PhD PROGRAMME in

CARDIOVASCULAR SCIENCES at Faculty of Medicine of the University of Porto

CAROTID ARTERY ATHEROSCLEROTIC DISEASE: TIMING OF INTERVENTION, PROCEDURAL OUTCOMES AND PATIENT REPORTED OUTCOME MEASURES

Andreia Pires Coelho

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FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

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DOENÇA ATEROSCLERÓTICA CAROTÍDEA: *TIMING* DE INTERVENÇÃO, *OUTCOMES* PERI-PROCEDIMENTO E MEDIDAS DE *OUTCOME* REPORTADOS PELO DOENTE

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ABBREVIATIONS

ABBREVIATIONS

95% CI. 95 Percent Confidence Interval

ACES. Asymptomatic Carotid Emboli Study

ACS. Asymptomatic Carotid Stenosis

ACSRS. Asymptomatic Carotid Stenosis and Risk of Stroke

ACST. Acute Carotid Stent Thrombosis

ACST-1. Asymptomatic Carotid Surgery Trial

ACST-2. Asymptomatic Carotid Surgery Trial

ACT-1. Asymptomatic Carotid Trial

BMT. Best Medical Treatment

CAS. Carotid Artery Stenting

CCA. Common Carotid Artery

CEA. Carotid Endarterectomy

CHUP. Centro Hospitalar Universitário do Porto

CHVNG/E. Centro Hospitalar Vila Nova de Gaia e Espinho

CME. Continuing Medical Education

CRD. Chronic Renal Disease

CREST. Carotid Revascularization Endarterectomy Versus Stenting Trial

DAPT. Dual Antiplatelet Therapy

DLS. Dual-Layer Stent

DM. Diabetes Mellitus

ECA. External Carotid Artery

ECST. European Carotid Surgery Trial

ESO. European Stroke Organization

ESVS. European Society for Vascular Surgery

EVA-3S. Endarterectomy Versus Stenting in Patients with Symptomatic Severe Carotid Stenosis

FEBVS. Fellow of the European Board of Vascular Surgery

FMUP. Faculty of Medicine of the University of Porto

HR. Hazard Ratio

ICA. Internal Carotid Artery

ICSS. International Carotid Stenting Study

IT. Intracranial Thrombectomy

IVT. Intravenous thrombolysis

MI. Myocardial Infarction

mTICI. Modified Treatment In Cerebral Ischemia

NASCET. North American Symptomatic Carotid Endarterectomy Trial

NIHSS. National Institutes of Health Stroke Scale

PROM. Patient Reported Outcome Measures

OR. Odds Ratio

QALY. Quality of Life-adjusted life year

QoL. Quality of Life

RCT. Randomized Controlled Trial

SAPPHIRE. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy

SD. Standard Deviation

SE. Standard Error

sICH. Symptomatic Intracranial Haemorrhage

SPACE. Stent Protected Angioplasty Versus Carotid Endarterectomy

SVS. Society for Vascular Surgery

TCAR. Transcarotid Artery Revascularization

TFCAS. Transfemoral Carotid Artery Stenting

TIA. Transient Ischemic Accident

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ABSTRACT

ABSTRACT

Carotid artery atherosclerotic disease is one of the main causes of ischemic stroke and transient ischemic accident (TIA) with estimates that up to 10-15% of all strokes follow thromboembolism from a previously asymptomatic internal carotid artery stenosis. Currently, carotid endarterectomy (CEA) is the gold standard for carotid artery revascularization. However, several technical developments may have unbalanced the relationship between CEA and carotid artery stenting (CAS). Also, in the acute phase after stroke, the optimal timing for intervention within the accepted 14-day interval is still under debate.

The aim of this thesis was to create more insight regarding carotid artery revascularization, exploring carotid intervention in the acute phase after stroke (**Part I**) and researching the duality between CAS and CEA, including analysis of the physiopathology of procedural stroke, of technical developments in CAS and of complementary outcomes to compare the different carotid interventions (**Part II**).

In **Chapter 1** the authors performed a systematic review and meta-analysis addressing the problematic of carotid artery revascularization in patients with tandem lesions (synchronous carotid artery stenosis and intracranial thrombus). **Chapter 2** focuses on the identification of the optimal timing for carotid artery intervention within the 14-day time frame for intervention after stroke.

Part II is dedicated to studying the duality CEA versus CAS. In **Chapter 3** the authors focus on resuming the different mechanisms of procedural stroke after CEA/CAS and on the development of standards of reporting of procedural stroke for future research studies. **Chapters 4** and **5** focus on the analysis of CAS technical developments: Transcervical Artery Revascularization (TCAR) and Dual-Layer Stents, respectively, which have been developed to reduce the risk for different mechanisms of procedural stroke. **Chapter 6** is a systematic review on acute carotid stent thrombosis with the final purpose of reporting on predictive factors, clinical presentation and early management. Finally, **Chapter 7** is a modified Delphi study with the purpose of defining a disease-specific patient reported outcome measure (PROM) for carotid artery stenosis.

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RESUMO

RESUMO

A doença aterosclerótica carotídea é uma das principais causas de acidente vascular cerebral (AVC) e de acidente isquémico transitório (AIT). Estima-se que cerca de 10-15% de todos os AVC ocorram após tromboembolismo com origem em estenose carotídea previamente assintomática. A endarterectomia carotídea (CEA) é atualmente o *gold standard* para revascularização carotídea, mas vários desenvolvimentos técnicos podem ter causado um desequilíbrio da relação entre a CEA e o *stenting* carotídeo (CAS). Adicionalmente, na fase aguda pós-AVC, o *timing* ótimo para realização de intervenção carotídea dentro do intervalo definido de 14 dias é ainda controverso.

O objetivo desta *Tese* foi ampliar o conhecimento na área da revascularização carotídea explorando a intervenção carotídea em fase aguda (**Parte I**) e investigando a dualidade entre CAS e CEA, incluindo uma análise da fisiopatologia do AVC peri-procedimento, dos desenvolvimentos técnicos na área do *stenting* carotídeo e de *outcomes* complementares para comparar diferentes abordagens à intervenção carotídea (**Parte II**).

No **capítulo 1** os autores desenvolveram uma revisão sistemática e meta-análise abordando a revascularização carotídea em doentes com lesões em *tandem* (estenose carotídea síncrona com trombo intracraniano). O **capítulo 2** foca-se na identificação do *timing* ótimo para intervenção carotídea dentro do intervalo de 14 dias previamente definido.

A **parte II** é dedicada a investigar a dualidade entre CEA e CAS. No **capítulo 3** os autores focaram-se no estudo dos diferentes mecanismos de AVC peri-procedimento após CEA/CAS e no desenvolvimento de *standards* para reportar AVC peri-procedimento para investigação futura. Os **capítulos 4** e **5** focam-se na análise de desenvolvimentos técnicos na área de CAS: revascularização carotídea transcervical e *stents* de dupla-camada, respetivamente, desenvolvidos para reduzir o risco de diferentes mecanismos de AVC peri-procedimento. O **capítulo 6** é uma revisão sistemática de trombose aguda de *stent* carotídeo com o objetivo de reportar fatores preditivos, apresentação clínica e abordagem precoce. Finalmente, o **capítulo 7** é um estudo Delphi modificado com o

objetivo de desenvolver uma medida de *outcome* reportada pelo doente (PROM) específico para doença aterosclerótica carotídea.

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INTRODUCTION

INTRODUCTION

The World Health Organization (WHO) defines stroke as ‘‘rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin”. (1) In Portugal, stroke remains the leading cause of death and permanent disability. Data from Direção Geral de Saúde (DGS) estimates an incidence of 2 cases/1000 habitants/year, with a mortality rate of 30% in the first year and 40% permanent disability in first-year survivors. (2)

Carotid artery atherosclerotic disease is one of the main causes of ischemic stroke and transient ischemic accident (TIA). It is estimated that up to 10-15% of all strokes follow thromboembolism from a previously asymptomatic internal carotid artery stenosis. (3)

Secondary or tertiary prevention can be attained with best medical treatment (BMT) alone or in combination with carotid artery revascularization. Even though carotid artery revascularization has been extensively studied, several questions remain unanswered which can be organized into three subjects: 1. in asymptomatic carotid artery stenosis, who to intervene; 2. in symptomatic carotid artery stenosis when to intervene; 3. how to intervene - carotid endarterectomy (CEA) versus carotid artery stenting (CAS). For the purpose of the present thesis, questions 2 and 3 will be addressed as follows:

1. Acute Phase After Stroke

Regarding carotid artery revascularization in the acute phase after stroke, the optimal timing for intervention within the 14-day interval is still under debate. The Swedish Vascular Registry (SWEDVASC) was the first to highlight concerns about intervening less than 48 hours of the index event, as they observed an 11.5% rate of 30-day death/stroke, compared with 3.6% (3-7 days), 4% (8-14 days) and 5.4% (>14 days) for CEA. (4) Other (larger) national registries have not corroborated the SWEDVASC findings (5) and a temporal trend towards a progressive decrease in delays from index event to undergoing CEA (or CAS) has been reported. (6-8)

On the other hand, developments in the treatment of acute stroke lead to an increasingly interventive attitude. Endovascular intracranial thrombectomy (IT) has established itself as the standard of care in treating large-vessel anterior circulation acute ischemic stroke (AIS). The combination of extracranial internal carotid artery (ICA) occlusion with synchronous intracranial thrombus represents 10-20% of all strokes, and such tandem lesions are strongly associated with poor patient outcome, severe disability and death. (9) Safety and efficacy of synchronous treatment of tandem lesions is under debate and the timing of carotid intervention in this setting is particularly controversial.

2. Carotid Artery Revascularization: CEA versus CAS

Probably the most studied question in the literature regarding carotid artery revascularization is the duality between CEA and CAS. A meta-analysis of pooled data from randomized controlled trials (RCTs) on symptomatic and asymptomatic patients revealed a significantly higher risk of procedural stroke with transfemoral CAS (TF-CAS) as compared with CEA. (10) However, if the procedural risk of stenting could be further reduced, CAS could assume an ever increasing role in clinical practice for long-term stroke prevention.

Procedural stroke is currently the Achilles' heel of CAS and it can present a myriad of physiopathologic mechanisms that must be clearly understood in order to further reduce its incidence. Several CAS technical developments have been achieved over time to overcome specific physiopathologic mechanisms of procedural stroke, but neither has been able to address the issue in a more comprehensive manner. Also, continuing introduction of technical developments has not been necessarily accompanied by evidence of non-inferiority (versus CEA).

On the other hand, the addition of validated Patient Reported Outcome Measures (PROM) to hard clinical outcomes (i.e. 30-day stroke, myocardial infarction and death) in patients undergoing carotid artery revascularization, could provide valuable data on quality of care and impact of treatment, especially as hard clinical outcomes are increasingly rare and comparison between different approaches to carotid artery stenosis becomes increasingly difficult based solely on these outcomes. (11)

The aim of this thesis was to create more insight regarding carotid artery revascularization, exploring carotid intervention in the acute phase after stroke (Part I) and researching the duality between CAS and CEA, including analysis of procedural stroke, of technical developments in CAS and of complementary standards to compare the different types of carotid intervention (Part II).

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PART I

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CHAPTER 1

OVERVIEW OF EVIDENCE ON EMERGENCY CAROTID STENTING IN PATIENTS WITH ACUTE ISCHEMIC STROKE DUE TO TANDEM OCCLUSIONS: A SYSTEMATIC REVIEW AND META- ANALYSIS

CHAPTER 1. Overview of Evidence on Emergency Carotid Stenting in Patients with Acute Ischemic Stroke due to Tandem Occlusions: A Systematic Review and Meta- Analysis

Systematic review and meta-analysis of the literature published in The *Journal of Cardiovascular Surgery*, indexed to PubMed/MEDLINE journal

- CiteScore of 3.0
- CiteScore Highest Percentile - Surgery - 66% (Second Quartile)
- Journal Impact Factor of 1.595

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Overview of Evidence on Emergency Carotid Stenting in Patients with Acute Ischemic Stroke due to Tandem Occlusions: A Systematic Review and Meta-Analysis

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Overview of Evidence on Emergency Carotid Stenting in Patients with Acute Ischemic Stroke due to Tandem Occlusions: A Systematic Review and Meta-Analysis

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Abstract

Introduction:

Endovascular intracranial thrombectomy (IT) has established itself as the standard of care in treating large-vessel anterior circulation acute ischemic stroke (AIS). However, internal carotid artery (ICA) stenosis/occlusion hampers distal access and controversy about simultaneous emergency ICA stenting ensues.

The purpose of this review was to evaluate the safety of emergency ICA stenting in combination with IT for AIS with tandem occlusions. To our knowledge this is the first meta-analysis to evaluate emergency ICA stenting in tandem occlusions, combining results from studies with a control group.

Evidence Acquisition:

A systematic review and meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

Evidence Synthesis:

A total of 649 potentially relevant articles were initially selected. After reviewing at title or abstract level, 87 articles were read in full and 23 were included. These studies recruited 1000 patients, 220 submitted to IT with no emergency ICA stenting and 780 to IT and emergency ICA stenting.

Successful revascularization (Thrombolysis in cerebral infarction scale - TICI≥2b) was achieved in 48.6-100%. Good outcome (modified Rankin scale - mRS≤2) ranged from 18.2-100%. Symptomatic intracranial haemorrhage (sICH) ranged from 0-45.7% (overall n=168; 17.2%). Mortality at 90 days ranged from 0-45.4% (overall n=114; 11.7%). Time to recanalization was significantly longer in the stenting group with an overall mean difference of 1.76 (95% Confidence Interval: 1.59-1.93).

Conclusions:

In this meta-analysis time to recanalization was significantly longer in the emergency ICA stenting group. There was no benefit from emergency stenting in parameters such as successful revascularization (TICI≥2b), clinical outcome (mRS≤2) or 90-day mortality. Data on sICH were scarce.

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Emergency ICA stenting appears to increase time to revascularization and increase the risk of complications with no demonstrated clinical benefit. Furthermore, no prospective, randomized controlled trials demonstrating relative efficacy and safety of concomitant ICA stenting have been published to date. Additional studies must be undertaken to define the role of angioplasty and stenting of the extracranial carotid arteries in the early management of acute stroke in tandem occlusions. Until then, we recommend that ICA stenting concommintant to thrombectomy in acute stroke patients should be avoided

Keywords

Stroke (MeSH); Carotid stenosis (MeSH); Endarterectomy, Carotid (MeSH); Stents (MeSH); Thrombectomy (MeSH); Thrombolytic therapy (MeSH);

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Manuscript

Introduction

Despite recent advances in the understanding, management and treatment of acute ischaemic stroke (AIS), it continues to represent a significant challenge. Endovascular Thrombectomy (ET) in association with intravenous thrombolysis has recently established itself as the new standard of care in treating large-vessel anterior circulation AIS, with 5 large volume randomized controlled trials demonstrating its superiority over isolated intravenous thrombolysis (IVT). (1) (2) (3) (4, 5) However most of these trials excluded patients with concomitant steno-occlusive disease of the extracranial circulation.

The combination of extracranial internal carotid artery (ICA) occlusion with synchronous intracranial thrombus represents 10-20% of all strokes, and such tandem lesions are strongly associated with poor patient outcome, severe disability and death. (6) (7)

Tandem lesions respond poorly to the administration of intravenous thrombolytic (IVT) within 4.5 hours of stroke onset. Therefore, treatment of acute stroke in this subgroup of patients remains a dilemma as they respond poorly to IVT and have been consistently excluded from high-volume randomized trials of endovascular treatment of acute ischemic stroke. (8) (9)

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Although endovascular thrombectomy seems a viable solution to the significant clot burden in the intracranial circulation, distal access in patients with ICA occlusion/stenosis is hampered. (10)

Carotid Artery Stenting (CAS) in the acute stage remains challenging because of the limited therapeutic window, the possible risk of hyperperfusion syndrome after revascularization and the subsequent risk of postinterventional symptomatic intracranial hemorrhage (sICH), which may be influenced by the mandatory aggressive antiplatelet medication after stent-placement (7) On the other hand, acute stent thrombosis is also a potential serious complication, and dual-layer stents seem to have a higher risk of acute occlusion when compared to single-layer. (11)

CAS is also associated with a non-negligible risk of procedural associated stroke. Mechanical irritation of atherosclerotic lesions by wires and catheters can release particles, which may embolize towards the brain and cause serious neurologic complications.

Data analysis from the Carotid Stenosis Trialists' Collaboration showed that the early days after plaque rupture carry a high risk for periprocedural complications after carotid artery stenting. The analysis of a large register series showed, that carotid artery stenting carried a significantly higher risk for complications in patients with and without cerebral infarction when performed within 48 hours after the onset of symptoms. (12)

Small retrospective studies have been published describing two diferent approaches to tandem occlusions, as distal access for mechanical intracranial thrombectomy is physically hampered (13) . The antegrade approach involves stent-assisted carotid angioplasty followed by intracranial thrombectomy. The retrograde approach involves intracranial thrombectomy with carotid angioplasty if necessary, and selective ICA stenting is considered after successful intracranial thrombectomy. Both procedures have specific advantages and disadvantages. (14) Also, bypassing the occluded ICA can be possible using collateral pathways through anterior or posterior communicating arteries for distal recanalization. (15)

A recent systematic review performed on acute anterior ischemic stroke with tandem occlusions treated with stent retriever and acute carotid stenting included 11

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observational studies with no control group and concluded emergency stent placement in the extracranial ICA in combination with anterior circulation thrombectomy is associated with 16% risk of sICH, probably related to early administration of antiplatelet therapy. (16) The risk of acute stent thrombosis is still underreported in the literature, but single-center reports can reach 17-21.3%. (17, 18)

The purpose of this review was to evaluate the feasibility of emergency carotid stent placement in combination with intracranial thrombectomy for acute ischemic stroke with tandem occlusions. We did not identify any meta-analysis performed with the purpose of evaluating emergency ICA stenting in tandem occlusions, combining results from studies with control group.

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. (19) (20)

Evidence Acquisition:

Search Strategy

Literature search was updated last on October 2017. Using the MEDLINE database and the following query "(stroke OR acute stroke) AND (((carotid occlusion OR carotid stenosis OR carotid thrombosis OR carotid stenting OR carotid acute stenting) AND (thrombectomy OR intra-cranial lesion OR intra-cranial thrombosis OR stent retriever)) OR (tandem occlusion OR tandem lesions OR tandem carotid lesion OR acute tandem))", a literature search was performed.
Using Scopus database and the following query *(TITLE-ABS-KEY (* stroke *AND* "carotid occlusion" *AND (* "tandem occlusion" *OR* thrombectomy *OR* "intra-cranial lesion" *OR* "intra-cranial thrombosis" *OR* "stent retriever" *OR* "tandem occlusion" *OR* "tandem lesions" *OR* "tandem carotid lesion" *)) OR TITLE-ABS-KEY (* stroke *AND* "carotid stenosis" *AND (* "tandem occlusion" *OR* thrombectomy *OR* "intra-cranial lesion" *OR* "intra-cranial thrombosis" *OR* "stent retriever" *OR* "tandem occlusion" *OR* "tandem lesions" *OR* "tandem carotid lesion" *)) OR TITLE-ABS-KEY (* stroke *AND* "carotid thrombosis" *AND (* "tandem occlusion" *OR* thrombectomy *OR* "intra-cranial lesion" *OR* "intra-cranial thrombosis" *OR* "stent

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retriever" *OR* "tandem occlusion" *OR* "tandem lesions" *OR* "tandem carotid lesion" *)) OR TITLE-ABS-KEY (* stroke *AND* "carotid stenting" *AND (* "tandem occlusion" *OR* thrombectomy *OR* "intra-cranial lesion" *OR* "intra-cranial thrombosis" *OR* "stent retriever" *OR* "tandem occlusion" *OR* "tandem lesions" *OR* "tandem carotid lesion" *)) OR TITLE-ABS-KEY (* "tandem occlusion" *OR* "tandem lesions" *OR* "tandem carotid lesion" *)) AND PUBYEAR* > 2009, a second literature search was performed.

The eligibility criteria included any publication reporting acute ischemic stroke attributable to tandem occlusion who had received endovascular treatment regardless of the study design. Tandem occlusion was defined as an extracranial ICA stenosis associated with an occlusion of the intracranial segment of the ICA or the initial segment of the MCA.

