retrieved. The search conduction using the PRISMA diagram is demonstrated in the Supplementary Figure, online only).

The eligibility criteria included any publication regarding the pathophysiologic mechanism of procedural stroke after carotid revascularization, comprising single-arm studies or comparisons between CEA and CAS. Only atherosclerotic steno-occlusive carotid disease was considered. Articles published from January 2000 to the present were considered. Exclusion criteria were (1) articles published in a language other than English and (2) case reports and literature reviews.

Stroke was defined as a rapidly developing clinical syndrome of focal disturbance of cerebral function lasting more than 24 hours or leading to death with no apparent cause other than that of vascular origin. Neurologic symptomatic status prior to the carotid intervention was defined as a transient ischemic attack (TIA) or minor disabling ischemic stroke in the previous 6 months attributable to the ipsilateral carotid artery territory.

Stroke was considered procedural if the event occurred at any time between the revascularization procedure (day 0) and day 30 after revascularization. Intraoperative stroke was defined as any new focal neurologic deficit (or worsening of a preexisting deficit), apparent intraoperatively when the procedure was performed under locoregional anesthesia or immediately following recovery from anesthesia and with symptoms lasting for more than 24 hours. Postoperative procedural stroke was defined as any new focal (or worsening) neurologic deficit, after full recovery from anesthesia with an initial symptom-free interval and whose symptoms last more than 24 hours. Similarly, procedural TIA was defined as any new focal neurologic deficit (or worsening of a preexisting deficit) with symptoms lasting for less than 24 hours, which occurred at any time between the revascularization procedure (day 0) and day 30 after revascularisation.[1] Stroke was classified as disabling if there was an increase in the modified Rankin score (mRS) to 3 or more, attributable to the event 30 days after the procedure.[1]

Two reviewers screened the identified studies independently (Supplementary Figure, online only) Collected data included type of study, year of publication, number of patients and consecutiveness, adjudication of events by a clinical event committee, age, sex, and criteria for carotid revascularization (presence of neurologic symptoms and their timing). Time of procedural stroke/TIA (regarding the revascularization event), territory, and associated disability (mRS) were also registered. The type of data used to define the mechanism of stroke (clinical data, brain imaging MRI, and carotid imaging, among others) and the inferred mechanism of stroke were also registered. When duplicate studies were identified, the most recent analysis was included, unless the earlier version reported more data on parameters included in our analysis.

The primary outcome was defined as the pathophysiologic mechanism of procedural stroke. The secondary outcome was defined as the topographic patterns of cerebral ischemic lesions.

Quality assessment. The methodology of the studies and the risk of bias were systematically assessed with the Methodological Index for Non-Randomized Studies

Table I. Analysis of study characteristics

Article	Year	Type of study	N o.	Consecutive patients	CEC	Type of carotid revascularization, No. (%)
Lareyre et al[7]	2017	Observational (retrospective)	19	Yes	NR	CEA: 19 (100)
Huibers et al[11] ACST-1 RCT	2016	Retrospective study (of prospectively collected data)	53	Yes	Yes	CEA: 53 (100)
Huibers et al[12] ICSS RCT	2015	Retrospective study (of prospectively collected data)	85	Yes	Yes	CEA: 27 (31.8) CAS: 58 (68.2)
Hill et al[13] CREST RCT	2012	Retrospective study (of prospectively collected data)	69	Yes	Yes	CEA: 21(30.4) CAS: 48 (69.6)
Fairman et al[14] CAPTURE Registry	2007	Retrospective study (of prospectively collected data)	170	Yes	Yes	CAS: 170 (100)
Rapp et al[10]	2007	Prospective study	2	Yes	Yes	CAS: 2 (100)
de Borst et al[15]	2001	Retrospective study (of prospectively collected data)	20	Yes	No	CEA: 20 (100)
Jacobowitz et al[16]	2001	Retrospective study	26	Yes	No	CEA: 26 (100)

CAS, Carotid artery stenting; *CEA*, carotid endarterectomy; *CEC*, clinical events committee; *CNI*, carotid nerve injury.

score,[9] with a maximum score of 16 for noncomparative and 24 for comparative studies. A score of 8 or lower was considered poor quality, 9 to 14 moderate quality, and 15 or 16 good quality for noncomparative studies. The cut-off points were 14 or less, 15 to 22, and 23 to 24, respectively, for comparative studies.