Only articles that used intracranial thrombectomy devices or those where we could extract the data on intracranial thrombectomy devices were included. Only studies with more than 1 case of stroke associated with tandem occlusion were included in our analysis to minimize the chance of anecdotal outcomes. Potentially relevant articles at title or abstract level were identified and the full text was obtained for detailed review. Exclusion criteria were defined as follows: Articles published before 2010; Language other than Portuguese and English; Not human research; Single case report, systematic review and meta-analysis; Articles with no cases of tandem lesions; Articles with no stent-retriever use; Articles with no cases of acute carotid stenting; Articles referring to carotid artery dissection or any other aetiology other than atherosclerosis for anterior circulation stroke.

Demonstration of the conduction of the search as proposed, using a PRISMA diagram is demonstrated in Figure 1.

Each study had to report recanalization rates, functional neurological outcomes symptomatic intracerebral haemorrhage (sICH) rates, and mortality rates. Successful recanalization was defined as "thrombolysis in cerebral infarction" (TICI) ≥2b revascularization of the MCA.(21) Favourable outcome was defined as modified Rankin Scale (mRS) ≤2 at 90 days.(22) Mortality was evaluated at discharge or 90 days as determined by each author. According to European Cooperative Acute Stroke Study II (ECASS-II) (16) sICH was defined as any parenchymal hematoma, subarachnoid

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haemorrhage, or intra- ventricular haemorrhage associated with worsening of the National Institutes of Health Stroke Scale (NIHSS) score by ≥4 within 24 h.

Data extraction and assessment of study quality

Two reviewers initially screened the identified studies. Further assessment of articles that potentially met inclusion criteria was performed using the full text. (Figure 1)

The reviewers systematically assessed the methodology of the studies and extracted data. Newcastle Ottawa Score was applied for assessing the quality of studies

Data collected and analysed included baseline NIHSS, baseline mRS, rate of thrombolysis, time to recanalization (minutes), rate of TICI≥2b, in-hospital or 90-day mortality, sICH, rate of 90-day mRS≤ 2 and rate of ICA thrombosis. An attempt was made to contact authors when information was missing. Authorship of the studies was not masked from the reviewers.

The main limitations of studies were as follows: no prespecification of selection criteria for the study population; no justification of sample size; no independent assessment of outcome measures across all study participants. Risk of bias assessment was systematically performed.

Statistical analysis

The software WinPepi was used to analyse data. Odds ratios (OR) and 95 per cent confidence intervals (c.i.) were used for dichotomous variables, and mean differences (MDs) with 95 per cent c.i. for continuous data.

Statistical heterogeneity, defined as a measure of the variability of outcomes between studies, was assessed by means of the χ^2 test, with $P < \cdot 100$ assumed to indicate significant heterogeneity. The degree of heterogeneity was quantified by the I^2 statistic. A random-effects model was used for meta- analysis if I^2 exceeded 50 per cent; otherwise a fixed-effect model was applied. Meta-analysis was performed when data for an outcome were available from two or more studies.

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Evidence Synthesis

A total of 649 potentially relevant articles were initially selected. After reviewing the records at title or abstract level, 87 articles were read in full and 21 were judged eligible for inclusion. Backword citation lead to the inclusion of 2 additional articles. (Figure1)
Two studies were prospective whereas 20 studies were retrospective in design. All studies but 3 were single centre. Seven studies were comparable with two groups: intra-cranial thrombectomy with ICA stenting or intra-cranial thrombectomy with no ICA stenting. The remaining studies evaluated intracranial thrombectomy with ICA stenting with no control group. When studies reported data on patients with no tandem occlusion, only data on patients with tandem occlusion were extracted. The 23 studies were evaluated in qualitative synthesis. Of the 7 studies with control group, data for quantitative synthesis (meta-analysis) was extracted from 4 studies. The methodological quality of trials and risk of bias is outlined in table 1.

Outcomes

The 23 studies recruited 1000 patients, 222 patients submitted to intracranial thrombectomy with no ICA stenting and 780 patients submitted to intracranial thrombectomy and emergency ICA stenting in the same procedure. It is noteworthy that all 244 patients in the control group came from 4 studies. No difference was reported between patients in both groups - "ICA stent" and "No ICA stent" (control group). Performance or not of ICA stenting was left to interventionist's discretion. Only information on patients with tandem occlusions was considered in this study.
All studies reported on the percentage of patients submitted to intravenous thrombolysis, 90-day mRS ≤ 2 and in-hospital or 90-day mortality. Most studies reported on patient age (n=22), patient gender (n=18), time to recanalization (n=17), successful recanalization as TICI $\geq$2b (n=21), symptomatic post-procedure haemorrhage as sICH (n=20) and thrombectomy device used in the procedure (n=22).
Patient mean age was similar throughout all studies, ranging from 51.6 to 68.7 years. The majority of patients were male, ranging from 41% of the total and 85.7%. A stent retriever device was used in the majority of the intracranial thrombectomy procedures (Solitaire®, Trevo Pro®, Merci® and Penumbra®). (Table 2)

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Average procedural duration ranged from 51 to 102 minutes. (Table 2) Some studies specify the difference in procedural time between antegrade and retrograde approach, and one study concluded that mean angiography time in minutes was significantly shorter in the retrograde approach (43.1±30.8 Vs 11±0.843; p<.001) (23)

Mean NIHSS at admission ranged from 12.6 to 23.4. (Table 2)

Intravenous thrombolysis prior to endovascular procedure was performed in 0% to 92%, but excluding two studies with discrepant values all remaining studies had intravenous thrombolysis in over 40% of cases. (Table 2)

Successful revascularization (TICI ≥2b) was achieved in 48.6% to 100% of patients.

Good outcome defined as mRS ≤2 had heterogeneous values ranging from 18.2% to 100%. (Table 3)

Mortality at 90 days occurred in a total of 114 patients (11.7%) ranging from 0% to 45.4% in the literature. (Table 3)

sICH ranged from 0% to 45.7%, overall affecting a total of 168 patients (17.2%). Although it was extremely variable, in one study 9 patients (20.9%) died during hospital stay, 55.6% of which as a result of sICH, all submitted to emergency stenting. (24) It is noteworthy that two of the largest series published on tandem occlusion releases no data on sICH. Malik *et al* makes no reference to intracranial haemorrhage (25). Grigoryan et al references intracranial haemorrhage according to European Cooperative Study Stroke Criteria (26), with 18% parenchymal haemorrhage not releasing data on the proportion of symptomatic patients. (27)

On the other hand, despite rather uniform protocols of a loading dose of clopidogrel (600mg) followed by maintenance of both aspirin (100mg) and clopidogrel (75mg) starting the day after the procedure, patients that received ICA stenting had a non-insignificant rate of ICA stent thrombosis. Studies that reported specifically ICA stent thrombosis had a rate that ranged from 0-21.3%. (Table 3) Steglich-Arnholm et al, reported eight (17%) acute stent thrombosis during procedure in adition to four (8.5%) late stent thrombosis. (17)

In 4 publications, there were two groups of patients whether emergency stenting was performed or not and data extraction on each group was possible.

The two groups were compared considering age, gender and NIHSS at admission. Gender was significantly different between groups, with a higher prevalence of male sex in the stenting group, with an overall odds ratio of 5.88 (95% c.i. 2.35, 14.72). Age was not statistically significantly different between groups with an overall mean

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difference (MD) of -1.30 (95% c.i. -4.91 to 2.32). Nor was there a significant difference between baseline NIHSS between groups (overall mean difference 0; 95% c.i. -0.95 to 0.95). (Figure 2)

Thrombolysis was performed prior to the endovascular procedure in the majority of patients in both groups. The rate of patients submitted to thrombolysis was no different between groups (OR 1.02; 95% c.i. 0.53 to 1.98).

Time to recanalization was significantly longer in the stenting group with an overall mean difference of 1.76 (95% c.i. 1.59 to 1.93). (Figure 3)

Successful revascularization expressed as TICI ≥ 2b was no different between groups (OR 1.08; 95% c.i. 0.52 to 2.25). (Figure 4A)

Data on sICH at 90 days evidenced no difference between groups (OR 2.06; 95% c.i. .82 to 5.15). (Figure 4B)

Modified Rankin Scale (mRS) ≤2 is established as a marker of good outcome. There was no statistically significant difference between both groups (OR 1.17; 95% c.i. 0.72 to 1.93). (Figure 4C)

In-hospital mortality and 90-day mortality were also evaluated outcomes, with no difference between groups (OR1.41; 95% c.i. 0.65 to 3.06). (Figure 4D)

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Conclusions

To our knowledge this is the first systematic review and meta-analysis performed to evaluate emergency ICA stenting in tandem occlusions, combining results from studies with control group (patients submitted to endovascular thrombectomy with no simultaneous emergency stenting). A major concern with the quantitative analysis would be the comparability between "ICA stent" and "no ICA stent groups". On the one hand baseline NIHSS score was no different between groups (overall mean difference 0.14; 95% c.i. -0.76 to 1.08). On the other hand, studies are not clear about the criteria adopted for deciding whether or not to perform ICA stenting. Most studies state selective stenting, apparently left to interventionist's discretion.

The aim of any stroke treatment must be to successfully revascularize as soon as possible. In tandem occlusion, the primary cause of symptoms and clinical outcome are mainly because of thrombus in the intracranial arteries rather than occlusion of the cervical ICA. (28)

Traversing an acutely occluded cervical ICA and emergent stent placement seems to have a high recanalization rate but also takes time to perform, during which brain infarction may be expanding. (18) Additionally, time-consuming complex procedures are associated with increased potential risk for complications. (15, 29)

Mpotsaris et al described that ICA emergency stenting prolonged the procedure by an average 10 minutes, whereas Stampf et al described an excess 20 minutes in the procedure.(30) (7) In this meta-analysis, time to recanalization was significantly longer in the emergency ICA stenting group compared with no stenting with an overall odds ratio 1.76 (95% c.i. 1.59 to 1.93). (Figure 6)

Revascularization time is significantly shorter in patients submitted to retrograde

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approach or "thrombectomy first". (4) Recanalization of an occluded cervical carotid before treatment of the intracranial lesion can delay the time to distal recanalization and thus potentially lead to less favorable outcome (31) One study reported mean angiography time was significantly shorter in the retrograde approach (43.1±-30.8 Vs 110.8±43; p<.001) (23)

One of the major concerns in patients submitted to emergent stent placement is the risk of postinterventional symptomatic intracranial hemorrhage (sICH), which may be influenced by the mandatory antiplatelet medication of the stent-placement procedure or it may be due to hyperperfusion syndrome.

The reported rate of sICH in tandem occlusions varies considerably in the literature, ranging from 0-45.4% and it might impose a higher risk for added morbidity and mortality in the post interventional phase. (32) Maurer et al described 5 cases (12.8%) of death due to sICH in the ICA emergency stenting group. (24) One of the largest studies on treatment of tandem occlusions that included 170 patients reported a 9% rate of sICH with a mortality rate of 73%. (32)

A logistic regression model for prediction of sICH according to European-Australasian Acute Stroke Study II Criteria concluded acute phase stenting was associated with an odds ratio of 7.307 for sICH. (33) Also the analysis of a large registry series, showed that carotid artery stenting carried a significantly higher risk for complications in patients with and without cerebral infarction when performed within 48 hours after the onset of symptoms. (12)

It is noteworthy that data on sICH are frequently missing, even though it is one of the most feared complications of tandem occlusion endovascular treatment. Two of the largest series on tandem occlusions do not report sICH. (25) (27) Quantitative analysis on sICH in this meta-analysis was hampered by the lack of data, with only two studies reporting the event adequately, so conclusions regarding emergency stenting are compromised. Dorado et al, concluded in their study comparing patients with tandem occlusions that were submitted or not to emergency stenting that emergency stenting is associated with an increased risk of sICH. (33) Akpinar et al, reported 15 cases in which tandem occlusions were treated with emergent intracranial thrombectomy, followed by CAS in another session (10-30 days after the initial procedure) if post-thrombectomy

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mRS ≤2. They concluded carotid angioplasty-assisted mechanical thrombectomy without urgent stenting seems a safer approach. (34)

Other concerns with emergent CAS include procedure´s technical feasibility, including the fact that it is time-consuming, the difficulty in stent insertion under severe stenosis or occlusion and the risk of distal embolization caused by manipulation of highly vulnerable plaque. The risk for acute in-stent stenosis/thrombosis is not insignificant, carrying potential complications, such as cerebral hypoperfusion syndrome. Steglich-Arnholm et al, reported eight (17%) acute stent thrombosis during procedure in addition to four (8.5%) late stent thrombosis, and they correlated the risk of in-stent thrombosis with procedural complexity and prolonged interventions. (17)

Finally, effectiveness of emergency stenting in improving patients neurologic deficits and long term outcomes have not been demonstrated. (35) In this meta-analysis there was no benefit from emergency stenting in parameters such as successful revascularization (TICI≥2b), good clinical outcome (mRS ≤2) or 90-day mortality.

Therefore, data on endovascular treatment for tandem occlusions are scarce, and no completed prospective, randomized controlled trials demonstrating relative efficacy and safety of angioplasty and stenting of the extracranial carotid in acute ischemic stroke has been published to date.(36)

As for quality of the evidence, the studies were all level III evidence, from observational studies only. No randomized controlled trials were identified. In only three studies were patients in each group matched in terms of demographics and anatomic factors of the repair.

As for conclusion, in this meta-analysis there was no apparent clinical benefit from emergency stenting, with significantly increased time to recanalization and exposure to potential hazardous consequences from SICH and acute stent thrombosis. A conservative approach would be salvage balloon dilatation of the ICA stenosis to complete intracranial thrombectomy and once patient stability and lack of haemorrhagic transformation of stroke was ascertained, carotid endarterectomy or carotid stenting could be performed.

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The relative role of endovascular versus surgical revascularization of the extracranial carotid artery in acute stroke remains to be determined, regardless of being tandem or single lesions. No studies have yet been performed to compare the utility of these alternative approaches for revascularization of the extracranial internal carotid artery in acute stroke. Additional studies must be undertaken to define the role of angioplasty and stenting of the extracranial carotid arteries in the early management of acute stroke in tandem occlusions. Until then, we recommend that ICA stenting concommintant to thrombectomy in acute stroke patients should be avoided
(36)

Disclosures: None

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Titles Of Tables

Table 1 – Methodological quality and risk of bias in included trials ; NOS: Newcastle-Ottowa Scale; NA: not applicable;

Table 2 – Qualitative analysis of included publications; SD – Standard deviation; ICA - Internal Carotid Artery; NA, Non-Applicable.

Table 3 - Qualitative analysis of included publications; * Yilmaz *et al* presented diferent ICA stent thrombosis rate depending on whether dual-layer or single-layer stents were used (45% versus 3.7%; p=0.001; odds ratio, 21.3; 95% confidence interval, 2.4-188.4); mRS – modified Rankin Scale; sCIH – Symptomatic intracerebral haemorrhage; SD – Standard deviation; TICI – Thrombolysis in cerebral infarction; ICA - Internal Carotid Artery; NA, Non-Applicable.

Titles of Figures

Figure 1 – PRISMA diagram summarizing literature screening process. PRISMA - Preferred Reporting Items for Systematic reviews and Meta-Analyses

Figure 2 - Forest Plot showing the mean difference in baseline NIHSS. A Mantel-Haenszel fixed effect model was used for meta-analysis. Mean differences are shown with 95% confidence intervals. NIHSS – National Institutes of Health Stroke Scale.

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Figure 3 - Forest Plot showing the mean difference in time to recanalization (hours). A Mantel-Haenszel fixed effect model was used for meta-analysis. Mean differences are shown with 95% confidence intervals.

Figure 4 – 4A: Forest Plot showing the odds ratio for successfull revascularization (TICI≥2b). 4B: Forest Plot showing the odds ratio for sCIH between groups. 4C: Forest Plot showing the odds ratio for mRS<2 between groups; 4D: Forest Plot showing the odds ratio for in-hospital and 30-day mortality between groups. A Mantel-Haenszel fixed effect model was used for meta-analysis. Odds ratio are shown with 95% confidence intervals. OR – Odds Ratio; TICI – Thrombolysis in cerebral infarction; sCIH – Symptomatic intracerebral haemorrhage; mRS – Modified Rankin Scale

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Article	Type of study	Year of publication	Multicentric / Unicentric	NOS Score	n	Control Group	Data Extraction for Quantitative Synthesis
Yilmaz, U.	Observational Study (Retrospective)	2017	Unicentric	3	47	no	NA
Grigoryan M, et al	Observational Study (Retrospective)	2016	Multicentric	4	100	yes	yes
Fahed R, et al	Observational Study (Retrospective)	2016	Unicentric	8	70	yes	yes
Behme D, et al	Observational Study (Retrospective)	2015	Multicentric	3	170	no	NA
Steglich-Arnholm H, et al	Observational Study (Retrospective)	2015	Unicentric	3	47	no	NA
Cohen JE, et al	Observational Study (Retrospective)	2015	Unicentric	3	24	no	NA
Heck DV, et al	Observational Study (Retrospective)	2015	Unicentric	3	23	no	NA
de Lucena AF, et al	Observational Study (Retrospective)	2015	Unicentric	3	20	no	NA
Spiotta AM, et al	Observational Study (Retrospective)	2015	Unicentric	3	16	no	NA
Mishra A, et al	Observational Study (Retrospective)	2015	Unicentric	3	7	no	NA
Maurer CJ, et al	Observational Study (Retrospective)	2014	Unicentric	3	43	yes	no
Lescher S, et al	Observational Study (Retrospective)	2014	Unicentric	5	39	yes	yes
Lockau H, et al	Observational Study (Retrospective)	2014	Unicentric	3	37	no	NA
Puri AS, et al	Observational Study (Retrospective)	2014	Multicentric	3	28	no	NA
Son S, et al	Observational Study (Retrospective)	2014	Unicentric	3	22	no	NA
Soize S, et al	Observational Study (Prospective)	2014	Unicentric	3	11	yes	No
Dabahneh H, et al	Observational Study (Retrospective)	2014	Unicentric	3	6	yes	No
Dorado L, et al	Observational Study (Retrospective)	2013	Unicentric	7	143	yes	yes
Mpotsaris A, et al	Observational Study (Retrospective)	2013	Unicentric	8	17	yes	no
Stampf S, et al	Observational Study (Prospective)	2013	Unicentric	3	24	no	NA
Cohen JE, et al	Observational Study (Retrospective)	2013	Unicentric	3	7	no	NA
Malik AM, et al	Observational Study (Retrospective)	2011	Unicentric	3	77	no	NA
Papanagiotou P, et al	Observational Study (Retrospective)	2011	Unicentric	3	22	no	NA

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Table 2.