Authorship of the studies was not masked from the reviewers. Discrepancies between the reviewers during the search, selection, and quality assessment were resolved by discussion. In case of persisting disagreement, a third reviewer was consulted.

RESULTS

A total of 797 potentially relevant articles were initially identified. After reviewing title or abstract, 22 articles were read in full and seven were judged eligible for inclusion (Supplementary Figure, online only). An additional article was included by backward citation. Agreement between the reviewers was reached for all articles and arbitration by a third reviewer was unnecessary.

Regarding quality analysis, studies were classified as moderate quality with no study reaching high quality standards (Supplementary Table I, online only). With one notable exception of a small prospective analysis,[10] only retrospective or post hoc analyses were found most of which analyzing prospectively collected data from RCTs or registries (Table I). Based on the overall heterogeneous and low-quality data, no formal data meta-analysis could be performed.

A total of four single-arm studies reviewed the mechanism of procedural stroke after CEA, one of which analyzed procedural stroke of a subset of patients from the Asymptomatic Carotid Stenosis Trial-1 (ACST-1; Table I). Procedural stroke after CAS was analyzed in two single-arm studies (Table I). Two studies analyzed and compared the mechanism of procedural stroke after CEA vs CAS in a subset of patients from two large RCTs: International Carotid Stenting Study (ICSS) and Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) respectively (Table I).

Data regarding patient age, sex, symptomatic status, and type of anesthesia are summarized in Table II. In symptomatic patients, timing of revascularization after the index event was not reported, with the exception of the ICSS RCT sub-analysis reporting a mean time gap of 14 days in 17 patients (20%).[12]

Procedural stroke and symptomatic status. A pooled analysis revealed symptomatic status in 41.6% of patients (95% CI, 0.0-87.6%). In one study, procedural stroke after CEA was significantly more likely in symptomatic than in asymptomatic patients (4.2% vs 1.7%; $P < .02$).[16] After CAS, a procedural stroke was more likely in symptomatic patients (8.9% vs 4.1%).[14] In the ICSS cohort, patients treated within 2 weeks of the index event (either with CEA or CAS) were more likely to develop a procedural stroke caused by a hemodynamic mechanism compared with patients treated thereafter (47% vs 18%; $P = .025$).[12] It is noteworthy that two studies reported on relevant periprocedural medication with over 90% of patients being treated with antiplatelet therapy in both studies (Table II).

Data on procedural stroke territory (ipsilateral vs contralateral) and stroke severity: nondisabling (mRS of 0-2) vs disabling (mRS of >2) are summarized in Table III.

The establishment of mechanisms of procedural stroke was either based on the brain MRI lesion pattern (n = 2) or a combination of clinical, carotid imaging, brain imaging, and electrocardiography (n = 6; Table II). Procedural stroke was classified into several categories: (1) intraprocedural or postprocedural (in the latter event timing was determined whenever possible) or (2) hemorrhagic

Table II. Demographic patient data on included studies

Article		Age, years	Male sex	Symptomatic	Perioperative medication	Timing	Definition of stroke mechanism	LRA
Lareyre et al,[7] 2017	CEA	73.9 ± 11.4	14 (73.7)	10 (52.6)	NR	NR	Brain imaging (MRI pattern)	NR
Huibers et al[11] ACST-1 RCT, 2016	CEA	NR	NR	0 (0)	Antiplatelet therapy only: 45 (95.7) Anticoagulation only: 1 (2) DAPT: 0 (0) No antiplatelet or anticoagulation 1 (2)	NA	Clinical data + carotid/brain imaging + ECG	27/37 (73)
Huibers et al[12] ICSS RCT, 2015	CEA CAS	NR	NR	85 (100)	NR	≤14 days: 17 (20)	Clinical data + carotid/brain imaging + ECG	NR
Hill et al[13] CREST RCT, 2012	CEA CAS	NR	NR	NR	Antiplatelet therapy: CAS vs CEA —45 (95.7) vs 21 (100) Statin therapy: CAS vs CEA —33 (94.3) vs 16 (94.1)	NR	Brain imaging (MRI or CT pattern)	NR
Fairman et al[14] CAPTURE Registry, 2007	CAS	75.8	91 (54.2)	43 (25.6)	NR	NR	Clinical data + brain imaging	NR
Rapp et al[10] 2007	CAS	NR	NR	NR	NR	NR	Brain imaging (MRI pattern)	NR
de Borst et al[15] 2001	CEA	68	17 (85)	7 (35)	NR	NR	Clinical data + carotid/brain imaging + EEG + TCD	0 (0)
Jacobowitz et al,[16] 2001	CEA	69.6	15 (59)	10 (38)	NR	NR	Clinical data + carotid/brain imaging	16 (61.5)