Reference		n	Age, years (mean ± SD)	Male sex n(%)	Baseline NIHSS (mean ± SD)	Stentretriever Device, n (%)	Tandem Occlusion, n (%)	Thrombolysis, n (%)	Antegrade Approach, n(%)	Time to recanalization, min. (mean ± SD)
Dorado L *et al,*	ICA stent	20	65.1 ± 9.5	19 (79.2%)	-	18 (75%)	13 (54.2%)	- (50%)	0 (0%)	97 ± 17.3
	No stent	119	66.2 ± 12.2	71 (62.9%)	-	99 (83.2%)	7 (5.9%)	- (47.9%)	NA	55 ± 15.8
	Total	143	66.1 ± 11.7	90 (62.9%)	-	117 (81.8%)	20 (14%)	69 (48.3%)	0 (0%)	63 ± 20
Lescher S *et al*	ICA stent	9	66 ± 7.5	-	15±1.5	9 (100%)	9 (100%)	7 (78%)	9 (100%)	76 ± 20
	No stent	30	65 ± 13.5	-	15±3.5	30 (100%)	30 (100%)	22 (73%)	NA	71 ± 38.3
	Total	39	68 ± 13.5	16 (41%)	14±3.5	39 (100%)	39 (100%)	29 (74%)	NA	61 ± 38.3
Fahed R *et al*	ICA stent	37	61.6 ± 10.2	30 (81.1%)	16±2.3	37 (100%)	37 (100%)	27 (73%)	-	83.9 ± 30.9
	No stent	33	63.8 ± 12.4	19 (57.6%)	16±2.0	33 (100%)	33 (100%)	25 (76%)	NA	80.0 ± 29.6
	Total	70	62.6 ± 11.3	49 (70%)	11±2.5	70 (100%)	70 (100%)	52 (74.3%)	-	82.3 ± 30.2
Grigoryan M *et al*	ICA stent	67	-	-	-	-	67 (100%)	-	-	-
	No stent	33	-	-	-	-	33 (100%)	-	NA	-
	Total	100	64.4 ± 12.5	64 (64%)	17.6±5.0	71 (71%)	100 (100%)	49 (49%)	-	101 ± 43
Mpotsaris A *et al*	ICA stent	17	59 ± 8.3	13 (76.5%)	16.5±3.5	17 (100%)	17 (100%)	14 (82%)	- (100%)	100.6 ± 33.8
Heck DV *et al*	ICA stent	23	69.5 ± 10.3	-	17±4.0	23 (100%)	23 (100%)	13 (56.5%)	23 (100%)	-
Cohen JE *et al*	ICA stent	7	64.1 ± 6.5	6 (85.7%)	23.4±2.5	7 (100%)	7 (100%)	0 (0%)	2 (28.6%)	54.7 ± 6.8
Dabahneh H *et al*	ICA stent	5	51.6 ± 11.8	2 (40%)	16.8±2.8	5 (100%)	5 (100%	3 (60%)	5 (100%)	-
	No stent	1	-	-	-	-	-	-	-	-
	Total	6	51.8 ± 11.8	3 (50%)	15.4±2.8	5 (83.3%)	6 (100%)	4 (66.7%)	5 (100%)	-
Spiotta AM *et al*	ICA stent	6	67.8 ± 12.3	8 (50%)	13.3±3.3	10 (63%)	16 (100%)	8 (50%)	15 (94%)	86 ± 29.3
Puri AS *et al*	ICA stent	28	58.7 ± 13.3	19 (67.9%)	18±5.0	22 (78.6%)	28 (100%)	7 (27.3%)	24 (85.7%)	105 ± 35.5
Soize S *et al*	ICA stent	11	68.7 ± 11.5	7 (63.6%)	18.8±6.4	11 (100%)	11/42 (26%)	6 (54.5%)	1 (9%)	53 ± 37
Papanagiotou P *et al*	ICA stent	22	64.8 ± 9	17 (77%)	17.2±3.3	18 /18 (100%)	18 (81.8%)	14 (63.6%)	18/18 (100%)	86 ± 20
Maurer CJ *et al*	ICA stent	39	-	-	-	-	-	-	-	-
	No stent	4	-	-	-	-	-	-	-	-
	Total	43	68 ± 13	30 (70%)	12.9±5.2	43 (100%)	43 (100%)	20 (46.5%)	43 (100%)	102 ± 60
Stampf S *et al*	ICA stent	24	67.2 ± 8.5	-	18±1.8	24 (100%)	24 (100%)	22 (92%)	21 (87.5%)	53.4 ± 20
Lockau H *et al*	ICA stent	37	63 ± 13.3	27 (73%)	17±6.8	37 (100%)	37 (100%)	20 (54.1%)	12 (32%)	73.5 ± 42.1
de Lucena AF *et al*	ICA stent	20	67.1 ± 11.4	14 (70%)	16±5.3	17 (85%)	20 (100%)	12 (60%)	0 (0%)	89 ± 46.9

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Malik AM *et al*	ICA stent	77	63.4 ± 10.9	55 (71.4%)	14.8±5.4	-	77 (100%)	-	77 (100%)	-
Steglich-Arnholm H *et al*	ICA stent	47	64.3 ± 12.5	34 (72%)	16±1.5	47 (100%)	47 (100%)	40 (85%)	18 (38%)	84.8 ± 46
Mishra A *et al*	ICA stent	7	66.4 ± 8	5 (71%)	18.3±4.0	7 (100%)	7 (100%)	2 (29%)	7 (100%)	52 ± 11.3
Cohen JE *et al*	ICA stent	24	66 ± 6.5	20 (83%)	20.4±3.5	24 (100%)	24 (100%)	10 (41.7%)	24 (100%)	51 ± 7.8
Behme D *et al*	ICA stent	170	64 ± 15.8	119 (70%)	15±1.8	170 (100%)	170 (100%)	122 (72%)	151 (78%)	88 ± 15.5
Son S *et al*	ICA stent	22	-	-	12.6±4.5	8/11 (73%)	11/22 (50%)	12 (55%)	11/11 (100%)	61 ± 26.8
Yilmaz, U *et al*	ICA stent	47	67±12	36 (76.6%)	-	47 (100%)	47 (100%	24 (51%)	47 (100%)	-

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Table 3.

Reference		n	Age, years (mean ± SD)	TICI ≥ 2b, n	In-hospital mortality, n	sICH, n	90-day mortality, n	90 day mRS < 2, n	ICA stent thrombosis, n
Dorado L *et al*	ICA stent	20	65.1 ± 9.5	19 (95.8%)	-	11 (45.8%)	4 (16.7%)	16 (80%)	-
	No stent	119	66.2 ± 12.2	100 (84%)	-	40 (33.6%)	6 (5%)	59 (50%)	-
	Total	143	66.1 ± 11.7	- (86%)	-	51 (35.7%)	10 (7%)	75 (53.2%)	-
Lescher S *et al*	ICA stent	9	66 ± 7.5	5 (56%)	-	0 (0%)	1 (11%)	3 (33%)	-
	No stent	30	65 ± 13.5	20 (67%)	-	3 (13%)	3 (10%)	11 (37%)	-
	Total	39	68 ± 13.5	25 (64%)	-	3 (8%)	4 (10%)	14 (36%)	-
Fahed R *et al*	ICA stent	37	61.6 ± 10.2	25 (67.6)	-	-	3/36 (8.3%)	18/36 (50%)	-
	No stent	33	63.8 ± 12.4	22 (66.7%)	-	-	6/31 (19.3%)	15/31 (48.4%)	-
	Total	70	62.6 ± 11.3	34 (48.6%)	-	-	9 (12.8%)	33 (47%)	-
Grigoryan M *et al*	ICA stent	67	-	-	-	-	-	28/67 (41.8%)	-
	No stent	33	-	-	-	-	-	14/33 (42.4%)	NA
	Total	100	64.4 ± 12.5	88 (88%)	-	20 (20%)	20 (20%)	42 (42%)	-
Mpotsaris A *et al*	ICA stent	17	59 ± 8.3	-	2 (11.7%)	-	4 (23.5%)	7 (41.2%)	-
Heck DV *et al*	ICA stent	23	69.5 ± 10.3	17 (74%)	0 (0%)	5 (22%)	9 (39%)	12 (52%)	1/18 (5.6%)
Cohen JE *et al*	ICA stent	7	64.1 ± 6.5	6 (85.7%)	1 (14%)	1 (14%)	1 (14%)	5 (72%)	-
Dabahneh H *et al*	ICA stent	5	51.6 ± 11.8	5 (100%)	0 (0%)	-	0 (0%)	4 (80%)	-
	No stent	1	-	-	-	-	-	-	-
	Total	6	51.8 ± 11.8	5 (83.3%)	0 (0%)	-	0 (0%)	4 (66.7%)	-
Spiotta AM *et al*	ICA stent	6	67.8 ± 12.3	16 (100%)	0 (0%)	1 (6%)	0 (0%)	8 (50%)	-
Puri AS *et al*	ICA stent	28	58.7 ± 13.3	13 (46%)	4 (14%)	2 (7%)	4 (14%)	16 (56.5%)	-
Soize S *et al*	ICA stent	11	68.7 ± 11.5	9 (81.8%)	-	5 (45.4%)	5 (45.4%)	2 (18.2%)	
Papanagiotou P *et al*	ICA stent	22	64.8 ± 9	14 (63%)	-	4 (18%)	3 (13.6%)	9 (41%)	
Maurer CJ *et al*	ICA stent	39	-	-	-	-	-	-	-
	No stent	4	-	-	-	-	-	-	-
	Total	43	68 ± 13	33 (76.7%)	9 (20.9%)	6 (14.3%)	9 (20.9%)	14 (32.6%)	-
Stampf S *et al*	ICA stent	24	67.2 ± 8.5	15 (63%)	-	4 (16.6%)	4 (16.6%)	7 (29.2%)	0 (0%)
Lockau H *et al*	ICA stent	37	63 ± 13.3	27 (73%)	-	4 (10.8%)	7 (18.9%)	13 (35.1%)	6 (16.2%)
de Lucena AF *et al*	ICA stent	20	67.1 ± 11.4	18 (85%)		1 (5%)	4 (20%)	7 (35%)	-
Malik AM *et al*	ICA stent	77	63.4 ± 10.9	28 (87.5)	-	8 (10.4%)	19 (24.7%)	32 (41.6%)	1 (1.3%)
Steglich-Arnholm H *et al*	ICA stent	47	64.3 ± 12.5	42 (87%)	-	2 (4%)	4 (9%)	32 (68%)	8 (17%)
Mishra A *et al*	ICA stent	7	66.4 ± 8	7 (100%)	0 (0%)	2 (29%)	0 (0%)	7 (100%)	-
Cohen JE *et al*	ICA stent	24	66 ± 6.5	19 (79%)	0 (0%)	0 (0%)	2 (8%)	13 (76%)	-
Behme D *et al*	ICA stent	170	64 ± 15.8	130 (77%)	32 (19%)	15 (9%)	-	61 (32%)	-
Son S *et al*	ICA stent	22	-	20 (90.9)	0 (0%)	1 (5%)	1 (5%)	20 (90.9%)	-
Yilmaz, U *et al*	ICA stent	47	67±12.0	-	-	6 (12.8%)	-	-	10 (21.3%)*

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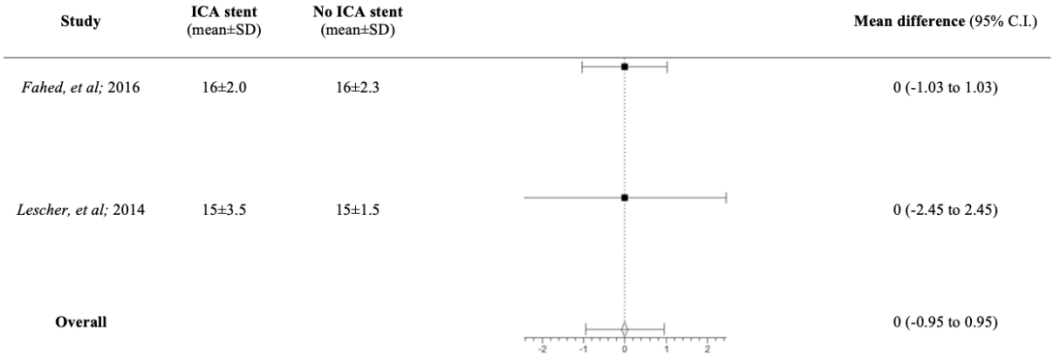

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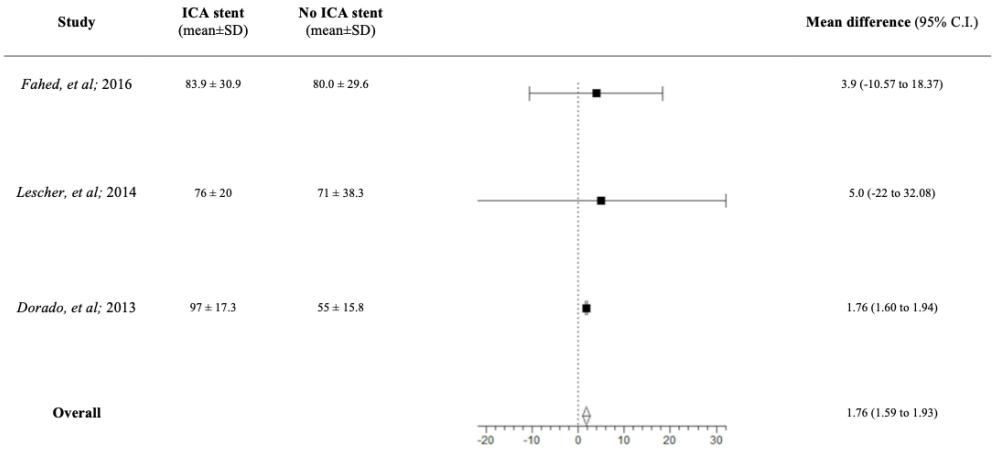

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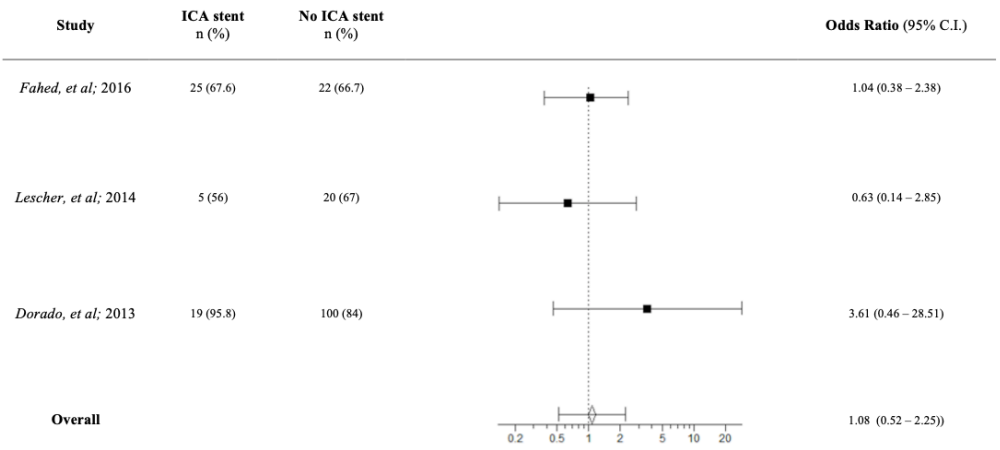

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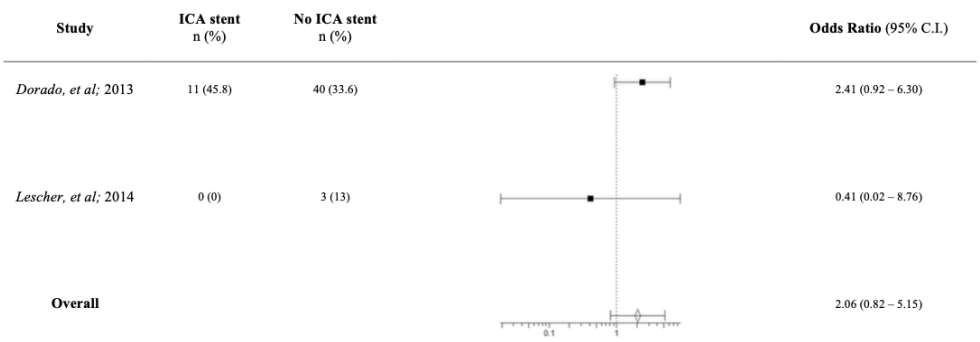

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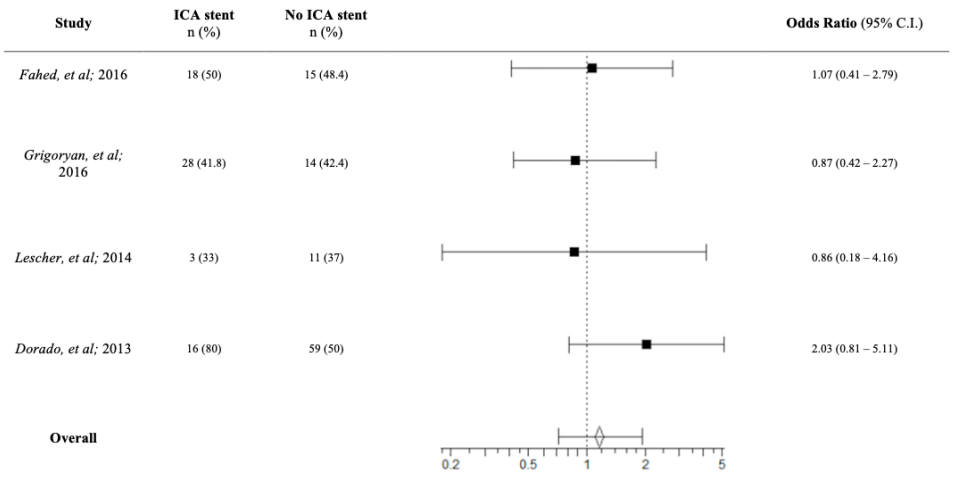

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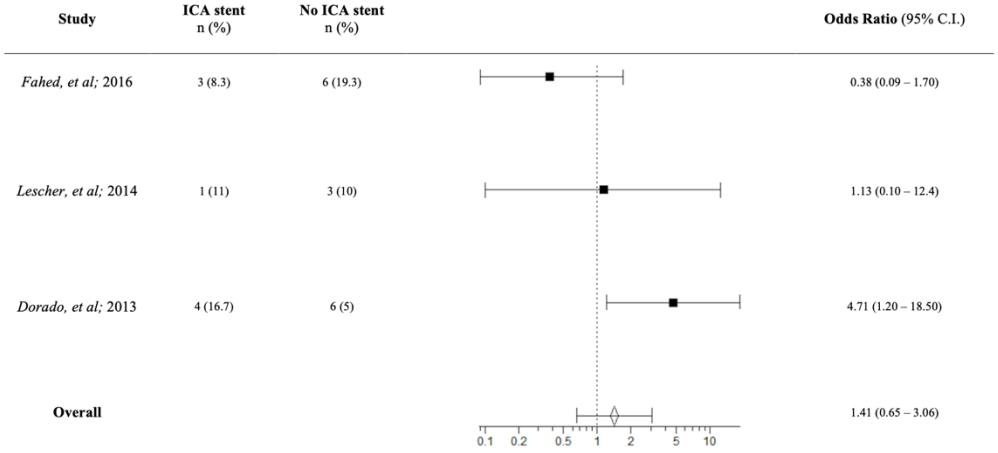

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CARDIOVASCULAR SCIENCES
at Faculdade de Medicina da Universidade do Porto

CHAPTER 2

TIMING OF CAROTID INTERVENTION IN SYMPTOMATIC CAROTID ARTERY STENOSIS: A SYSTEMATIC REVIEW AND META-ANALYSIS

CHAPTER 2. Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis

Systematic review and meta-analysis of the literature published in *The European Journal of Vascular and Endovascular Surgery*, indexed to PubMed/MEDLINE journal

- CiteScore of 7.1
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Carotid and Supra-aortic Arteries

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SYSTEMATIC REVIEW

Editor's Choice – Timing of Carotid Intervention in Symptomatic Carotid Artery Stenosis: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

The evidence from this systematic review and meta-analysis suggests that (at present) carotid endarterectomy (CEA) is safer than carotid artery stenting (CAS) when performed within two or seven days of the index event. Also, considering absolute rates of 30 day stroke, mortality, and death/stroke, CEA performed within two days of the index event complies with the accepted thresholds in international guidelines. The findings of this analysis will guide clinical practice when deciding on the type of intervention in the symptomatic patient with severe carotid stenosis. The ideal timing for performing CAS (when indicated against CEA) is not yet defined.

Objective: This review aimed to analyse the timing of carotid endarterectomy (CEA) and carotid artery stenting (CAS) after the index event as well as 30 day outcomes at varying time periods within 14 days of symptom onset.
Methods: A systematic review was performed according to the Preferred Reporting Items for Systematic reviews and Meta-analysis statement, comprising an online search of the Medline and Cochrane databases. Methodical quality assessment of the included studies was performed. Endpoints included procedural stroke and/or death stratified by delay from the index event and surgical technique (CEA/CAS).
Results: Seventy-one studies with 232 952 symptomatic patients were included. Overall, 34 retrospective analyses of prospective databases, nine prospective, three RCT, three case control, and 22 retrospective studies were included. Compared with CEA, CAS was associated with higher 30 day stroke (OR 0.70; 95% CI 0.58 — 0.85) and mortality rates (OR 0.41; 95% CI 0.31 — 0.53) when performed $\leq$ 2 days of symptom onset. Patients undergoing CEA/CAS were analysed in different time frames ($\leq$ 2 *vs.* 3 — 14 and $\leq$ 7 *vs.* 8 — 14 days). Expedited CEA (*vs.* 3 — 14 days) presented a sampled 30 day stroke rate of 1.4%; 95% CI 0.9 — 1.8 *vs.* 1.8%; 95% CI 1.8 — 2.0, with no statistically significant difference. Expedited CAS (*vs.* 3 — 14 days) was associated with no difference in stroke rate but statistically significantly higher mortality rate (OR 2.76; 95% CI 1.39 — 5.50).
Conclusion: At present, CEA is safer than transfemoral CAS within 2/7 days of symptom onset. Also, considering absolute rates, expedited CEA complies with the accepted thresholds in international guidelines. The ideal timing for performing CAS (when indicated against CEA) is not yet defined. Additional granular data and standard reporting of timing of intervention will facilitate future monitoring.

Keywords: Carotid stenosis, Death, Endarterectomy, carotid, Stent, Stroke
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INTRODUCTION

Carotid revascularisation improves long term stroke free survival in patients with recent ischaemic stroke or transient ischaemic attack (TIA). Recency of the index event has been recognised as a key determinant of the effectiveness of revascularisation, balancing the natural history risk of a

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second (more severe) event against the potential for a higher peri-procedural risk when carotid interventions are performed very early after the onset of symptoms.