CAS, Carotid artery stenting; *CEA*, carotid endarterectomy; *CT*, computed tomography; *ECG*, electrocardiography; *LRA*, locoregional anesthesia; *MRI*, magnetic resonance imaging; *NR*, not reported; *TCD*, transcranial Doppler.
Values are mean ± standard deviation or number (%).

or ischemic, and the latter was subclassified as hemodynamic, embolic (carotid embolic or cardioembolic) or carotid occlusion derived.

Procedural stroke time. In the included studies, most procedural strokes occurred within the first 24 hours after the procedure Table III. An intraprocedural stroke was reported separately in five studies, and relative frequency ranged from 18.5% to 34% of patients after CEA vs 22% to 50% after CAS (Table III). In one study, intraprocedural events after CAS were significantly more common than after CEA (34% vs 19%; $P = .014$).[12] A pooled analysis of intraprocedural stroke incidence was 29.0% (95% CI, 0.0-59.1) after CEA and 25.2% (95% CI, 6.9-43.5) after CAS. Post-procedural stroke at day 0 presented an incidence of 48.0% (95% CI, 1.2-94.8) after CEA and 21.3% (95% CI, 0.0-56.8%) after CAS.

The time of onset of different mechanisms of stroke has been studied. In one study, a trend was seen toward an increased rate of carotid embolic and hemodynamic (hypoperfusion) mechanisms on day 0. For days 1 to 30, there was a trend toward an increased rate of thrombotic occlusion of the ICA. Hyperperfusion-related events occurred most commonly after the first day.[12]

Procedural stroke etiology. When considering procedural stroke after CEA or CAS, embolic etiology ranged from 15% to 63.2% associated with CEA vs 19% to 100% associated with CAS; hypoperfusion from 0% to 18.5% vs 0% to 25.9%; carotid occlusion from 0% to 50% vs 10.4% to 19.0%; and intracranial hemorrhage from 7.5% to 18.5% vs 3.4% to 18%. Finally, hyperperfusion ranged from 5.0% to 7.4% after CEA and was the cause of 3.4% of events in a single study after CAS (Table III). Overall, a pooled analysis of procedural stroke etiology after CEA

Table III. Procedural stroke data on included studies

Article		Stroke territory	Stroke timing, days	Stroke mechanism	MRI patterns	Circle of Willis	Severity mRS
Lareyre et al,[7] 2017	CEA	NR	2.1 ± 3.3	Embolic: 5 (26.3) Hemodynamic: 2 (10.5) Mixed: 5 (26.3)	Type 1: 4 (21.1) Type 2: 2 (10.5) Type 3: 2 (10.5) Type 4: 3 (15.8) Type 5: 8 (42.1)	Normal: 3 (15.8)	NR
Huibers et al[11] ACST-1 RCT, 2016	CEA	Ipsilateral: 42 (79) Contralateral: 9 (17) Vertebrobasilar: 2 (4)	2.4 ± 5.6 Intraprocedural: 20 (38) Postprocedural day 0: 32 (60.4)	Embolic: 9 (17.0) (Carotid embolic: 6 [11.3]; Cardioembolic: 3 [5.7]) Hemodynamic: 4 (7.5) Hemorrhagic: 4 (7.5) Carotid occlusion: 9 (17.0) Hyperperfusion: 3 (5.7) Mixed: 8 (15) Undetermined/ unknown: 16 (30)	NR	NR	Nondisabling (0-2): 26 (49) Disabling (3-5): 14 (26) Death (6): 13 (25)
Huibers et al[12] ICSS RCT, 2015	CEA (n = 27)	Ipsilateral: 25 (92.6) Contralateral/ vertebrobasilar: 2 (7.4)	2.6 ± 5.2 Intraprocedural: 5 (18.5) Postprocedural day 0: 7 (25.9)	Embolic: 7 (25.9) (Carotid embolic: 4 [14.8] Cardioembolic: 3 [11.1]) Hemodynamic: 5 (18.5) Hemorrhagic: 5 (18.5) Carotid occlusion: 3 (11.1) Hyperperfusion: 2 (7.4) Undetermined/ unknown: 9 (33.3)			Nondisabling (0-2): 11 (40.7) Disabling (3-6): 16 (59.3)
	CAS (n = 58)	Ipsilateral: 52 (89.7) Contralateral/ vertebrobasilar: 4 (6.9) Unknown: 2 (3.4)	2.2 ± 5.2 Intraprocedural: 20 (34) Postprocedural day 0: 23 (39.7)	Embolic: 11 (19.0) (Carotid embolic: 9 [15.5] Cardioembolic: 2 [3.4]) Hemodynamic: 15 (25.9) Hemorrhagic: 2 (3.4) Carotid occlusion: 11 (19.0) Hyperperfusion: 2 (3.4) Hemorrhagic: 2 (3.4) Undetermined/ unknown: 17 (29.3)	NR	NR	Nondisabling (0-2): 36(62.1) Disabling (3-6): 22(37.9)
Hill et al[13] CREST RCT, 2012	CEA	Ipsilateral: 15 (83.3) Contralateral: 2 (11.1) Vertebrobasilar: 1(5.6)	Median (IQR): 1 (7)	Embolic: 9 (18.9) Hemodynamic: 0 (0) Hemorrhagic: 2 (11) Carotid occlusion: 4 (19)	Type 1: 4 (31) Type 2: 4 (31) Type 3: 0 (0) Type 4: 5 (38)	NR	Nondisabling (0-2): 49 (76.6) Disabling (3-5): 15 (23.4) CEA median (IQR): 1 (2) CAS median (IQR): 1 (1.5)
	CAS	Ipsilateral: 40 (90.9) Contralateral: 2 (4.6) Vertebrobasilar: 2 (4.6)	Median (IQR): 0 (3.5)	Embolic: 24 (50) Hemodynamic: 0 (0) Hemorrhagic: 3 (8) Carotid occlusion: 5 (10.4)	Type 1: 9 (31) Type 2: 5 (17) Type 3: 4 (14) Type 4: 11 (38)	NR	
Fairman et al[14] CAPTURE Registry, 2007	CAS	Ipsilateral: 139 (82) Nonipsilateral: 31 (18)	Intraprocedural: 37 (22) Postprocedural day 0: 25 (14.7)	Ischemic: 150 (82) Hemorrhagic: 20 (18)	NR	NR	Nondisabling (0-2): 102 (60) Disabling (3-5): 68 (40)
Rapp et al[10] 2007	CAS	Ipsilateral: 2 (100)	Intraprocedural: 1 (50) Postprocedural day 0: 1 (50)	Embolic: 2 (100)			Nondisabling (0-2): 2 (100)

(Continued on next page)

Table III. Continued.

Article		Stroke territory	Stroke timing, days	Stroke mechanism	MRI patterns	Circle of Willis	Severity mRS
de Borst et al[15] 2001(39)	CEA	Ipsilateral: 18 (90) Nonpsilateral: 2 (10)	Mean: 0.58 ± 0.78 Median (IQR): 0 (1) Intraprocedural: 4 (20) Postprocedural day 0: 9 (45)	Embolic: 3 (15) Hemodynamic: 1 (5) Hemorrhagic: 1 (5) Carotid occlusion: 10 (50) Contralateral carotid occlusion: 1 (5) Hyperperfusion: 1 (5) Undetermined/ unknown: 3 (15)	NR	NR	Nondisabling (0-2): 9 (45) Disabling (3-5): 11 (55)
Jacobowitz et al,[16] 2001	CEA	Ipsilateral: 23 (88.4) Nonipsilateral: 3 (11.5)	NR	Embolic 15 (57.7) (carotid embolic: 14 [53.8] Cardioembolic: 1 [4]) Hemodynamic: 5 (19.2) Hemorrhagic: 4 (15.4) Undetermined/ unknown: 2 (7.7)	NR	NR	NR