The optimal timing for carotid revascularisation, by either carotid endarterectomy (CEA) or carotid artery stenting (CAS), remains a matter for debate. The 2017 European Society for Vascular Surgery (ESVS) guidelines advise that CEA should be performed within 14 days of the index neurological event, as this was the highest risk time period for recurrent stroke.[1] This is particularly true for neurologically stable patients presenting with TIA or minor stroke. However, it remains unclear as to the optimal timing of either CEA or CAS within this 14 day time period (i.e., Is it better for the carotid intervention to be performed $<$ 2 days, $<$ 7 days, or perhaps 8 — 14 days after symptom onset?).

A recent systematic review reported that the risk of recurrent stroke can vary from 6% within 2 — 3 days of the index event, to 20% within 7 days, and up to 26% within 14 days of the index event.[2] Conversely, a meta-analysis of published studies comparing expedited carotid interventions (2 days) *vs.* early (3 — 14 days) found a significantly higher risk of procedural stroke when CEA was performed within 2 days of the index event.[3] However, this systematic review did not include two large national CEA registries ($>$ 70 000 CEAs), which confounds meaningful interpretation of their data. In the case of CAS, the available data on safety very early after the onset of symptoms appears limited.[4]

The lack of high quality evidence and consensus definitions for what constitutes "early" or "urgent" carotid interventions has contributed to conflicting results in the literature. Heterogeneity regarding patient symptoms, medical therapy, and varying surgical approaches have also led to polarised debates about the timing of CEA in patients who present with neurological symptoms.[5]

The aims of the current systematic review and meta-analysis were to analyse temporal changes in the timing of carotid interventions after symptom onset and to determine 30 day outcomes following CEA and CAS when performed at varying time periods in the first 14 days after onset of symptoms, to define the optimal timing and carotid intervention (CEA *vs.* CAS) in recently symptomatic patients.

METHODS

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement.[6]

The literature search was from January 1995 to January 2021. Using the Medline and Cochrane databases, the following query (((“Carotid Stenosis”[Mesh]) AND “Stents”[Mesh]) OR “Endarterectomy, Carotid”[Mesh]) AND (“Stroke”[Mesh] OR Symptomatic OR timing of intervention) was used for online search.

Eligibility criteria included any publication regarding the revascularisation of symptomatic carotid artery stenosis by either CAS or CEA. Timing of intervention and impact of delay on procedural risks were documented. Only atherosclerotic stenotic carotid disease was considered, with exclusion of procedures performed for non-atherosclerotic pathologies.

Exclusion criteria were (1) articles published in a language other than English; and (2) case reports and literature reviews.

Endpoints included any stroke and/or death within 30 days of intervention stratified by delay of intervention after the index event and by intervention technique (CEA and

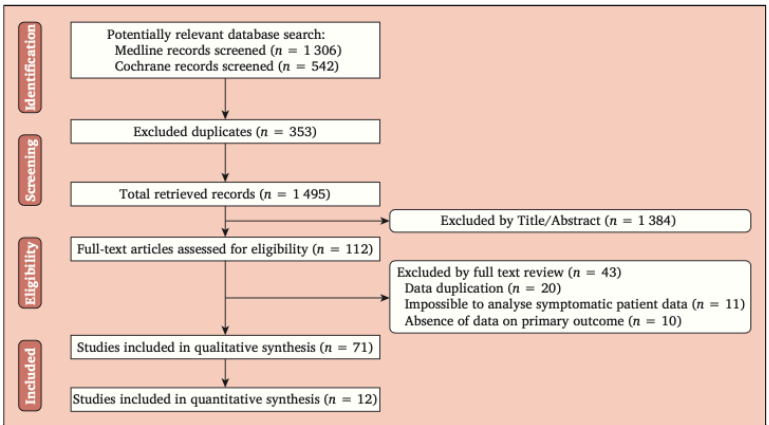

Figure 1. Preferred reporting items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram summarising literature screening process for studies of timing after index event and outcome after carotid endarterectomy (CEA) or carotid artery stenting (CAS).

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Table 1. Analysis of study characteristics and intervention delay for carotid endarterectomy (CEA) or carotid artery stenting (CAS) after index event

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
Kashyap[34] (2020) *Stroke*	Prosp; Multicentre	CAS	632	164 (26)	NR	NR	NR
Karpenko[35] (2020) *J Stroke Cerebrovasc Dis*	Retrosp; Single centre	CEA/CAS	1 791 CEA: 1215 (57); CAS: 917 (43)	160 (8.9)	NR	NR	NR
Jankowitz[13] (2020) *Neurosurgery*	Retrosp analysis of prosp data; Single centre	CEA/CAS	120 CEA: 59 (49.2); CAS: 61 (59.8)	120 (100)	Urgent (0–2)	0–2 d: 120 (100)	CEA: 1.6 ± 0.8; CAS: 1.0 ± 0.7; p <.001
Roussopoulo[9] (2019) *Eur J Neurol*	Prosp; Multicentre	CEA	311	311 (100)	Urgent (0–2); Early (3–14)	0–2 d: 63 (20.3); 3–14 d: 248 (79.7)	NR
Howie[36] (2019) *World Neurosurg*	Retrosp; Single centre	CEA/CAS	314 CEA: 204 (64.9); CAS: 110 (35.1)	265 (84.5)	NR	NR	NR
Vang[37] (2019) *Surgery*	Retrosp; Single centre	CEA	1233	509 (41.3)	NR	NR	NR
Lee[38] (2018) *Ann Vasc Surg*	Retrosp; Multicentre	CEA/CAS	677 CEA: 331 (48.9); CAS: 346 (51.1)	677 (100)	NR	NR	NR
Huang[14] (2018) *J Vasc Surg*	Retrosp; Single centre	CEA	238	238 (100)	Early (0–14); (0 −2); (3–7); (8–14); Delayed (15–180)	0–2 d: 11 (4.6); 3–7 d: 23 (9.7); 8–14 d: 23 (9.7); 15–180 d: 181 (76.1)	NR
Rocco[20] (2018) *J Vasc Interv Radiol*	Retrosp analysis of prosp data; Single centre	CEA/CAS	110 CEA: 48 (43.6); CAS: 62 (56.4)	110 (100)	NR	NR	CEA: 1.7 ± 2.4; CAS: 2.8 ± 2.1
Seguchi[10] (2017) *J Stroke CerebrovascDis*	Retrosp; Single centre	CAS	105	105 (100)	Early (0–2); Delayed (3–180)	0–2 d: 40 (38.1); 3–180 d: 65 (61.9)	NR
Rantner[44] (2017) *Stroke* EVA-3S, SPACE, ICSS, CREST	Retrosp analysis of prosp data; Multicentre	CEA *vs.* CAS	4 138	4 138 (100)	Early (0–7); Delayed (8–180)	0–7 d: 513 (12.4); 8–180 d: 3625 (87.6)	
		CEA	2 045 (49.4)	2 045 (100)	Early (0–7); Delayed (8–180)	0–7 d: 226 (11); 8–180 d: 1819 (89)	34.5 ± 15.6
		CAS	2 093 (50.6)	2 093 (100)	Early (0–7); Delayed (8–180)	0–7 d: 287 (14); 8–180 d: 1806 (86)	31 ± 14.4
Hobeanu[42] (2017) *Stroke*	Nested case control study	CEA/CAS *vs.* BMT	561 CEA/CAS: 187 (33.3) BMT: 374 (66.7)	187 (100)	NR	NR	12.8 ± 4.9
Nordanstig[8] (2017) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CEA	418	418 (100)	Early (0–2); Delayed (3–14)	0–2 d: 46 (11); 3–14 d: 372 (89)	Early: 1.3 ± 0.69 Delayed: 6.7 ± 2.9
Kazandjian[46] (2016) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	114	114 (100)	Early (0–14); Delayed (15–180)	0–14 d: 32 (28); 15–180 d: 82 (72)	22 ± 33
Tsantilas[23] (2016) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	401	401 (100)	Early (0–14); (0 −2); (3–7); (8–14); Delayed (15–180)	0–2 d: 60 (15); 3–7 d: 110 (27.4); 8–14 d: 65 (16.2); 15–180 d: 166 (41.4)	NR
Charbonneau[17] (2016) *J Vasc Surg*	Retrosp; Single centre	CEA	103	103 (100)	(0–14); (15–90); (91–180)	0–14 d: 40 (38.8); 15–90 d: 37 (35.9); 91–180 d: 26 (25.2)	36.5 ± 21.4
Chisci[19] (2015) *Ann Vasc Surg*	Retrosp; Single centre	CEA	322	322 (100)	Early (0–14); Delayed (15–30);	0–14 d: 100 (31.1); 15–30 d: 222 (68.9)	16.8 ± 9.2 4.6 ± 3.1 22.3 ± 4.6
Kretz[26] (2015) *Ann Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	417	417 (100)	Early (0–15); Deferred (16–45); Delayed (46–180)	0–15 d: 158 (37.9); 16–45 d: 79 (18.9); 46–180 d: 180 (43.2)	7.7 ± 3.8 28.3 ± 8.6 89.4 ± 36.7
Charmoille[47] (2014) *Ann Vasc Surg*	Retrosp; Single centre	CEA	149	149 (100)	Early (0–14); Late (15–180)	0–14 d: 62 (41.6); 15–180 d: 87 (58.4)	NR
Rantner[45] (2014) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	761	761 (100)	Early (0–14); (0 −2); (3–7); (8–14); Delayed (15–180)	0–2 d: 206 (27.1); 3–7 d: 219 (28.8); 8–14 d: 136 (17.9); 15–180 d: 200 (26.3)	NR
Tsivgoulis[49] (2014) *Eur J Neurol*	Prosp; Multicentre	CEA	165	165 (100)	Ultra-Early (0–2); Early (3–14)	0–2 d: 20 (12); 3–14 d: 145 (88)	6 ± 1.7
Mo[51] (2014) *J NeuroIntervent Surg*	Retrosp analysis of prosp data; Single centre	CAS	402	169 (42.0)	NR	NR	NR
Shahidi[53] (2013) *Stroke*	Prosp; Single centre	CEA	115	115 (100)	Early (0–14); Deferred (15–30); Delayed (31–180)	NR	36.3 ± 25.1

Continued

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Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD – d
Sharpe[18] (2013) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	475	475 (100)	Early (0–14); Hyperacute (0–2); (3–7); (8–14); Delayed (15–180)	0–2 d: 41 (8.6); 3–7 d: 167 (35.2); 8–14 d: 133 (28.0); 15–180 d: 134 (28.2)	NR
Faggioli[54] (2013) *Ann Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	610	162 (27)	Early (0–14); Deferred (15–30); Delayed (31–180)	0–14 d: 60 (37.0); 15–30 d: 18 (11.1); 31–180 d: 84 (51.9)	NR
Hartog[5] (2013) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	555	555 (100)	Early (0–14); Delayed (15–180)	0–14 d: 105 (18.9); 15–180 d: 450 (81.1)	40.3 ± 15.9
Tas[52] (2013) *Adv Ther*	Retrosp; Single centre	CEA/CAS	65 CEA 32 (49.2); CAS 33 (50.8)	65 (100)	NR	NR	NR
Annambhotla[59] (2012) *J Vasc Surg*	Retrosp; Single centre	CEA	312	312 (100)	Early (0–30); (0 –7); (8–14); (15 –21); (22–30); Delayed (31–180)	0–7 d: 27 (8.7); 8–14 d: 17 (5.4); 15–21 d: 12 (3.8); 22–30 d: 12 (3.8); 31–180 d: 243 (77.9)	NR
Kessler[56] (2012) *J Neuroradiol*	Retrosp; Single centre	CAS	55	55 (100)	NR	NR	NR
Kimiagar[57] (2012) *Vasc Endovascular Surg*	Retrosp; Single centre	CEA/CAS	116	116 (100)	NR	NR	NR
Lin[61] (2009) *J NeuroIntervent Surg*	Retrosp; Single centre	CAS	224	224 (100)	Early (0–30); Ultra-Early (0–14); Delayed (31–180)	0–30 d: 122 (54.5); 31–180 d: 102 (45.5)	NR
Gray[64] (2009) *Circ Cardiovasc Intervent* EXACT CAPTURE-2	Prosp; Multicentre	CAS	6320	759 (12.0)	NR	NR	NR
Ballotta[68] (2008) *J Vasc Surg*	Retrosp; Single centre	CEA	102	102 (100)	Early (0–14)	0–14 d: 102 (100)	6.3 ± 3.2
Setacci[69] (2008) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CAS	57	57 (100)	Deferred for TIA (1 –2); Deferred for Stroke (14–30)	1–2 d (TIA): 24 (42); 14–30 (Stroke): 33 (58)	NR
Massop[67] (2008) *Catheter Cardiovasc Interv*	SAPPHIRE Registry	CEA/CAS	2001	555 (27.7)	NR	NR	NR
Steinbauer[70] (2008) *J Vasc Surg*	RCT	CEA/CAS	87 CEA: 44 (50.6); CAS: 43 (49.4)	87 (100)	NR	NR	NR
Topakian[73] (2007) *Eur J Neurol*	Retrosp; Single centre	CAS	77	77 (100)	Early (0–14)	0–14 d: 23 (29.9); 15–180 d: 54 (70.1)	NR
Suzue[74] (2007) *J Vasc Surg*	Retrosp; Single centre	CEA	72	72 (100)	Early (0–30); Delayed (31–180)	0–30 d: 15 (20.8); 31–180 d: 57 (79.2)	NR
Dellagrammaticas[71] (2007) *Clin Med* GALA TRIAL	RCT	CEA	1 001	867 (86.6)	NR	NR	86 ± 30.0
Flanigan[72] (2007) *J Vasc Surg*	Retrosp analysis of prosp data; Single centre	CEA	442	170 (38.5)	NR	NR	NR
Sbarigia[76] (2006) *Eur J Vasc Endovasc Surg*	Prosp; Multicentre	CEA	96	96 (100)	NR	NR	1.5 ± 2
Imai[77] (2005) *Am J Neuroradiol*	Retrosp; Single centre	CAS	17	17 (100)	NR	NR	2.3 ± 2.4
Rantner[78] (2005) *Eur J Vasc Endovasc Surg*	Retrosp; Single centre	CEA	104	104 (100)	Acute (0–24 hours); Ultra-Early (0–6 hours); (0–27); (28 –180)	0 d: 7 (6.7); <28 d: 29 (27.9); ≥28 d: 62 (59.6)	
Ecker[80] (2004) *J Neurosurg*	Case Control	CEA/CAS	436 CEA: 391 (89.7) CAS: 45 (10.3)	436 (100)	NR	NR	NR
Kastrup[83] (2003) *Cerebrovasc Dis*	Case Control	CEA/CAS	242 CEA: 142 (58.7); CAS: 100 (41.3)	155 (64.0)	NR	NR	NR
Welsh[81] (2003) *Cerebrovasc Dis*	Prosp; Multicentre	CEA	40	40 (100)	Early (0–1); Delayed (60–180)	0–1 d: 19 (47.5); 60–180 d: 21 (52.5)	NR
ECST[84] (1988) *Lancet*	RCT	CEA *vs.* BMT	1 807	1 807 (100)	NR	NR	NR

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Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
National Registry							
Kuhrij[21] (2019) *Eur J Vasc Endovasc Surg* Dutch Audit for Carotid Intervention	Retrosp analysis of prosp data; Multicentre	CEA	8 620	8 620 (100)	Early (0−14)	0−14 d: 6645 (78)	11 ± 1.7
Faateh[39] (2018) *J Vasc Surg* National Quality Improvement	Retrosp analysis of prosp data; Multicentre	CEA	9 271	9 271 (100)	Emergency: Performed within the same hospitalisation OR reported as emergency by the team	Emergency: 546 (5.9); Non-emergency: 8725 (94.1)	NR
Tsantilas[40] (2018) *J Am Heart Assoc* German Statutory Quality Assurance	Retrosp analysis of prosp data; Multicentre	CAS	4 717	4 717 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 550 (11.6); 3−7 d: 1579 (33.4); 8−14 d: 1244 (26.3); 15−180 d: 1344 (28.4)	NR
Blay[41] (2018) *Ann Vasc Surg* ACS-NSQIP	Retrosp analysis of prosp data; Multicentre	CEA	3 427	3 427 (100)	Early (0−7); Delayed (8−180)	0−7 d: 3247 (94.7); 8−180 d: 180 (5.3)	NR
Avgerinos[43] (2017) *J Vasc Surg* VSGNE Database	Retrosp analysis of prosp data; Multicentre	CEA	989	989 (100)		0 d: 96 (9.8); 1−2 d: 322 (32.6) 3−5 d: 94 (9.1); 6−180 d: 477 (48.2)	NR
Venermo[45] (2017) *Eur J Vasc Endovasc Surg* VQI/Vascunet	Retrosp analysis of prosp data; Multicentre	CEA/CAS	58 607 CEA: 52 434 (89.5); CAS: 6 173 (10.5)	30 520 (52.1)	NR	NR	NR
Kjorstad[18] (2017) *Eur J Vasc Endovasc Surg* National Norwegian Carotid Study	Retrosp analysis of prosp data; Multicentre	CEA	368	368 (100)	Early (0−14)	0−14 d: 227 (61.7); 15−180 d: 141 (36.8)	12.75 ± 4.3
Loftus[24] (2016) *Eur J Vasc Endovasc Surg* UK National Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	33 194	23 235 (70.0)	Early (0−14); (0 −2); (3−7); (8−14); (15−21); Delayed (22−180)	0−2 d: 780 (3.4); 3−7 d: 5126 (22.1); 8−14 d: 6292 (27.1); 15−21 d: 2765 (11.9); 22−180 d: 8272 (35.6)	2009: 9.3 ± 4.9; 2010: 7.0 ± 4.1; 2011: 5.5 ± 2.90; 2012: 5.0 ± 2.3; 2013: 4.5 ± 2.3; 2014: 5.75 ± 6.7
Jonsson[16] (2015) *Eur J Vasc Endovasc Surg* Swedvasc Registry	Retrosp analysis of prosp data; Multicentre	CAS	323	323 (100)	Early (0−14); (0 −2); (3−7); (8−14); Delayed (15−180)	0−2 d: 13 (4.0); 3−7 d: 85 (26.3); 8−14 d: 80 (24.8); 15−180 d: 145 (44.9)	NR
Geraghty[50] (2014) *J Vasc Surg* SVS Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA/CAS	8 640 CEA: 5 758 (66.6); CAS: 2 882 (33.3)	2 904 (33.6)	Symptomatic: Neurologic events in the previous 12 months	NR	NR
Villwock[12] (2014) *J Stroke Cerebrovasc Dis* Nationwide Inpatient Sample	Retrosp analysis of prosp data; Multicentre	CEA *vs.* CAS	72 797 CEA: 62 327 (85.6); CAS: 13 470 (18.4)	72 797 (100)	Ultra-Early (0−2); Early (3−14)	0−2 d: 41008 (56.3); 3−14 d: 31789 (43.7)	NR
Witt[25] (2013) *Stroke* Danish Stroke Registry/Danish Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	813	813 (100)	Early (0−14)	NR	Decrease in the delay to CEA with time: 13% underwent CEA in two weeks in 2007, 33% in 2008, 37% in 2009, 47% in 2010 (OR 5.8, 95% CI 4.3−10.1)
Schermerhorn[55] (2013) *J Vasc Surg* CMS	Retrosp analysis of prosp data; Multicentre	CEA/CAS	10 107 CEA: 6 370 (63.0); CAS: 3 737 (37.0)	3 916 (38.7)	NR	NR	NR
Nolan[58] (2012) *J Vasc Surg* VSGNE 2003−2010	Retrosp analysis of prosp data; Multicentre	CEA/CAS	8 079 CEA: 7 649 (94.6); CAS: 430 (5.4)	2 763 (34.2)	NR	NR	NR

Continued

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Table 1-*continued*

Article (Year) Journal	Type of article	CEA/ CAS	Patients	Symptomatic	Definition delay (days)	Timing of intervention	Mean delay ± SD − d
Stromberg[87] (2012) *Stroke* Swedvasc Registry	Retrosp analysis of prosp data; Multicentre	CEA	2 596	2 596 (100)		0–2 d: 148 (5.7); 3–7 d: 804 (31.0); 8–14 d: 677 (26.1); 15–180 d: 967 (37.2)	NR
Garg[60] (2011) *Ann Vasc Surg* National Surgery Quality Improvement	Retrosp analysis of prosp data; Multicentre	CEA	17 388	8 103 (46.6)	NR	NR	NR
Palombo[62] (2009) *J Cardiovasc Surg* Italian Vascular Registry	Retrosp analysis of prosp data; Multicentre	CEA	5 809	1 894 (32.6)	NR	NR	NR
Halliday[86] (2009) *BMJ* UK Surgeons undertaking CEA	Retrosp analysis of prosp data; Multicentre	CEA	5 513	4 576 (83)	Early (0–12); (0 –2); (2–4); (5–12); Delayed (13–180);	0–2 d: 944 (20.0); 3–4 d: 654 (14); 5–12 d: 1621 (34); 13–180 d: 1372 (30)	45.3 ± 19.4
Vogel[65] (2009) *J Vasc Surg* Nationwide Inpatient Sample (2005)	Retrosp analysis of prosp data; Multicentre	CEA/CAS	80 498 CEA: 73 929 (91.8); CAS 6 569 (8.2)	2 237 (2.8)	NR	NR	NR
Gladstone[63] (2009) *Stroke* Canadian Stroke Network	Retrosp analysis of prosp data; Multicentre	CEA	105	105 (100)	Early (0–14); Deferred (15–30); Delayed (31–180)	0–14 d: 38 (36.2); 15–30 d: 53 (50.5); 31–180 d: 26 (24.8)	37.8 ± 20.5
Goodney[66] (2008) *J Vasc Surg* VSGNE 2003 –2007	Retrosp analysis of prosp data; Multicentree	CEA	3 092	1 360 (44)	Emergency (0–6 h); Urgent (0–24 h)	0–1 d: 309 (10)	NR
McPhee[75] (2007) *J Vasc Surg* Nationwide Inpatient Sample	Retrosp analysis of prosp data; Multicentre	CEA/CAS	259 080 CEA: 245 045 (94.6); CAS 14 035 (5.4)	20 750 (8)	NR	NR	NR
Pell[79] (2004) *Scott Med J* National Prospective Survey Scotland	Retrosp analysis of prosp data; Multicentre	CEA	877	855 (97.5)	Early (0–30); Deferred (31–60)	0–30 d: 103 (27); 31–60 d: 222 (58)	NR
Tu[82] (2003) *Stroke* Ontario Carotid Endarterectomy Registry	Retrosp analysis of prosp data; Multicentre	CEA	6 038	4 192 (69.4)	NR	NR	NR

Data are presented as *n* (%) unless stated otherwise. NR = not reported; Retrosp = retrospective; Prosp = prospective.