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy; *ECG,* electrocardiography; *IQR,* interquartile range; *MRI,* magnetic resonance imaging; *mRS,* modified Rankin Score; *NR,* not reported; *RCT,* randomized controlled trial.
Values are mean ± standard deviation or number (%).

revealed embolic etiology embarked 28.9% (95% CI, 10.9-47.0), hemodynamic etiology 10.2% (95% CI, 3.0-17.5), hemorrhagic stroke 11.6% (95% CI, 5.7-17.4), and ICA occlusion 18.4% (95% CI, 0.9-35.8). After CAS, a pooled analysis revealed embolic etiology embarked 34.3% (95% CI, 0.0-91.5), hemodynamic etiology 13.9% (95% CI, 0.0-60.9), hemorrhagic stroke 9.0% (95% CI, 1.3-16.7), and ICA occlusion 14.8% (95% CI, 0.0-30.5).

Brain DW-MRI pattern of clinical stroke was analyzed in two studies, classifying the stroke mechanism according to five previously described lesion patterns related to a stroke mechanism[6]:; 1 (territorial infarction), distal ICA embolism; type 2 (subcortical infarction), middle cerebral artery occlusion with patent collaterals; type 3 (territorial infarction with fragmentation), embolization with partial fragmentation; type 4 (scattered small lesions), distal microembolism; and type 5 (border zone infarction), hemodynamic stroke.

In one study, the main pattern of post-CAS stroke in MRI was type 5 (42.1%), but only 10.5% of patients were classified as purely hemodynamic strokes.[7] An analysis of DW-MRI from the CREST CAS and CEA cohorts revealed that type 4 (microembolism) was the most common pattern, with no patients presenting type 5 pattern.[13]

DISCUSSION

In this review, focusing on the mechanism of procedural stroke in carotid revascularization, very limited data from moderate methodologic quality studies were available. No study achieved high quality standards and only retrospective or post hoc analyses from RCT or registries could be found (with the exception of one small prospective study[10]). Most studies on procedural stroke were attained by vascular surgeons, with little focus from neurology, the medical specialty devoted to the study of stroke in all its different features.

Despite a considerable body of evidence concerning the occurrence of procedural stroke after CEA and CAS in the literature, a comprehensive analysis of its mechanism are surprisingly scarce. The present review strengthened our conviction of the importance of categorizing procedural stroke. Different etiologies have different potentially avoidable causes and additional data on the relative incidence of each category are crucial.

Recent technical advances in CAS have focused on decreasing the risk for procedural stroke, focusing mainly on decreasing the risk for carotid embolic events. Studies of different types of stent, comparing open cell, closed cell, and the more recent dual layer stents aimed to find the optimal design to reduce plaque protrusion through the stent struts.[17,18] Also, the development of transcarotid artery revascularization is a perfect example of how the understanding of the pathophysiologic mechanism of stroke in CAS has led to further refinement of the stenting technique, here by avoiding the aortic arch during carotid access and decreasing the risk of embolism related to target lesion traversal.[19,20] A recent retrospective comparative analysis between transfemoral CAS and transcarotid artery revascularization concluded that the latter was associated to lower risk of procedural stroke owing to dynamic flow reversal.[21] However, we believe this conclusion was mostly speculative, because the procedural stroke etiology was not scrutinized in the cited study.