CAS). An analysis of reporting of timing of CEA and CAS after the index event was also performed.

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. Stroke was considered procedural if the event occurred at any time between the revascularisation procedure (day 0) and day 30 after revascularisation.

Stroke was classified as disabling if there was an increase in the modified Rankin score (mRS) to $\geq$ 3, attributable to the event 30 days after the procedure. Neurological symptomatic status was defined as a transient ischaemic attack or minor disabling ischaemic stroke in the previous six months attributable to the ipsilateral carotid artery territory.

For the purpose of this meta-analysis, "expedited intervention" was used to define any intervention performed within two days of the index event. Index event was defined as the symptom that led the patient to seek medical advice as suggested in the ESVS guidelines.[1]

Two reviewers (AC and JP) screened the identified studies independently and were also responsible for data extraction (Fig. 1). Collected data included type of study, year of publication, number of patients and consecutiveness, adjudication of events by a clinical event committee (CEC), age, gender, and criteria for carotid revascularisation (presence and type of neurological symptoms and their timing). The definition of intervention delay regarding the index event was registered in different studies. Neurological events after the index event and before intervention were registered as well as procedural (30 day) events: stroke, myocardial infarction (MI), and death. Comparative data between early and delayed intervention were analysed, especially for interventions performed $\leq$ 2 days *vs.* between 3 and 14 days and for interventions performed $\leq$ 7 days *vs.* between 8 and 14 days of the index event.

When duplicates were identified, the most recent study was included unless the earlier version reported more data on specific parameters included in the analysis.

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Table 2. Analysis of patient characteristics including the type of neurological symptoms undergoing carotid endarterectomy (CEA) or carotid artery stenting (CAS) after index event

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Jankowitz[13] (2020)	CEA *vs.* CAS	All (0–2 d)	120 (100)							
	CEA		59 (49.2)	68.4 ± 11.3	38 (64)	NR	NR	NR	NR	NR
	CAS		61 (50.8)	71.5 ± 12.9	42 (71)	NR	NR	NR	NR	NR
Roussopoulo[9] (2019)	CEA	All (0–14 d)	311 (100)	69 ± 11	230 (74)	128 (41)	28 (9)	–	183 (59)	NR
		0–2 d	63 (20.3)	67 ± 15	45 (71)	31 (49)	13 (21)	–	32 (51)	NR
		3–14 d	248 (79.7)	69 ± 10	186 (75)	99 (40)	17 (7)	–	124 (50)	NR
Huang[14] (2018)	CEA	All (0–180 d)	238 (100)	72 ± 9.1	158 (68)	176 (74)	–	71 (30)	62 (26)	NR
		Group 1 (0–14 d)	57 (23.9)	72 ± 10	34 (60.7)	48 (84)	–	18 (32)	9 (16)	NR
		0–2 d	11 (4.6)							
		3–7 d	23 (9.7)							
		8–14 d	23 (9.7)							
		Group 2 (14–180 d)	181 (76.1)	72 ± 8.8	124 (70)	128 (71)	–	53 (29)	53 (29)	NR
Seguchi[10] (2017)	CAS	All (0–180 d)	105 (100)							
		0–2 d	40 (38.1)	74.8 ± 2.5	37 (92.5)	9 (22.5)	25 (62.5)	–	31 (77.5)	NR
		3–180 d	65 (61.9)	77.0 ± 3.5	59 (90.8)	NR	0 (0)	NR	NR	NR
Rantner[44] (2017) EVA-3S, SPACE, ICSS, CREST	CEA *vs.* CAS	All (0–180 d)	4138 (100)							
	CEA *vs.* CAS	0–7 d	513 (12.4)		355 (8.6)	258 (6.2)	–	258 (6.2)	67 (1.6)	NR
	CEA		226 (11)	69.2 ± 8.9	157 (3.8)	112 (2.7)	–	112 (2.7)	30 (0.7)	NR
	CAS		287 (14)	68.3 ± 9.0	198 (4.9)	146 (3.5)	–	146 (3.5)	37 (0.9)	NR
	CEA *vs.* CAS	8–180 d	3625 (87.6)		2536 (61.3)	1277 (30.9)	–	1277 (30.9)	643 (15.5)	NR
	CEA		1819 (89)	69.6 ± 9.4	1285 (31.1)	649 (15.7)	–	649 (15.7)	317 (7.7)	NR
	CAS		1806 (86)	69.6 ± 9.2	1251 (30.2)	628 (15.2)	–	628 (15.2)	326 (7.9)	NR
Nordanstig[8] (2017)	CEA	0–2 d*	75 (18)	73.0 ± 8.5	55 (73)	28 (37)	14 (19)	18 (24)	15 (20)	NA
		3–14 d*	343 (82)	73.7 ± 8.5	237 (69)	106 (31)	17 (5)	12 (24)	138 (40)	NA
Tsantilas[23] (2016)	CEA	All (0–180 d)	401 (100)	69.8 ± 3.7	273 (68.1)	174 (43.4)	–	102 (25.4)	125 (31.1)	NR
		0–2 d	60 (15)	70.8 ± 10.1	44 (72)	32 (53)	–	13 (22)	15 (3.7)	NR
		3–7 d	110 (27.4)	70.8 ± 14.1	75 (68)	46 (42)	–	29 (26)	35 (8.7)	NR
		8–14 d	65 (16.2)	70.8 ± 18.8	41 (63.1)	25 (39)	–	9 (14)	31 (7.7)	NR
		14–180 d	166 (41.4)	68.5 ± 3.5	113 (68.1)	71 (43)	–	51 (31)	44 (10.9)	NR
Charbonneau[17] (2016)	CEA	All (0–180 d)	103 (100)	68.5 ± 13.3	71 (68.9)	42 (40.8)	–	21 (20.4)	40 (38.8)	43 (42)
		0–14 d	40 (38.8)		26 (36.6)	12 (28.6)	–	5 (23.8)	23 (57.5)	NR
		15–90 d	37 (35.9)		26 (36.6)	18 (42.9)	–	7 (33.3)	12 (30.0)	NR
		91–180 d	26 (25.2)		19 (26.8)	12 (28.6)	–	9 (42.9)	5 (12.5)	NR
Chisci[19] (2015)	CEA	All (0–30 d)	322 (100)	73.2 ± 9	235 (73)	166 (51)	43 (13)	27 (9)	129 (40)	NR
		0–14 d	100 (31.1)	72.5 ± 9.1	75 (75)	52 (52)	17 (17)	5 (5)	43 (43)	NR
		15–30 d	222 (68.9)	73.5 ± 8.9	160 (72)	114 (51)	26 (12)	22 (10)	86 (39)	NR
				$p = .35$	$p = .68$					
Kretz[26] (2015)	CEA	All (0–180 d)	417 (100)							
		0–15	158 (37.9)	73.8 ± 10	116 (73.4)	58 (36.7)	–	20 (12.7)	56 (35.4)	NR
		16–45	79 (18.9)	73.8 ± 11	53 (67.1)	33 (41.8)	–	9 (11.4)	24 (30.4)	NR
		46–180	180 (43.2)	73.1 ± 9.6	136 (75.6)	55 (30.6)	–	21 (11.7)	77 (42.8)	NR
Jonsson[16] (2015)	CAS	All (0–180 d)	323 (100)							
		0–2 d	13 (4.0)	69 ± 6.4	10 (76.9)	2 (15.4)	0 (0)	2 (15.4)	9 (69.2)	NR
		3–7 d	85 (26.3)	71 ± 8.7	58 (68.2)	37 (43.5)	0 (0)	15 (17.6)	33 (38.9)	NR
		8–14 d	80 (24.8)	72 ± 9.3	60 (74.1)	37 (46.3)	1 (1.3)	9 (11.1	34 (30)	NR
		15–180 d	145 (44.9)	70 ± 8.7	98 (67.6)	62 (42.8)	0 (0)	35 (24.1)	38 (33.1)	NR
Charmoille[47] (2014)	CEA	All (0–180 d)	149 (100)	71.5	119 (79.9)	60 (40.3)	19 (12.7)	14 (9.4)	75 (50.3)	NR
		0–14 d	62 (41.6)	69.7 ± 10.9	68 (78.2)	29 (46.8)	11 (17.7)	6 (9.7)	27 (43.5)	NR
		15–180 d	87 (58.4)	71.2 ± 13.3	51 (82.3)	31 (35.6)	8 (21.8)	8 (9.2)	48 (55.2)	NR
Rantner[48] (2014)	CEA	All (0–180 d)	761 (100)	70.1 ± 9.7	559 (73.5)	305 (40.1)	–	162 (21.3)	294 (38.6)	NR
		0–2 d	206 (27.1)	70.1 ± 10.3	152 (73.8)	115 (55.8)	–	37 (18)	54 (26.2)	NR
		3–7 d	219 (28.8)	70.9 ± 9.4	159 (72.6)	91 (41.6)	–	51 (23.3)	77 (35.2)	NR
		8–14 d	136 (17.9)	71.0 ± 9.2	102 (75.0)	54 (39.7)	–	33 (24.3)	49 (36.0)	NR
		15–180 d	200 (26.3)	68.5 ± 9.5	146 (73.0)	45 (22.5)	–	41 (20.5)	114 (57.0)	NR

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Table 2-*continued*

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Tsivgoulis[49] (2014)	CEA	All (0–14 d)	165 (100)	69 ± 10	114 (69)	50 (30)	–	–	115 (70)	NR
		0–2 d	20 (12)	70±12	11 (55)	7 (35)	–	–	13 (65)	NR
		3–14 d	145 (88)	68 ± 10	154 (71)	44 (30)	–	–	101 (70)	NR
Shahidi[53] (2013)	CEA	All	115 (100)	NR	NR	39 (34)	–	11 (9)	65 (56.5)	NR
Sharpe[15] (2013)	CEA	All	475 (100)	NR	NR	72 (57)	–	94 (20)	109 (23)	
Faggioli[54] (2013)	CEA	All (0–180 d)	162 (100)	NR	NR	81 (50)	–	9 (5.6)	72 (44.4)	NR
		0–14	60 (37)	NR	NR	36 (60)	–	2 (3.3)	22	NR
		15–30	18 (11.1)	NR	NR	12 (66.7)	–	2 (11.1)	4	NR
		31–180	84 (51.9)	NR	NR	33 (39.3)	–	5 (5.9)	46	NR
Annambhotla[59] (2012)	CEA	All (0–180 d)	312 (100)	NR	200 (64.1)	106 (34.0)	–	–	205 (65.6)	
		0–7 d	27 (8.7)	68.6 ± 9.8	16 (59.3)	7 (25.9)	–	–	20 (74.1)	
		8–14 d	17 (5.4)	68.8 ± 14.7	9 (52.9)	3 (17.6)	–	–	14 (82.4)	
		15–21 d	12 (3.8)	67.5 ± 14.3	8 (66.7)	3 (25)	–	–	9 (75)	
		22–30 d	12 (3.8)	70.7 ± 9.3	8 (66.7)	1 (8.3)	–	–	11 (91.7)	
		31–180 d	243 (77.9)	70.4 ± 9.7	159 (65)	92 (38)	–	–	151 (62)	
Lin[61] (2009)	CAS	All (0–180 d)	224 (100)							
		0–30 d[†]	122 (54.5)	72 ± 10.2	80 (65.6)	77 (62.6)	–	–	46 (37.4)	
		31–180 d	102 (45.5)	69 ± 9.9	63 (61.8)	72 (71.3)	–	–	29 (28.7)	
				$p = .002$	$p = .39$					
Ballotta[68] (2008)	CEA	0–14 d	102 (100)	NR	65 (65.7)	0 (0)	0 (0)	0 (0)	102 (100)[‡]	NR
Setacci[69] (2008)	CAS	All (0–30 d)	57 (100)	76.7 ± 8.0	37 (64.9)	–	–	–	–	NR
		0–2 d	24 (42)	–	–	24 (100)	–	–	0 (0)	NR
		14–30 d	33 (58)	–	–	0 (0)	–	–	33 (100)	NR
Suzue[74] (2007)	CEA	All (0–180 d)	72 (100)							NR
		0–30 d	15 (20.8)	65.4 ± 7.0	14 (93.3)	7 (46.7)	–	–	8 (14.0)	NR
		31–180 d	57 (79.2)	69.2 ± 7.4	47 (76.9)	27 (47.4)	–	–	30 (52.6)	NR
Dellagrammaticas[71] (2007) GALA Trial	CEA		867 (100)	71.5 ± 3.5	687 (69)	303 (35)	–	146 (17)	231 (27)	NR
Flanigan[72] (2007)	CEA		170 (38.5)	NR	NR	NR	NR	NR	NR	NR
Sbarigia[76] (2006)	CEA		96 (100)	69.4 ± 9.8	81 (84.3)	NR	NR	NR	NR	NR
Imai[77] (2005)	CAS		17 (100)	69.9	13 (76.4)	NR	NR	NR	NR	NR
Rantner[78] (2005)	CEA	All (0–180 d)	104 (100)	69.4 ± 9.8	80 (87.1)	NR	NR	NR	NR	NR
		0–6 hours	7 (6.7)							
		0–27 d	29 (27.9)							
		28–180 d	62 (59.6)							
Welsh[81] (2003)	CEA	All (0–180 d)	40 (100)							
		0–1 d	19 (47.5)	65.8 ± 8.9	11 (57.9)	NR	NR	NR	NR	NR
		60–180 d	21 (52.5)	68.3 ± 9.5	12 (57.1)	NR	NR	NR	NR	NR
ECST[84] (1988)	CEA *vs.* BMT		1 807 (100)	NR	NR	NR	NR	NR	NR	NR
National audits										
Kuhrij[21] (2019) Dutch Audit for Carotid Intervention	CEA	All	8 620 (100)	72 ± 9.0	6010 (70)	NR	NR	NR	NR	NR
		0–14 d	6 645 (78)	NR	NR	NR	NR	NR	NR	NR
Faateh[39] (2018) National Quality Improvement	CEA	All	9 271 (100)	NR	NR	NR	NR	NR	NR	NR
	eCEA		546 (5.9)	70.5 ± 11.2	348 (63.7)	206 (37.7)	–	61 (11.2)	279 (51.1)	NR
	Non-eCEA		8 725 (94.1)	70.8 ± 9.9	5 390 (61.8)	3 282 (37.6)	–	1 507 (17.3)	3 935 (45.1)	NR
Tsantilas[40] (2018) German Statutory Quality Assurance	CAS	All (0–180 d)	4 717 (100)	69.8 ± 9.8	3 201 (67.8)	1 351 (28.6)	–	797 (16.9)	2 126 (45.1)	NR
		0–2 d	550 (11.6)	69.1 ± 10.1	386 (70.2)	155 (28.2)	–	65 (11.8)	268 (48.7)	NR
		3–7 d	1 579 (33.4)	69.6 ± 9.9	1070 (67.8)	472 (29.9)	–	212 (13.4)	796 (50.4)	
		8–14 d	1 244 (26.3)	70.1 ± 9.9	835 (67.1)	306 (24.6)	–	234 (18.8)	622 (50.0)	NR
		15–180 d	1 344 (28.4)	69.9 ± 9.5	910 (67.7)	418 (31.1)	–	286 (21.3)	440 (32.7)	NR
Blay[41] (2018)	CEA	All (0–180 d)	3 427 (100)	NR	2181 (63.6)	NR	NR	NR	NR	NR
ACS-NSQIP		0–7d	3 247 (94.7)	NR	NR	NR	NR	NR	NR	NR
		8–180 d	180 (5.3)	NR	NR	NR	NR	NR	NR	NR
Rocco[20] (2018)	CEA / CAS		110 (100)	NR	78 (70.9)	10 (9.1)	–	–	100 (90.9)	NR

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Table 2-*continued*

Article (Year)	CEA / CAS	Time periods	Symptomatic CEA / CAS	Age	Male sex	Type of event				New events before intervention
						TIA	Crescendo TIA / stroke in evolution	Afx	Minor / major stroke	
Avgerinos[83] (2017) VSGNE Database	CEA	All (0–180 d)	989 (100)	69.6 ± 10.7	653 (66)	NR	NR	NR	NR	NR
		0 d	477 (48.2)	69.4 ± 10.5	307 (64.4)	NR	NR	NR	NR	NR
		1–2 d	96 (9.8)	70.1 ± 10.9	66 (68.8)	NR	NR	NR	NR	NR
		3–5 d	322 (32.6)	69.9 ± 10.8	210 (65.2)	NR	NR	NR	NR	NR
		6–180 d	94 (9.1)	69.3 ± 11.4	70 (74.5)	NR	NR	NR	NR	NR
Kjorstad[18] (2017) National Norwegian Carotid Study	CEA		368 (100)	NR	NR	135 (36.7)	–	64 (17.4)	167 (45.4)	12 (3.3%)
Hobeanu[42] (2017)	CEA/CAS		187 (100)	71 ± 10	142 (75.9)	NR	NR	NR	NR	NR
Loftus[24] (2016) UK National Vascular Registry	CEA		23 235 (70.0)	72.8 ± 3.7	15 510 (66.8)	11 029 (47.5)	–	3 553 (15.3)	8 229 (35.4)	NR
Villwock[12] (2014) NIS Registry	CEA *vs.* CAS	All (0–14 d)	72 797 (100)	NR				NR		
		0–2 d	41 008 (56.3)	NR	22 601 (55.1)	38 001 (52.2)	3 007 (4.1)	NR		NR
	CEA		31 899 (43.8)	NR	17 105	29 936 (41.1)	1 963 (2.7)	NR		NR
	CAS		9 109 (12.5)	NR	5 496	8065 (11.1)	1 044 (1.4)	NR		NR
		3–14 d	31 789 (43.7)	NR	25 146 (79.1)	22 207 (30.5)	12 582 (17.3)	NR		NR
	CEA		30 428 (41.8)	NR	22 436	19 729 (27.1)	10 699 (14.7)	NR		NR
	CAS		4 361 (6.0)	NR	2 710	2 478 (3.4)	1 883 (2.6)	NR		NR
Stromberg[27] (2012) Swedvasc Registry	CEA	All (0–180 d)	2 596 (100)	71.9 ± 8.2	1 731 (66.7)	1 041 (40.1)	54 (2.1)	508 (19.6)	993 (38.3)	NR
		0–2 d	148 (100)	69.8 ± 8.6	104 (70.3)	70 (47.3)	17 (11.5)	23 (15.5)	38 (25.7)	NR
		3–7 d	804 (100)	72.6 ± 8.2	526 (65.4)	363 (45.1)	19 (2.4)	122 (15.2)	300 (37.3)	NR
		8–14 d	677 (100)	72.7 ± 8.2	438 (64.7)	279 (41.2)	14 (2.1)	107 (15.8)	259 (38.3)	NR
		15–180 d	967 (100)	71.0 ± 8.1	663 (68.6)	329 (34.0)	4 (0.4)	256 (26.5)	411 (42.5)	NR
Garg[60] (2011) National Surgery Quality Improvement	CEA		8 103 (46.6)	NR	NR	NR	NR	NR	NR	NR
Palombo[62] (2009) Italian Vascular Registry	CEA		1 894 (32.6)	NR	NR	NR	NR	NR	NR	NR
Halliday[86] (2009) UK Surgeons undertaking CEA	CEA	All (0–180 d)	4 576 (100)	NR	NR	1 914 (41.8)	–	916 (20.0)	1 634 (35.7)	NR
		0–2 d	944 (20.6)	NR	NR	NR	NR	NR	NR	NR
		3–4 d	654 (14.3)	NR	NR	NR	NR	NR	NR	NR
		5–12 d	1 621 (35.4)	NR	NR	NR	NR	NR	NR	NR
		13–180 d	1 372 (30.0)	NR	NR	NR	NR	NR	NR	NR
Vogel[65] (2009) Nationwide Inpatient Sample (2005)	CEA/CAS		2 237 (100)	NR	NR	NR	NR	NR	NR	NR
Gladstone[63] (2009) Canadian Stroke Network	CEA		105 (100)	NR	NR	NR	NR	NR	NR	NR
Goodney[66] (2008) VSGNE (2003–2007)	CEA	All	1 360 (100)	NR	NR	680 (50)	–	572 (42.1)	340 (25)	NR
		Emergency / Urgent	309 (22.7)	NR	NR	NR	–	NR	NR	NR
Pell[79] (2004) National Prospective Survey Scotland	CEA	All (0–60 d)	855 (100)	NR	510 (58.2)	NR	NR	NR	NR	NR
		0–30 d	103 (27)	NR	NR	NR	NR	NR	NR	NR
		31–60 d	222 (58)	NR	NR	NR	NR	NR	NR	NR
Tu[82] (2003) Ontario Carotid Endarterectomy Registry	CEA		4 192 (69.4)	NR	NR	NR	NR	NR	NR	NR

Data are presented as *n* (%) or mean ± standard deviation, unless stated otherwise. NA = not applicable; NR = not reported. *p* value is considered significant if ≤ .050.

* Of the most recent neurological event before intervention.

† Early category was subclassified into ultra-early (0–14 d) with not significant difference compared with other categories.

‡ Only minor strokes were included.

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Table 3. Analysis of post-procedural outcomes after carotid endarterectomy (CEA) or carotid artery stenting (CAS), stratified by delay after index event

Study, year	CEA/CAS	0–2 d	3–7 d	8–14 d	15–30 d	31–180 d
30 day stroke – % (n)						
Jankowittz, 2020[13]	CEA	5.1 (3)	–	–		–
	CAS	3.3 (2)	–	–		–
Huang, 2018[14]	CEA	27 (3)	0 (0)	4.3 (1)		0.6 (1)
Tsantilas, 2018[40] German Statutory Quality	CAS	3.8 (21)	3.5 (56)	1.8 (22)		2.2 (30)
Sharpe, 2013[15]	CEA	2.4 (1)	1.8 (3)	0.8 (1)		0.8 (1)
Stromberg, 2012 Swedvasc[27]	CEA	10.8 (16)	2.5 (20)	3.4 (23)		4.0 (39)
Nordanstig, 2017[8]	CEA	8.0 (6)	3.0 (9)			–
Avgerinos, 2017 VSGNE[43]	CEA	3.5 (20)		2.4 (10)		
Tsantilas, 2016[23]	CEA	0 (0)	1.8 (2)	1.5 (1)		1.8 (3)
Loftus, 2016 UK National Vascular Registry[24]	CEA	3.1 (24)	2.0 (103)	1.7 (107)		1.8 (199)
Jonsson, 2015[16]	CAS	0 (0)	3.5 (3)	6.3 (5)		3.5 (5)
Rantner, 2014[48]	CEA	8 (3.9)	4 (1.8)	6 (4.4)		5 (2.5)
Villwock, 2014	CEA	1.1 (341)	1.6 (496)			–
NIS *,[12]	CAS	1.7 (154)	1.8 (77)			–
Roussopoulou, 2019[9]	CEA	7.9 (5)	4.4 (11)		–	–
Seguchi, 2017[10]	CAS	2.5 (1)	–		6.2 (4)	
Setacci, 2007[69]	CEA	0 (0)	0 (0)		–	–
Blay, 2018 ACS-NSQIP[41]	CEA	2.7 (86)			2.8 (5)	
Rantner, 2017[44]	CEA	1.3 (3)			3.4 (63)	
	CAS	8.0 (23)			6.8 (122)	
Annambhotla, 2012[59]	CEA	0 (0)		0 (0)		1.6 (4)
Chisci, 2016[19]	CEA	3.0 (3)			0.4 (1)	–
Kretz, 2015[26]	CEA	1.3 (2)				1.5 (4)
Charmoille, 2014[47]	CEA	0 (0)				3.5 (3)
Faggioli, 2013[54]	CEA	6.6 (4)				2.9 (3)
Ballotta, 2008[68]	CEA	0 (0)			–	–
Suzue, 2007[74]	CEA	0 (0)				0 (0)
30 day myocardial infarction – % (n)						
Jankowittz, 2020[13]	CEA	3.4 (2)	–	–		–
	CAS	4.9 (3)	–	–		–
Huang, 2018[14]	CEA	0 (0)	0 (0)	0 (0)		3.3 (6)
Tsantilas, 2018 German Statutory Quality[40]	CAS	0.3 (1)	0.1 (1)	0 (0)		0.1 (1)
Jonsson, 2015[16]	CAS	0 (0)	3.5 (3.0)	2.5 (2)		1.4 (2)
Avgerinos, 2017 VSGNE[43]	CEA	1.4 (8)		1.2 (5)		
Tsantilas, 2016[23]	CEA	2.0 (1)	1.0 (1)	0 (0)		1.0 (1)
Roussopoulo, 2019[9]	CEA	0 (0)	0.8 (2)		–	–
Seguchi, 2017[10]	CAS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Setacci, 2007[69]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Annambhotla, 2012[59]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0.8 (2)
Chisci, 2016[19]	CEA	0 (0)	0 (0)	0 (0)	1.8 (4)	–
Charmoille, 2014[47]	CEA	0 (0)	0 (0)	0 (0)		3.5 (3)
Faggioli, 2013[54]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ballotta, 2008[68]	CEA	0 (0)	0 (0)	0 (0)	–	–
Blay, 2018 ACS-NSQIP[41]	CEA	0.99 (32)			0.56 (1)	
Kretz, 2015[26]	CEA		0.6 (1)			1.2 (3)
30 day mortality – % (n)						
Jankowittz, 2020[13]	CEA	0 (0)	–	–		–
	CAS	1.6 (1)	–	–		–
Huang, 2018[14]	CEA	0 (0)	0 (0)	0 (0)		0.6 (1)
Tsantilas, 2018 German Statutory Quality[40]	CAS	2.2 (12)	0.9 (14)	0.6 (8)		0.7 (10)
Jonsson, 2015[16]	CAS	0 (0)	0 (0)	3.8 (3)		0.7 (1)
Sharpe, 2013[15]	CEA	0 (0)	0 (0)	0.8 (1)		0 (0)
Stromberg, 2012 Swedvasc[27]	CEA	2.0 (3)	1.2 (10)	1.5 (10)		1.7 (16)
Avgerinos, 2017 VSGNE[43]	CEA	1.2 (7)		1.4 (6)		
Tsantilas, 2016[23]	CEA	3.0 (2)	1.0 (1)	0 (0)		1.0 (1)
Loftus, 2016[24] UK National Vascular Registry	CEA	1.0 (8)	0.9 (46)	0.7 (44)		0.8 (88)
Rantner, 2014[48]	CEA	0.5 (1)	0 (0)	0.7 (1)		0.5 (1)
Villwock, 2014	CEA	0.4 (129)	0.8 (258)		–	–
NIS *,[12]	CAS	2.1 (191)	1.6 (69)		–	–
Roussopoulo, 2019[9]	CEA	0 (0)	0.4 (1)		–	–
Nordanstig, 2017[8]	CEA	0 (0)	0.3 (1)		0 (0)	0 (0)
Seguchi, 2017[10]	CAS	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Annambhotla, 2012[59]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Chisci, 2016[19]	CEA	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

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Table 3-*continued*

Study, year	CEA/CAS	0–2 d	3–7 d	8–14 d	15–30 d	31–180 d
Blay, 2018 ACS-NSQIP[41]	CEA	1.2 (38)			2.8 (5)	
Kretz, 2015[26]	CEA		1.9 (3)		1.5 (4)	
Charmoille, 2014[47]	CEA		1.7 (1)		1.2 (1)	
Faggioli, 2013[54]	CEA		1.6 (1)		0 (0)	3.6 (3)
Ballotta, 2008[68]	CEA		0 (0)		–	–
30 day death / stroke – % (n)						
Jankowittz, 2020[13]	CEA	5.1 (3)	–	–		–
	CAS	4.9 (3)	–	–		–
Roussopoulou, 2019[9]	CEA	7.9 (5)	4.8 (12)	–		–
Huang, 2018[14]	CEA	27 (3)	0 (0)	4.3 (1)		1.1 (2)
Nordanstig, 2017[8]	CEA	8.0 (6)	3.0 (9)			–
Tsantilas, 2016[23]	CEA	3.0 (2)	3.0 (3)	2.0 (1)		2.0 (3)
Loftus, 2016 UK National Vascular Registry[24]	CEA	29 (3.7)	128 (2.5)	132 (2.1)		254 (2.3)
Jonsson, 2015[16]	CAS	0 (0)	4.7 (4)	6.3 (6)		4.1 (6)
Rantner, 2014[48]	CEA	4.4 (9)	1.8 (4)	5.1 (7)		2.5 (5)
Sharpe, 2013[15]	CEA	2.4 (1)	1.8 (3)	0.8 (1)		0.8 (1)
Stromberg, 2012	CEA	11.5 (17)	3.6 (29)	4.0 (27)		5.4 (52)
Swedvasc[27]						
Nordanstig, 2017[8]	CEA	6 (8)	10 (3)			–
Seguchi, 2017[10]	CAS	2.5 (1)		6.2 (4)		
Rantner, 2017[44]	CEA	1.3 (3)			3.6 (65)	
	CAS	8.4 (24)			7.1 (129)	
Chisci, 2016[19]	CEA		3.0 (3)		0.4 (1)	–
Mean 30 day death / stroke ± standard deviation						
Jankowittz, 2020[13]	CEA	5.6±3.2	–	–		–
	CAS	5.3±4.1	–	–		–
		p=.66	–	–		–
Huang, 2018[14]	CEA	4.7±7.2	3.3±1.7	2.0±1.5		1.8±1.5
Tsantilas, 2018 German Statutory Quality[40]	CAS	3.5±1.2	3.3±0.9	2.5±0.6	–	–
Villwock, 2014[12] NIS*	CEA for Stroke	3.5±1.2	7.3±1.5		–	–
	CAS for Stroke	4.3±1.5	7.3±1.5		–	–
	CEA for TIA/AFX	1.8±0.1	6.5±1.2		–	–
	CAS for TIA/AFX	1.3±0.4	6.0±1.2		–	–
Roussopoulo, 2019[9]	CEA	6.5±1.7	10.3±2.0		–	–
Seguchi, 2017[10]	CAS	22.5±6.3		21.5±4.6		
Chisci, 2016[19]	CEA		3.7±2.2		2.5±1.5	–

TIA = transient ischaemic attack; AFX = amaurosis fugax
* In hospital data

Quality assessment

The methodology of the studies and risk of bias were systematically assessed by two independent reviewers (AC and JP) using the Methodological Index for Non-Randomized Studies (MINORS) score,[7] with a maximum score of 16 for non-comparative and 24 for comparative studies. A score $\leq$ 8 was considered poor quality, 9 — 14 moderate quality, and 15 — 16 good quality for non-comparative studies. Cut off points were $\leq$ 14, 15 — 22, and 23 — 24, respectively, for comparative studies.

Authorship of the studies was unblinded during review. 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.

Statistical analysis

The software Review Manager 5.4 (REVMAN) was used to analyse data. Odds ratios (OR) and 95% confidence intervals (CI) were used for dichotomous variables, and mean differences (MDs) with 95% CI for continuous data.

Statistical heterogeneity, defined as a measure of the variability of outcomes between studies, was assessed by the Cochran's Q test: the H^2 test (Higgins and Thompson) was used to quantify the magnitude of heterogeneity. The parameter I^2 retrieved from the H^2 test was used with a cut off of 25% for low, 25% — 50% for intermediate, and above 50% for high heterogeneity. A fixed effects model was used when heterogeneity (I^2) was less than 50% and a random effects model was used when heterogeneity (I^2) was high.

RESULTS

A total of 1 495 potentially relevant articles were identified initially. After reviewing title or abstract, 112 articles were retrieved and 71 judged eligible for inclusion (Fig. 1). Agreement between reviewers was reached for all articles and arbitration by the third reviewer was unnecessary.

Overall, there were 24 retrospective analyses of prospective national databases, 10 retrospective analyses of prospective databases, nine prospective studies, three RCTs, and three case control studies. The remaining 22 studies

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were retrospective, single centre, or multicentre, analysis of patient data. The total number of symptomatic patients in the constituent studies was 232 952 (Table 1). Methodological quality is reported in Supplementary Table S1. A total of 18 non-comparative studies of moderate quality and 53 comparative studies (50 moderate, two poor quality, and one good quality) were included (Supplementary Table S1).

Definitions

The definitions of "delay" and "index event" were heterogeneous (Table 1). Most studies defined "early intervention" when CEA or CAS were performed within 14 days of the index event, although some studies applied stricter or looser definitions (Table 1). Stratification of the timing of events within the first 14 days was described in some studies, for example as "acute/urgent/emergency/ultra-early interventions" (Table 1). One study was identified that defined the timing of intervention as the time from the qualifying event (defined as the most recent neurological event before intervention, rather than the index event).[8]

Symptomatic status and timing of intervention

Considering all symptomatic patients (232 952), the time to intervention was reported for 148 653 patients (63.8%), of whom 44 410 (29.9%) underwent either CEA or CAS within the first 48 hours and 108 139 (72.7%) within the first 14 days after the index event.

Thirty-five studies reported outcomes after CEA alone (73 242), while five studies reported outcomes after CAS alone (5 443). Five studies reported mixed outcomes, three of which compared CEA (64 430) with CAS (15 624) (Table 2).

Stratification of demographic data, type of neurological index event, and occurrence of new neurological symptoms, stratified by intervention delay are detailed in Table 2.

Where reported, patients presenting with crescendo TIAs were more likely to undergo an early intervention.[9,10] The remaining presenting events (TIA, amaurosis fugax and stroke) were evenly distributed by intervention delay, with few exceptions (Table 2).

Primary and secondary outcomes

Peri-operative (30 day) outcomes along with data on hospitalisation duration (in days), stratified by intervention delay and by type of revascularisation (CEA *vs.* CAS) are detailed in Table 3. Almost all of the CAS procedures in the varying meta-analyses were performed via the transfemoral route. No published studies have evaluated outcomes for transcarotid artery revascularisation (TCAR) *vs.* CEA, with stratification for delays to treatment.[11]

Carotid endarterectomy *vs.* carotid artery stenting

Overall data. Outcome data from eight CEA studies (88 129) and two CAS studies (3 551) are detailed in Table 4. In CEA patients, 30 day stroke was 1.4% (95% CI 0.9 — 1.8) when performed within 0 — 2 days, *vs.* 1.8% (95% CI. 1.5 — 2.0) when performed between three and 14 days. In CAS patients, 30 day stroke was 1.8% (95% CI 1.3 — 2.3) when performed within two days, *vs.* 2.2% (95% CI 0.3 — 4.2) between three and 14 days (Table 4). Across all intervention timings, there were higher rates of stroke after CAS (*vs.* CEA), while there were higher rates for MI after CEA (*vs.* CAS). Individual study data used to calculate the pooled rates are available in Supplementary Table S2 (Supplementary material).

Carotid endarterectomy vs. carotid artery stenting when performed ≤ 2 days after the index event. Two moderate quality studies reported outcomes after CEA *vs.* CAS (75 917) when performed within two days of the index event, including one retrospective analysis of prospective single centre data (120) and one retrospective analysis of Nationwide Inpatient Sample (NIS) database (72 797).[12,13] Compared with CEA, meta-analysed data revealed significantly higher risks for 30 day stroke when CAS was performed within ≤ 2 days (OR 0.70; 95% CI 0.58 — 0.85) as well as significantly higher rates of 30 day death (OR 0.41; 95% CI 0.31 — 0.53) (Fig. 2). One of the above mentioned registries (72 797) analysed patients with and without cerebral infarction separately and concluded that expedited revascularisation in patients with cerebral infarction on admission increased the risk of iatrogenic stroke and death; the increase in mortality was more dramatically seen in patients treated by CAS. No differences were found in stroke/death rates between CEA and CAS if patients presented without infarction.[12]

Carotid endarterectomy vs. carotid artery stenting when performed 3 — 14 days after index event. The same large national registry (72 797) cited in the previous section also reported comparative outcomes between CEA *vs.* CAS when performed 3 — 14 days after the index event (with or without cerebral infarction). There was no statistically significant difference in 30 day stroke after CAS (1.8%) *vs.* after CEA (1.6%; OR 1.1; 95% CI 0.9 — 1.4). However, 30 day mortality was statistically significantly higher after CAS (1.6%) *vs.* after CEA (0.8%; OR 1.9; 95% CI 1.4 — 2.5). Again, no differences were found in stroke/death rates between CEA and CAS if patients presented without infarction.[12]

Outcomes after carotid endarterectomy

≤ 2 days vs. 3 — 14 days after index event. A total of nine moderate quality manuscripts were included in this analysis, three of which were retrospective analyses of national registries, two prospective multicentre studies, and four retrospective studies. CEA performed 3 — 14 days after the index event was associated with a statistically significantly lower 30 day death/stroke risk (OR 2.05; 95% CI 1.56 — 2.68) compared with performing CEA within ≤ 2 days of index event. No statistically significant difference was attained regarding 30 day stroke, MI, and mortality (OR 1.87; 95% CI 0.99 — 3.51, OR 1.50; 95% CI 0.21 — 10.45, and OR 1.11; 95% CI 0.58 — 2.14, respectively) (Fig. 3).

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Meta-analysis of 30 day stroke, mortality, and MI included the same core studies, while in the analysis of 30 day death/stroke, three studies were excluded as they did not report the composite outcome,[9,12,14] while one study was included that only reported combined stroke/death data, with worse outcomes reported in the expedited cohort (Fig. 3).[15]

≤ 7 days vs. 8 – 14 days after index event. A total of five moderate quality manuscripts were included in this analysis, two of which were retrospective analyses of national registries and three retrospective studies. Meta-analyses (Fig. 4) revealed that CEA performed within 7 days of the index event was associated with a significantly lower risk of 30 day stroke compared with 8 – 14 days (OR 0.67; 95% CI 0.54 – 0.84). There was no difference regarding CEA performed within 7 days of the index event (*vs.* 8 – 14) in the outcomes 30 day mortality (OR 1.86; 95% CI 0.19 – 18.21), 30 day death/stroke (OR 0.79; 95% CI 0.47 – 1.34), or 30 day MI (OR 1.94; 95% CI 0.09 – 41.03) (Fig. 4).