Besides technical improvements, evidence suggests that targeted monitoring and quality control strategies may reduce perioperative stroke. Quality control techniques are defined as the conjunct of intraoperative strategies to prevent technical error and subsequent

perioperative adverse outcomes, including (1) to diagnose embolization during carotid dissection (transcranial Doppler imaging), (2) to ensure a shunt is functioning (transcranial Doppler imaging, CEA under locoregional anesthesia), or (3) to identify the rare cases of intraoperative ICA occlusion after finalizing the endarterectomy (Doppler ultrasound examination).[1] Even though reliance on a single quality control strategy is unlikely to make a significant difference, because of the myriad of possible causes of procedural stroke,[1] the systematic use of these techniques may have decreased technical errors and altered the overall procedural stroke etiology.[22]

Stroke location

Stroke location in imaging studies (most notably DW-MRI patterns) has been used to predict the underlying etiology, along with clinical inference. Hemodynamically significant extracranial ICA stenosis may cause hemodynamic changes in the distal regions of the hemispheric blood supply, whereas embolism from ICA stenosis is believed to disproportionately affect the middle cerebral artery stem and distal branches producing territorial infarction, often including the deep lenticulostriate territory.[23]

DW-MRI analysis could potentially bring some additional understanding to this matter, but DW-MRI data on procedural stroke are scarce.[6] Also, the establishment of the pathophysiology of border zone infarcts is not as straightforward as some studies report.[24] Substantial evidence supports both low flow and multiple microembolic mechanisms as causes for type 5 lesions and may play a synergistic role: the decreased perfusion reduces clearance of microemboli, and the blocked vessels extend the hypoperfused area.[25]

Nearly all ischemic procedural strokes are ipsilateral; nonipsilateral ischemic strokes can be related to a catheter-related disruption of the plaque in the aortic arch or to hemodynamic disturbance in patients undergoing CAS. In one cohort, three out of four nonipsilateral strokes after CAS presented a catheterization-related thromboembolic mechanism.[26]

Time of procedural stroke

The timing of a procedural stroke is crucial to understand the underlying mechanism and a clear distinction should be made between intraprocedural and postprocedural strokes. In the literature, intraprocedural stroke has decreased significantly after CEA but remains a concern with CAS (also including silent ischemia). Intraprocedural stroke during CEA can occur owing to cerebral hypoperfusion or thromboembolism from the endarterectomy zone. During CAS, embolization from catheter manipulation in the aortic arch or during cerebral protection device introduction and cerebral hypoperfusion are the main causes of intraprocedural strokes.[1]

The most reported causes of postprocedural stroke after CEA are thrombosis or embolism from the endarterectomy zone. Similarly, after CAS acute stent thrombosis or embolism after plaque protrusion were the most reported. As the time gap from the carotid intervention to procedural stroke increases hyperperfusion syndrome (HS) and intracranial hemorrhage became more likely.[1]

Hemodynamic. In this review, the rate of strokes attributable to hemodynamic depression was extremely variable in both CEA and CAS groups. While in some studies it was negligible, in the ICSS subset analysis it was responsible for up to one-third of events, in both CEA and CAS-related stroke.[12]

Intraprocedural hemodynamic depression is likely to result from manipulation of the carotid sinus and baroreceptor dysfunction. Other potential causes are difficulty in placing the shunt and prolonged clamping (in CEA) or balloon dilation (in CAS). A decrease in blood pressure in the first days after carotid intervention is common with the magnitude being greater in CAS compared with CEA.[27]

A recent study analyzed the full scope of patients with procedural hemodynamic events and correlated them to immediate procedural stroke (defined as occurring intraprocedurally or in the first 6 hours after the operation). There was a 76% decrease in immediate procedural stroke for patients who did not experience a procedural hemodynamic event (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.16-0.35; $P < .001$).[28] This study pointed toward the importance of anticipating and promptly addressing hemodynamic events during carotid revascularization.[29,30]

Hemorrhagic stroke. Procedural hemorrhagic stroke may occur either in the ipsilateral or contralateral hemisphere. Most result from untreated postoperative hypertension and/or as a consequence of HS, especially in patients with reestablishment of flow in previously infarcted cerebral tissue and when anticoagulation or antiplatelet therapy are administered.[29]

HS is a rare clinical entity whose pathophysiology involves dysregulation of the cerebral vascular system in the setting of an increase in cerebral blood flow in both ipsilateral and contralateral hemisphere.[31] It is usually associated with postoperative hypertension and can lead to hemorrhagic transformation. In this review, procedural stroke was attributed to this entity in up to 7.4% and 3.4% of CEA and CAS patients, respectively (Table III). In contrast, a review on HS including 4689 CEA and 4446 CAS procedures reported the incidence of HS after CAS at 1.16% and following CEA at 1.9%.[32]

Embolization. A cerebral deficit caused by carotid embolization can occur intraprocedurally when atherothrombotic debris are released by manipulation of the carotid plaque (lesion traversal and stent insertion in CAS or dissection phase, shunt insertion and shunt dysfunction in CEA). Early postprocedural embolization

may be caused by embolus formation on the endarterectomized surface, a loose intimal flap, or originate from the external carotid artery. Very rarely, embolization occurs in the late postprocedural period.[12]

ICA occlusion. ICA occlusion was the assumed cause of up to 19% of events in both CAS and CEA groups (Table III). The main underlying pathophysiologic mechanism for stroke development after ICA occlusion is brain hypoperfusion, even though distal thromboembolism can also play a role. It is classified as a separate entity from the former two owing to a distinct underlying etiology and treatment. In the past, most ICA thrombotic occlusions in the early post-CEA period have been suggested to be caused by technical error.[33,34] Owing to intraoperative quality measures, the rate of intraoperative stroke in CEA has significantly decrease[35]; an intraoperative duplex scan may identify ICA occlusion and prevent deleterious post-CEA events.

In contrast, a recent review article on acute carotid stent thrombosis concluded that antiplatelet therapy noncompliance was the main cause of stent thrombosis, followed by plaque protrusion.[36] The thrombogenicity of new stent materials in the acute phase may also indicate the need for adjusted antiplatelet therapy in the early periprocedural phase.[18] Consequently, in recent years more and more "aggressive" dual antiplatelet therapy strategies have been established.

Standards for reporting

Procedural stroke is a universal primary outcome in RCTs reporting safety and efficacy of revascularization procedures on carotid artery stenosis (CEA and/or CAS). However, as discussed elsewhere in this article, a myriad of different pathophysiologic mechanisms are encompassed by this definition. We believe that RCTs and administrative dataset registries should record further granular data regarding time of procedural event and most likely etiology and we propose a subclassification into hemodynamic, hemorrhagic, embolic, or ICA-thrombosis related.

The prospective collection of systematic data for classification for stroke mechanism could help additional investigation in this area and is already underway for the Asymptomatic Carotid Surgery Trial-2 (ACST-2).[37] As evidenced in our suggested protocol, initiated and introduced by Gert J. de Borst and currently implemented in the ACST-2 protocol for post hoc analysis (Appendix, online only), the definition of the stroke mechanism should be established by an attending stroke physician, based on the following data: time of procedural event, location and affected territory, severity (mRS) and territory of the stroke. Also, relevant procedural and postprocedural data should be reported to support the inferred stroke mechanism (Appendix, online only).

Study limitations

There are several limitations to this study, including (1) underreporting of the mechanism of procedural stroke in RCT and nationwide registries, (2) the lack of high-quality data, (3) the heterogeneity in the criteria for the definition of the most likely mechanism of stroke, and (4) the lack of data on how procedural strokes were managed discriminated by presumed etiology (especially for intraoperative vs postoperative strokes).

CONCLUSIONS

Because the long-term prevention of stroke is still hampered by a significant number of procedural events, we need to understand the underlying mechanism to take further measures to reduce these potentially preventable neurologic complications owing to the intervention itself. Additional granular data and the use of standards to report on procedural stroke in RCTs and other future prospective research on carotid artery revascularization will facilitate future data comparison and individualized patient data meta-analysis.

AUTHOR CONTRIBUTIONS

Conception and design: APC, JP, GB
Analysis and interpretation: APC, JP, AC, LK, GB
Data collection: APC, AM, GB
Writing the article: APC, AC, LK, AM, GB
Critical revision of the article: APC, LK, GB
Final approval of the article: APC, JP, AC, LK, AM, GB
Statistical analysis: APC
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Overall responsibility: GB