Outcomes after carotid artery stenting

≤ 2 days vs. 3 – 14 days after index event. This systematic review identified 17 578 patients who underwent CAS ≤ 14 days of symptom onset, including 9 833 (55.9%) who underwent CAS within ≤ 2 days of the index symptom. Two moderate quality national registries compared outcomes when CAS was performed within ≤ 2 days vs. 3 – 14 days of the index symptom.[14,16] Compared with CAS interventions within 3 – 14 days, performing CAS ≤ 2 days was not associated with significant differences in 30 day stroke (OR 1.36; 95% CI 0.84 – 2.21) or 30 day MI (OR 2.23; 95% CI 0.34 – 14.41) However, performing CAS within ≤ 2 days of the index symptom was associated with significantly higher risks of 30 day death (OR 2.76; 95% CI 1.39 – 5.50) compared with CAS interventions within 3 – 14 days of the index event (Fig. 5). A single study ($n = 323$) reported the results of a comparative analysis of 30 day death/stroke and showed no significant difference when CAS was performed in either time period (OR 0.61; 95% CI 0.03 – 11.06).[16]

≤ 7 days vs. 8 – 14 days after index event. The same national registries that compared outcomes when CAS was performed ≤ 2 days *vs.* 3 – 14 days, also analysed outcomes ≤ 7 days *vs.* 8 – 14 days.[14,16] Forest Plot analyses (Fig. 6) revealed that there was no significant difference in 30 day stroke, MI, or mortality when CAS was performed ≤ 7 days *vs.* 8 – 14 days after the index event (OR 1.18; 95% CI 0.29 – 4.83, OR 1.62; 95% CI 0.35 – 7.43, and OR 0.67; 95% CI 0.04 – 10.12, respectively).

Recurrent events while awaiting a carotid intervention

Recurrent neurological events occurring after a decision to perform CEA but before it was performed were reported rarely. In one single centre study, 42% of patients who waited 0 – 180 days to undergo CEA suffered a recurrent TIA or stroke prior to CEA.[17] The National Norwegian Carotid Study reported that 3.3% suffered recurrent symptoms prior to undergoing CEA within 14 days of the index event (Table 2).[18]

Neurological outcome

Surprisingly, few studies used the National Institutes of Health Stroke Scale (NIHSS) to quantify improvements in neurological disability after carotid interventions, stratified for the timing of carotid interventions (Table 3). A single centre study reported improved neurological outcomes for interventions performed within 14 days *vs.* 15 – 30 days of the index event (NIHSS range 0.9 ± 0.4 *vs.* 0.5 ± 0.2; $p = .011$).[19] Other studies report NIHSS range but with no discriminative data concerning carotid intervention delay from index event.[13,18,20]

Hospital stay

Hospital stay analysis presented a trend towards prolonged stay in patients undergoing CEA between 3 – 14 days after the index event *vs.* ≤ 2 days, with a mean difference (MD) of −1.28 (95% CI −6.96 – 4.40) (Fig. 7).

Only one study[10] reported length of hospital stay after CAS, with non-significant difference between intervention ≤ 2 *vs.* 3 – 14 days (MD −1.0; 95% CI −3.1 – 1.1).

DISCUSSION

The ESVS guidelines advise that CEA (CAS) should be performed within 14 days of symptom onset.[1] Evidence suggests that there has been a major drive towards performing interventions < 14 days (especially in Europe), where the median delay to CEA is now 11 days in the Netherlands,[21] 7 days in Sweden,[22] 9 days in Germany,[23] and 11 days in the UK.[24] A temporal trend towards a progressive decrease in delays from index event to undergoing CEA (or CAS) has been reported by several national registries.[24–26] The proportion of Danish Stroke Registry patients[17] undergoing carotid interventions within two weeks of the index event increased from 13% in 2007 to 47% by 2010 (OR 5.8; 95% CI 4.3 – 10.1).[25] Similar findings were reported by the UK National Vascular Registry.[24] However, uncertainty persists regarding the ideal timing for either CEA or CAS within the 14 day time frame to balance the dichotomy between recurrent stroke prevention and minimising peri-operative risks.[25]

The Swedish Vascular Registry (Swedvasc) were the first to highlight concerns about intervening within ≤ 48 hours of the index event, as they observed an 11.5% rate of 30 day death/stroke, compared with 3.6% (3 – 7 days), 4% (8 – 14 days), and 5.4% (> 14 days) for CEA. However, only a small proportion of Swedvasc patients were treated ≤ 48 hours (5.7%), which may have limited the generalisability of the Swedish registry data.[27] Other (much larger) national

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Table 4. Pooled estimated prevalence in different sized samples on main outcomes, stratified by intervention timing and type of procedure

	CEA		CAS	
	0–2 days – % (95% CI)	3–14 days – % (95% CI)	0–2 days – % (95% CI)	3–14 days – % (95% CI)
30 d stroke	1.4 (0.9–1.8); SE 0.2[*,‡]	1.8 (1.5–2.0); SE 0.1[†,‡]	1.8 (1.3–2.3); SE 0.2[*,‡]	2.2 (0.3–4.2); SE 0.5[†,‡]
30 d MI	1.5 (0.7–2.2); SE 0.2	0.9 (0.0–1.7); SE 0.2	0.6 (0.0–2.5); SE 0.6	0.2 (0.0–1.3); SE 0.3
30 d mortality	0.5 (0.4–0.6); SE 0.0	0.8 (0.8–0.9); SE 0.0	2.2 (1.8–2.6); SE 1.4	1.3 (0.3–2.2); SE 0.3
30 d death/stroke	4.9 (2.0–7.9); SE 1.2	2.5 (1.8–3.2); SE 0.2	3.5 (0.0–8.4)	2.4 (0.7–6.1)

CAS = carotid artery stenting; CEA = carotid endarterectomy; CI = confidence interval; MI = myocardial infarction; SE = standard error.
* Lower risk of stroke with CEA *vs.* CAS within two days of index event.
† Lower risk of stroke with CEA *vs.* CAS within 3–14 days of index event.
‡ In either category (CEA or CAS) stroke risk is lower within two days *vs.* 3–14 days of index event.

registries have not corroborated the Swedvasc findings. In the German CEA registry (56 000 CEAs), there was no difference in 30 day death/stroke between patients treated ≤ 48 hours by CEA (3%) *vs.* later time periods (2.5% between 3 – 7 days; 2.6% between 8 – 14 days; 2.3% for CEA thereafter).[23] In the UK national registry involving 20 000 patients, conclusions were that the pathway from most recent symptom to surgery for patients with symptomatic carotid stenosis, could be shortened to maximise the benefit of intervention, without increased peri-operative risk in the period. However, they admitted a slight increase in peri-operative risk of stroke and death in the first 48 hours.[24]

In this systematic review, 44 410 (29.9%) carotid interventions were undertaken within ≤ 2 days of the index event with no significant difference in 30 day stroke, mortality, and MI, while CEA performed 3 – 14 days after the index event was associated with a significantly lower risk of the composite outcome 30 day death/stroke. On the other hand, CEA within 7 days was associated with a significantly lower risk of stroke (*vs.* 8 – 14 days).

These contradictory results may be explained by the differences in included studies in each analysis, as already shown. Compared with the analysis of the outcomes stroke and mortality, analysis of the composite outcome stroke/death did not include data from two national registries and one prospective multicentre study,[9,12,14] while it included data from one retrospective single centre study that only reported combined stroke/death data.[15] Therefore, studies included in the analysis of 30 day stroke, death, and MI are of better study design compared with the studies in the 30 day death/stroke analysis, even though quality assessment is similar.

There were inconsistent findings regarding timing and outcomes in CAS patients. In patients undergoing CAS ≤ 2 days of the index event (*vs.* 3 – 14), there was no apparent difference in 30 day stroke or MI but there was a statistically significantly higher risk of death. Conversely, there were no differences in 30 day outcomes between CAS performed ≤ 7 days (*vs.* 8 – 14). The pathophysiology of procedural stroke may differ with expedited (*vs.* delayed) interventions in line with acute changes in atherosclerotic plaque vulnerability, which have been associated with an increased risk of embolism and neurological events after CAS.[28]

The systematic review also addressed the question of whether CEA or CAS was safer (or equivalent) when performed in the first 14 days after symptom onset. Compared

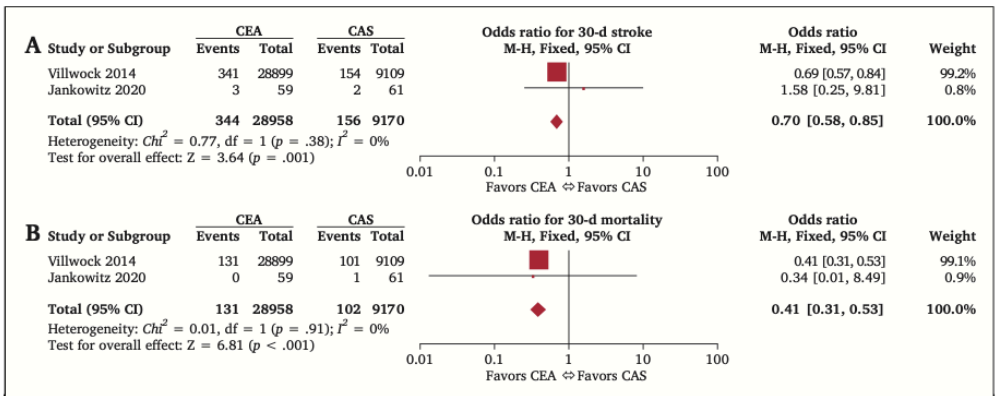

Figure 2. Forest plot showing the odds ratio (OR) for (A) 30 day stroke and (B) 30 day mortality after carotid endarterectomy (CEA) *vs.* carotid artery stenting (CAS) within two days of index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

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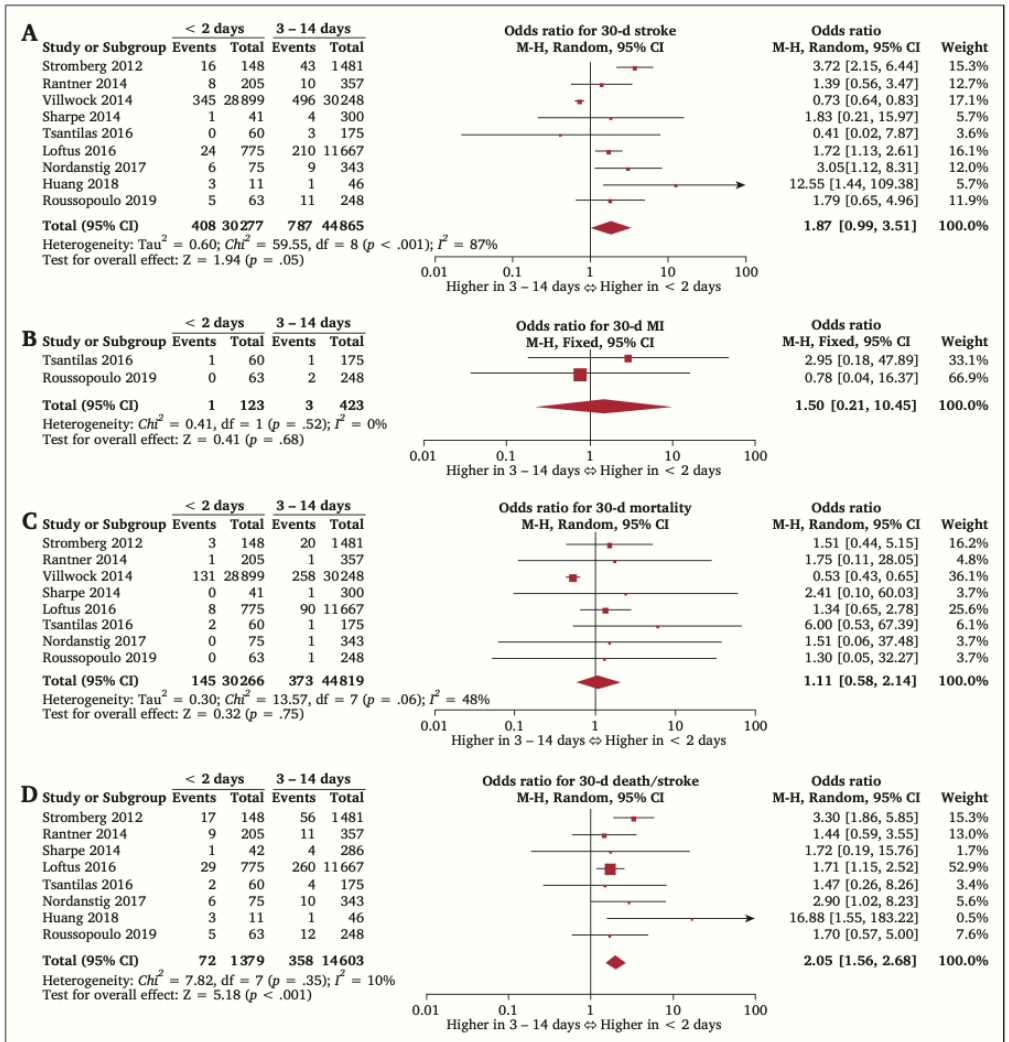

Figure 3. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), (C) 30 day mortality, and (D) stroke/mortality after carotid endarterectomy (CEA) within $\leq$ 2 *vs.* 3 – 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

with CEA, CAS was associated with significantly higher 30 day stroke and death rates when performed within $\leq$ 2 days of symptom onset. In an individual patient meta-analysis of data from the four largest RCTs comparing CEA with CAS (4 138 patients), CAS was associated with significantly higher risks of 30 day stroke, mortality, and death/stroke when performed within $\leq$ 7 days of the index event.[12]

These data suggest that, at the current time, CEA is probably safer than CAS both when performed $\leq$ 2 days and $\leq$ 7 days after symptom onset. However, virtually all of the CAS procedures in the current meta-analyses were performed via the transfemoral route. Registry data suggest that TCAR can be performed with 30 day outcomes similar to CEA in symptomatic patients.[29] Unfortunately, no studies

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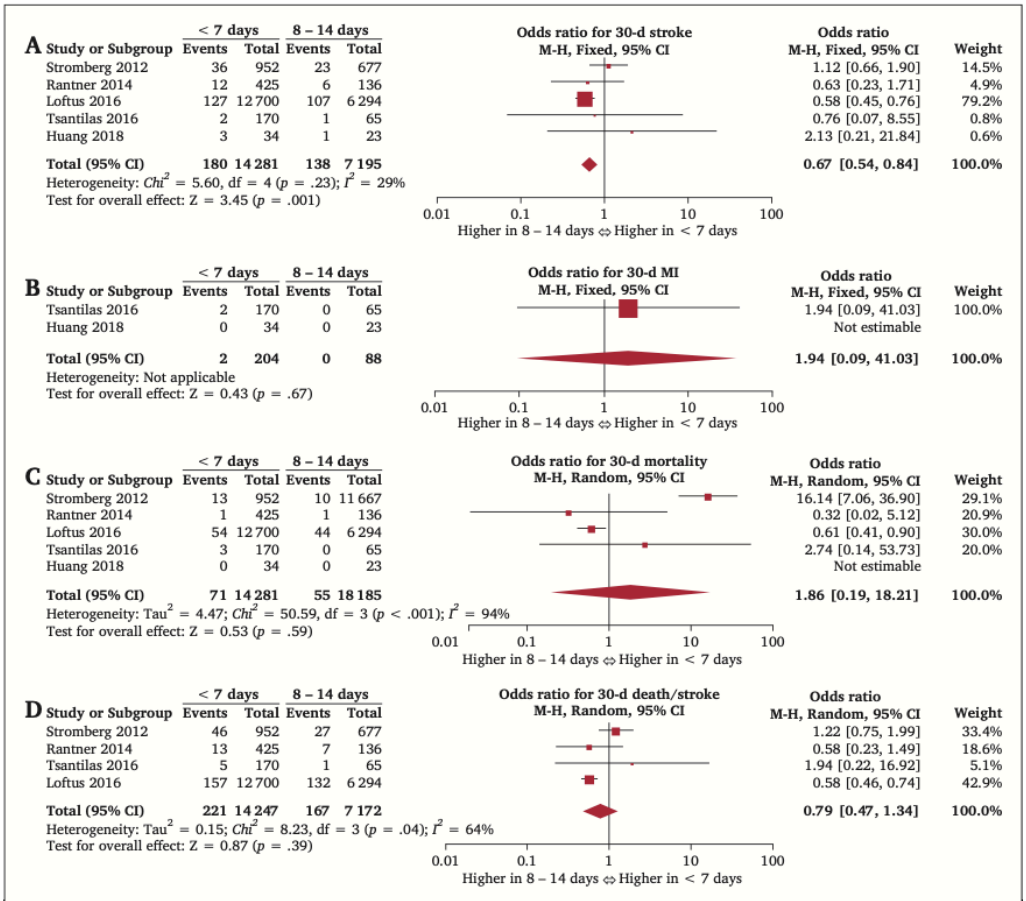

Figure 4. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), (C) 30 day mortality, and (D) stroke/mortality after carotid endarterectomy (CEA) within ≤ 7 *vs.* 8 – 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

have published outcome data for TCAR when used in the first 14 days after symptom onset,[11] and these data are keenly awaited.

There are relatively few data published on the incidence of recurrent events prior to expedited interventions. A prospective cohort study concluded that the risk was about 12% with modern best medical therapy, but that half of all recurrent events occurred within two days of the index event.[30] On the other hand, a recent meta-analysis revealed a cumulative 120 day risk of recurrent stroke of 1.97% (95% CI 0.75 — 3.17) in recent large RCTs, which was statistically significantly lower than in historical controls.[31]

Historically, vascular surgeons have not really considered the prevention of recurrent stroke in the time period between initiating investigation and initial management and undergoing CEA as being their primary responsibility. However, this attitude is likely to change as more symptomatic patients are started on dual antiplatelet therapy (DAPT) within 24 hours of symptom onset. The 2017 ESVS guidelines recommended that early treatment with DAPT "may be considered" to prevent recurrent events (prior to CEA) in patients with TIA or minor ischaemic stroke and an ipsilateral 50% — 99% stenosis awaiting CEA (Evidence IIb, Level C).[1] At the time, the ESVS Writing Group were unable to recommend routine DAPT in all symptomatic patients because there was no compelling evidence that this strategy conferred additional benefit over antiplatelet monotherapy.

However, based on a meta-analysis of three recent RCTs (CHANCE, POINT, and FASTER) in which 10 447 patients

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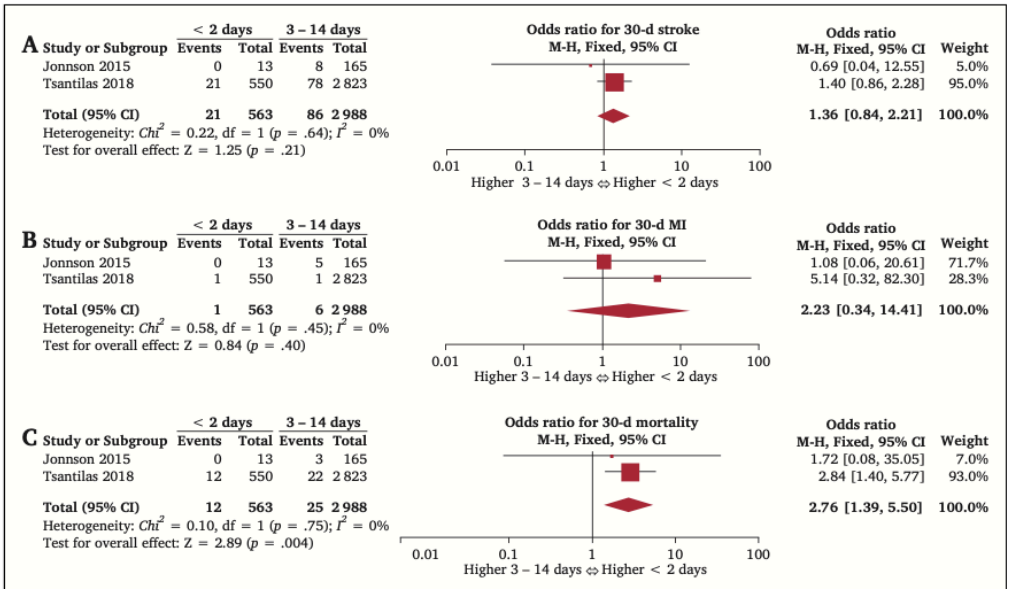

Figure 5. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), and (C) 30 day mortality after carotid artery stenting (CAS) within ≤ 2 *vs.* 3 – 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

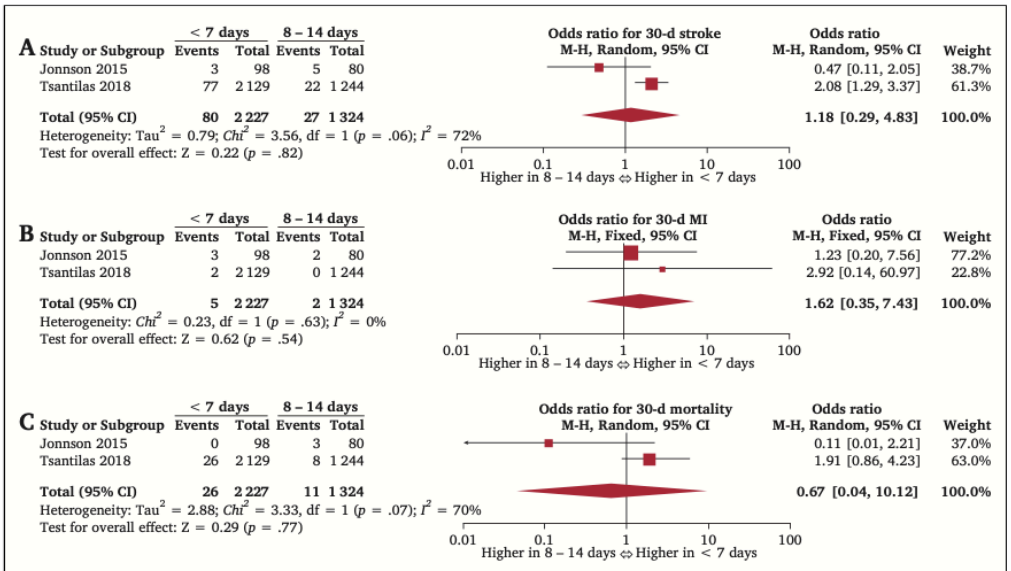

Figure 6. Forest plot showing the odds ratio (OR) for (A) 30 day stroke, (B) 30 day myocardial infarction (MI), and (C) 30 day mortality after carotid artery stenting (CAS) within ≤ 7 *vs.* 8 – 14 days of the index event. A Mantel-Haenszel (M-H) fixed effect model was used for meta-analysis. OR are shown with 95% confidence intervals (CI).