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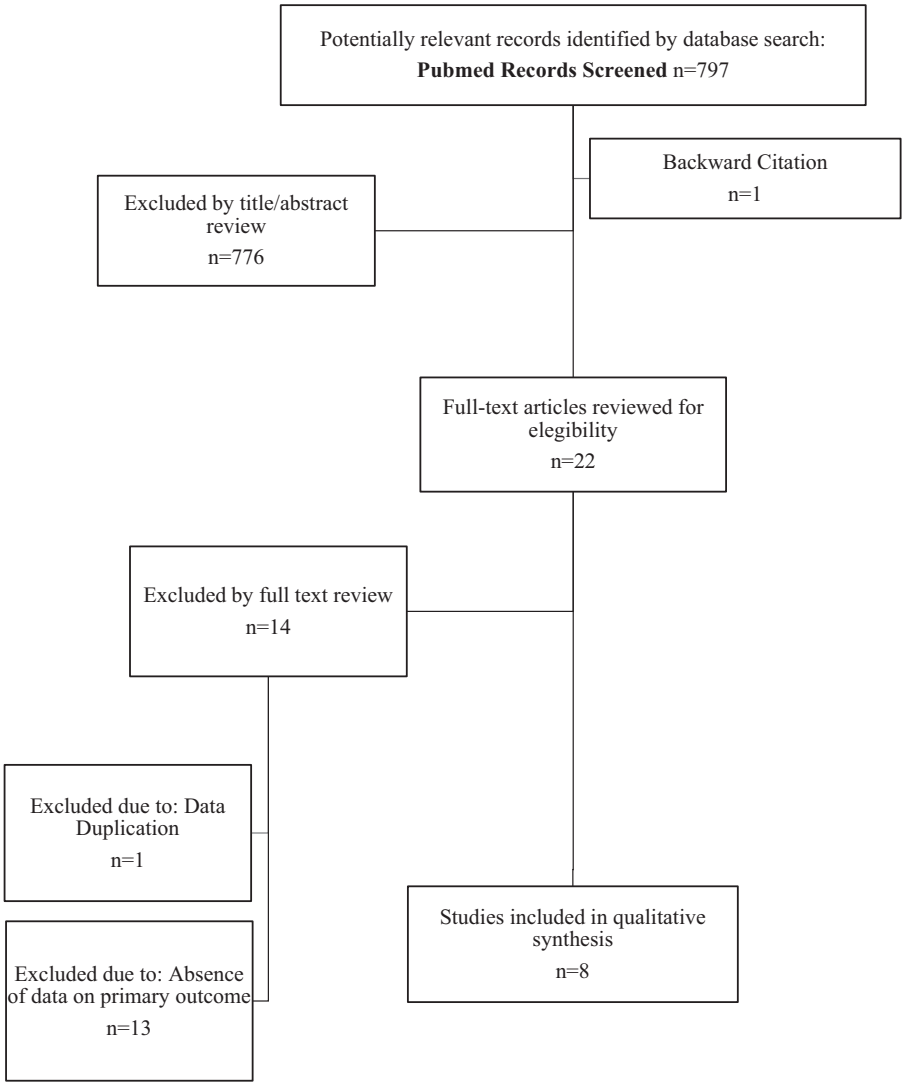

Supplementary Fig (online only). PRISMA diagram summarizing literature screening process.

Supplementary Table (online only). Methodologic quality assessment of included articles: Methodological Index for Non-Randomized Studies (*MINORS*) score

	Lareyre et al,[7] 2017	Huibers et al,[36] 2016	Huiberset al,[11] 2015	Hill et al,[37] 2012	Fairman et al,[38] 2007	Rapp et al,[10] 2007	de Borst et al,[39] 2001	Jacobowitz et al,[12] 2001
A clearly stated aim	2	2	2	2	2	2	2	2
Inclusion of consecutive patients	2	2	2	2	2	2	2	2
Prospective collection of data	0	2	2	2	2	2	2	0
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2
Unbiased assessment of the study end point	0	0	0	0	2	2	0	0
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2
Loss to follow-up of <5%	2	2	2	2	2	2	2	2
Prospective calculation of the study size	0	0	0	0	0	0	0	0
Additional criteria for a comparative study								
An adequate control group	–	–	2	2	–	–	–	–
Contemporary groups	–	–	2	2	–	–	–	–
Baseline equivalence of groups	–	–	2	2	–	–	–	–
Adequate statistical analyses	–	–	0	0	–	–	–	–
Total MINORS score	10	12	18	18	14	14	12	10
Maximum possible score	16	16	24	24	16	16	16	16
Quality assessment	–	–	–	–	–	–	–	–