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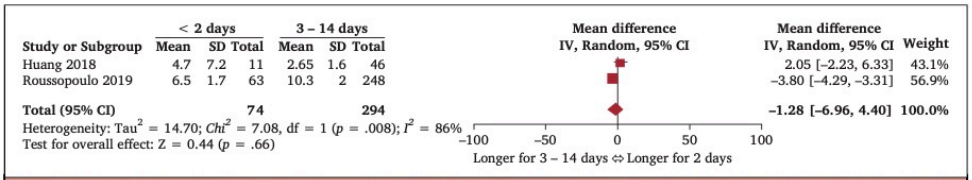

Figure 7. Forest plot showing the mean difference for hospital stay after carotid endarterectomy (CEA) within ≤ 2 vs. 3 − 14 days after the index event. Mean differences are shown with 95% confidence intervals (CI). SD = standard deviation; IV = inverse variance.

were randomised within 24 hours of experiencing a minor ischaemic stroke (NIHSS ≤ 3) or "high risk TIA" (ABCD[2] score ≥ 4) to aspirin monotherapy or short term aspirin and clopidogrel DAPT, there is now compelling evidence to support short term treatment with DAPT in these patient subgroups.[32] A recently published RCT also proved that in the subgroup of stroke patients with carotid artery stenosis, ticagrelor added to aspirin in the first 24 hours after the event, had greater absolute risk reduction of stroke or death at 30 days than stroke patients without carotid artery stenosis with a clinically meaningful benefit with a number needed to treat of 34 (95% CI 19 − 171).[33]

Methodological quality assessment revealed that the included studies are moderate to low quality, with a single high quality study in this analysis. Only a small number of studies was eligible for quantitative analysis, hindering conclusions. Also, heterogeneity of quantitative synthesis is significant, as determined by the I^2 test. Risk of bias is therefore significant. Probably one of the main biases was introduced in the election for CAS/CEA (selection bias), with fit patients treated by CEA while high risk patients were treated by CAS. Also, with the inclusion of mainly prospective cohort studies the risk of confounding is inherent.

In conclusion, the predicted magnitude of procedural risks will ultimately determine whether CEA or CAS is safer in the early time period after onset of symptoms.[34] The evidence from the current systematic review and meta-analysis suggests that (at present) CEA is still safer than transfemoral CAS when performed ≤ 2 days of the index event. Also, considering absolute rates, expedited CEA complies with the accepted thresholds in international guidelines. The ideal timing for performing CAS (when indicated against CEA) is not yet defined and it remains to be seen whether newer CAS technologies (such as TCAR) can provide outcomes similar to CEA when performed in the first 2 − 7 days after symptom onset. Additional granular data and standard reporting of timing of intervention will facilitate future clinical decisions.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.08.021.

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CARDIOVASCULAR SCIENCES
at Faculdade de Medicina da Universidade do Porto

PART II

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CHAPTER 3

CRITICAL ANALYSIS OF THE LITERATURE AND STANDARDS OF REPORTING ON STROKE AFTER CAROTID REVASCULARIZATION

CHAPTER 3. Critical Analysis of the Literature and Standards of Reporting on Stroke after Carotid Revascularization

Systematic review and meta-analysis of the literature published in the *Journal of Vascular Surgery*, indexed to PubMed/MEDLINE journal

- CiteScore of 6.5
- CiteScore Highest Percentile - Surgery - 95% (First Quartile)
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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. Postprocedural 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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CHAPTER 4

4.1 CRITICAL APPRAISAL ON THE QUALITY OF STUDIES REPORTING ON SAFETY AND EFFICACY OF TRANSCAROTID ARTERY STENTING WITH FLOW REVERSAL

CHAPTER 4

4.1 Critical Appraisal on the Quality of Studies Reporting on Safety and Efficacy of Transcarotid Artery Stenting with Flow Reversal

Systematic review of the literature published in the *Stroke*, indexed to PubMed/MEDLINE journal

- CiteScore of 16.2
- CiteScore Highest Percentile - Neurology - 93% (First Quartile)
- Journal Impact Factor of 10.170

Stroke

TOPICAL REVIEW

Critical Appraisal on the Quality of Reporting on Safety and Efficacy of Transcarotid Artery Stenting With Flow Reversal

Andreia Coelho, MD, MSc; Tossapol Prassaparo, MD; Armando Mansilha, MD, PhD; Jaap Kappelle, MD, PhD; Ross Naylor, MD, PhD; Gert J. de Borst, MD, PhD

ABSTRACT: Transcarotid revascularization is an alternative to transfemoral carotid artery stenting, designed to avoid aortic arch manipulation and concomitant periprocedural stroke. This article aims to perform a detailed analysis on the quality of the currently available evidence on safety and efficacy of transcarotid artery revascularization. Although current evidence is promising, independent randomized controlled studies comparing transcarotid artery revascularization with carotid endarterectomy in recently symptomatic patients are lacking and will be necessary to establish the true value of transcarotid artery revascularization in carotid artery revascularization.

Key Words: aorta, thoracic ■ carotid artery, common ■ carotid stenosis ■ endarterectomy ■ stents

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Transfemoral carotid artery stenting (TF-CAS) has been extensively studied as an alternative to carotid endarterectomy (CEA). A meta-analysis of pooled data from randomized controlled trials on symptomatic and asymptomatic patients revealed a significantly higher risk of procedural stroke with TF-CAS than with CEA.[1] This difference was mainly driven by a higher prevalence of nondisabling ipsilateral stroke.[2] TF-CAS was also associated with a 4× higher procedural risk of new ischemic brain lesions measured by diffusion-weighted magnetic resonance imaging (DW-MRI).[3,4] After the first 30 days, the long-term risk of any stroke appeared to be virtually the same for both TF-CAS and CEA.[5]

See related articles, p 2608 and p 2620

The European Society for Vascular Surgery clinical practice guidelines still recommend CEA as the first-line treatment for both asymptomatic and symptomatic patients with low-to-moderate surgical risk.[6] However, if the procedural risk of stenting could be further reduced, carotid artery stenting (CAS) may assume an ever increasing role in clinical practice for long-term stroke prevention.[7]

Several technical improvements in stent design (ie, mesh-covered stents) and in catheterization routing have been developed and are currently being tested.[8,9]

Transcarotid artery revascularization (TCAR) with flow reversal was initially designed to overcome aortic arch catheterization–related embolic complications, with the ultimate aim of emulating the neuroprotective mechanism of CEA.[10] The ENROUTE Transcarotid Neuroprotection System (Silk Road Medical, Inc, Sunnyvale, CA) is a commercially available device with flow reversal assisted by an extracorporeal low-resistance arteriovenous circuit.[11,12]

Several cohort series and 2 single-arm trials have recently been published claiming favorable procedural stroke and death rates for TCAR as compared with TF-CAS.[13–17] However, most TCAR studies

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TOPICAL REVIEW

Nonstandard Abbreviations and Acronyms

CAS	carotid artery stenting
CEA	carotid endarterectomy
CNI	cranial nerve injury
ICSS	International Carotid Stenting Study
TCAR	transcarotid artery revascularization
TF-CAS	transfemoral carotid artery stenting
VQI	Vascular Quality Initiative

included heterogeneous patient populations and only reported procedural outcome, whereas proper comparison of TCAR versus CEA in symptomatic patients (those with the potential highest benefit from safe revascularization) has thus far not been performed.

The purpose of this systematic review was to perform a detailed analysis on the quality of the currently available evidence on safety and efficacy of TCAR with flow reversal in both symptomatic and asymptomatic patients with atherosclerotic CAS.

METHODS

The authors declare that all supporting data are available within the article.

A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.[18]

Literature search was updated last on March 18, 2020, using the PUBMED database and the following query (transcarotid or transcervical and carotid artery stenting). The search conduction using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram is demonstrated in Figure I in the Data Supplement.

The eligibility criteria included any publication regarding TCAR with flow reversal, comprising single-arm studies or comparisons with CEA or TF-CAS. Only atherosclerotic stenotic carotid disease and restenosis after CEA were considered, with exclusion of procedures performed for nonatherosclerotic pathogeneses. The technique was described for the first time in 2004, and accordingly, only articles published afterward were considered.

Exclusion criteria were (1) articles published in a language other than English; (2) case reports, reviews, and case series with <5 patients; and (3) studies reporting on CAS performed by transcervical route using a distal filter.

Two reviewers (A.C. and T.P.) screened the identified studies independently. Collected data included age, sex, type of study, year of publication, and criteria for carotid revascularization (the presence and timing of neurological symptoms). Neurological symptomatic status was defined as a transient ischemic attack or minor disabling ischemic stroke in the previous 6 months in the carotid artery territory. The presence of contralateral internal carotid artery occlusion, previous ipsilateral CEA, cervical radiation, and type of embolic protection device (self-made versus commercial device) were recorded. In addition, the evaluation of outcomes was assessed (Clinical Events Committee). For this review, primary outcome was defined as 30-day or in-hospital incidence of stroke, myocardial infarction, or death. Other complications registered included flow reversal intolerance, cranial nerve injury (CNI), common carotid artery dissection, and other access site complications and rate of conversion to CEA.

When duplicates were identified, the most recent analysis was included unless the earlier version reported more data on parameters included in our analysis.

Quality Assessment

The methodology of the studies and the risk of bias were systematically assessed with the Methodological Index for Non-Randomized Studies score.[19] A score ≤8 was considered poor, 9 to 14 moderate, and 15 to 16 good quality for noncomparative studies. Cutoff points were ≤14, 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 (G.J.d.B.).

RESULTS

A total of 91 potentially relevant articles were initially identified. After reviewing title or abstract, 33 articles were read in full and 18 were judged eligible for inclusion (Figure I in the Data Supplement). Agreement between the reviewers was reached for all articles, and arbitration by the third reviewer was unnecessary. The methodological quality analysis is reported in Table 1, with 6 studies classified as moderate and the remaining articles classified as poor quality. The 18 studies comprised single-arm studies (n=11); 2-arm studies comparing TCAR versus TF-CAS (n=4) or versus CEA (n=2). One study compared TCAR versus both TF-CAS and CEA (Tables 2 and 3).

Two studies were single-arm prospective trials,[11,15] 2 studies were prospective observational,[23,29] and 3 studies were retrospective analyses of prospectively collected data from the Society for Vascular Quality Initiative (VQI) TCAR Surveillance Project registry.[13,14,20] The remaining were retrospective uni- or multicentric studies (Tables 2 and 3).

Three studies reported in-hospital events rather than 30-day events,[14,23,30] and 1 study did not report the evaluation timing.[32] Inclusion of consecutive patients was the norm but was not stated unambiguously in one study (Tables 2 and 3). Based on the overall heterogeneous and low-quality data, no formal data meta-analysis could be performed. Therefore, we limited our review to a detailed quality assessment trying to identify future needs and challenges.

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Table 1. Methodological Quality Assessment of Included Articles

	Schermerhorn et al[13]	Schermerhorn et al[20]	Wang et al[21]	Kashyap et al[16]	Malas et al[14]	King et al[22]	Alpaslan et al[15]	Plessers et al[23]	Kwolek et al[11]	Cirbian et al[24]	Leal et al[25]	Alvarez et al[26]	Faraglia et al[17]	Matas et al[27]	Criado et al[28]	Lin et al[29]	Pipinos et al[30]	Chang et al[31]
Clear aim	2	2	2	2	2	2	2	1	2	2	2	2	2	1	2	2	2	2
Consecutive patients	2	2	2	2	2	2	2	0	2	2	2	2	1	2	2	2	2	2
Prospective data collection	2	2	0	2	2	1	2	1	2	2	2	2	0	0	0	0	0	2
Appropriate end points	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	1	1	2
Unbiased assessment of study end point	0	0	0	0	0	0	2	0	2	0	2	2	0	2	0	0	1	2
Appropriate follow-up period	2	2	2	2	0	2	2	0	2	2	2	2	1	0	0	0	0	2
Loss to follow-up <5%	0	0	0	0	0	0	2	0	0	2	0	0	0	0	0	0	0	0
Prospective calculation of study size	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Comparative study																		
Adequate control group	1	1		2	1			1			2					2		
Contemporary groups	0	0		2	0			0			1					2		
Baseline group equivalence	1	1		2	1			2			2					0		
Adequate statistical analyses	2	2		2	2			2			2					0		
Total score	14	14	8	18	12	9	14	9	12	12	19	12	5	7	6	9	6	12
Maximum possible score	24	24	16	24	24	16	16	24	16	16	24	16	16	16	16	24	16	16

Single-Arm Studies (11 Studies; 939 Patients)

Patient mean age ranged from 65 to 79.9 years, and most were men (60%–88.2%; Table 2).[11,15,17,21,22,24,26–28,30,31] All studies reported on symptomatic status, ranging from 16% to 62% of cases, but no study reported delays between the index event and carotid intervention (Table 2). Contralateral internal carotid artery occlusion was reported in 8 of 11 studies ranging from 3.7% to 14.8% (Table 2). No study reported on the association between contralateral internal carotid artery occlusion and flow reversal intolerance.

One study reported on anatomic nonsuitability for TCAR (5.1% rate).[15] In the ROADSTER trial (Reverse Flow Used During Carotid Artery Stenting Procedure), 16 patients (3.2%) were excluded for inadequate clavicle to bifurcation distance, but no other information regarding anatomic nonsuitability criteria was provided.[11]

Seventy-eight patients (8.3%) underwent transcarotid revascularization for restenosis after CEA (Table 2). Overall, in 7 of 11 studies, the original transcervical technique[10] was performed while the remaining studies (n=4) used the ENROUTE Transcarotid Neuroprotection System (Table 2).

Clinical Events Committee outcome evaluation was performed in 5 studies[11,15,26,27,31]; in 1 study by the attending surgeon, while in the remaining studies, information about the outcome evaluation was missing (Table 2).

Primary outcomes ranged from 1.2% to 5.2% for 30-day stroke, 0% to 2.1% for 30-day myocardial infarction, and 0% to 2.7% for 30-day death (Table 2). One study reported in-hospital events only.[30]

Procedural complications were described inconsistently. Common carotid artery dissection was rarely reported but occurred in 5.7% of 141 patients in 1 study.[11] In total, 21 common carotid artery dissections were reported in 7 studies (2.9% overall).[11,15,17,21,26–28] Treatment of common carotid artery dissection included additional stent deployment (n=2; 9.5%), conversion to CEA (n=2; 9.5%), conversion to surgical repair other than CEA (n=5; 23.8%), or conservative management (n=12; 57%; Table 2).

TCAR Versus CEA (2 Studies; 1474 Versus 11168 Patients)

Two studies retrospectively compared TCAR versus CEA.[13,16]

TCAR patients from the VQI TCAR Surveillance Project Registry were compared with patients from the Society for Vascular Surgery VQI CEA database. The discrepancy in the number of included patients in each cohort was substantial (1182 TCAR versus 19797 CEA).[13] One-third of the patients in the TCAR group were symptomatic at baseline (n=378 [32%] versus just over one-fourth of the CEA patients n=2915 [27%]; *P*=0.001). The delay between onset

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Table 2. Single-Arm Studies

Reference	n	Consecutive Patients	Demographic Data		Neurologically Symptomatic		High Risk for CEA Criteria	
			Age, y (Mean±SD)	Male Sex, n (%)	n (%)	Timing	Contralateral ICA Occlusion, n (%)	Restenosis After CEA, n (%)
Single arm								
Wang et al[21]	75	Yes	70.5±9.4	61 (81.3)	35 (46.7)	NR	3 (3.7)	12 (16)
King et al[22]	81	Yes	72.8±8	61 (75.3)	27 (33.3)	NR	12 (14.8)	7 (8.6)
Alpaslan et al[15]	75	Yes	72.6	45 (60)	12 (16)	NR	NR	18 (24)
Kwolek et al[11]	141	Yes	72.9±9	91 (65)	36 (25.5)	NR	11 (7.8)	29 (20.6)
Cirbian et al[24]	97	Yes	73.9±11.2	78 (80.4)	54 (55.7)	NR	NR	NR
Alvarez et al[26]	219	Yes	79.9±4.9	168 (79.2)	97 (44.3)	NR	8 (3.7)	6 (2.7)
Faraglia et al[17]	48	Yes	78.9±3.8	35 (73)	10 (21)	NR	1 (2)	0 (0)
Criado et al[28]	103	Yes	72±10.4	82 (80)	37 (36)	NR	10 (9.7)	NR
Matas et al[27]	62	Yes	76.5±10.4	52 (83.9)	24 (38.7)	NR	7 (11.3)	2 (3.2)
Pipinos et al[30]	17	Yes	65±8.1	15 (88.2)	8 (47.1)	NR	NR	NR
Chang et al[31]	21	Yes	73	17 (80.9)	13 (62)	NR	0 (0)	4 (19)

(*Continued*)

Stroke

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of the index symptom and undergoing either CEA or TCAR was not mentioned. Patients in the TCAR group had a higher rate of contralateral internal carotid artery occlusion (n=118 [10%] versus n=432 [4.2%]; *P*<0.001) and a higher rate of restenosis post-CEA (n=189 [16%] versus n=205 [1.9%]; *P*<0.001) than in the CEA group.

Also, patients in the TCAR group were significantly less likely to be treated under local anesthesia. No significant difference was identified in primary outcomes (30-day stroke rate, 1.4% for TCAR versus 1.2% for CEA; *P*=0.682[13]; Table 3). Rates of CEA conversion or flow reversal intolerance were not reported. CNI (defined as deficits persistent at hospital discharge) was reported in both groups, with a significantly lower incidence in the TCAR group (7 [0.6%] versus 194 [1.8%]; *P*<0.001).[13]

The second study[16] reported a comparative analysis between 292 patients, who were also included within the VQI TCAR Surveillance Project Registry. It remains unclear whether these 292 patients were also included in the previous study.[13] No significant difference was attained between groups regarding the primary outcomes (Table 3).

TCAR Versus TF-CAS (4 Studies; 5951 Versus 16 834 Patients)

Four studies report on comparative analysis between TCAR versus TF-CAS, 2 of which analyzed data VQI TCAR Surveillance Project Registry comparing it with data from a TF-CAS registry.[14,20,25,29] In-hospital stroke was significantly lower in the TCAR group (1.9% versus 3.3%; *P*=0.04) in 1 study,[14] and 30-day stroke rate was lower in the TCAR group in the second study (1.3% versus 2.5%; *P*=0.001[20]; Table 3).

A DW-MRI study[25] focused on identification of new ischemic brain lesions on repeat examination at 24 to 48 hours after the procedures. The majority of patients was defined as symptomatic, but the timing of the intervention (relative to the index event) was not reported (Table 3). New lesions were identified after 4 (12.9%) TCAR versus 11 TF-CAS procedures (33.3%; *P*=0.03).

TCAR Versus CEA Versus TF-CAS (1 Study; 16 Versus 10 Versus 8 Patients)

A pilot study focused on embolization rates during the different phases of CEA, TCAR, and TF-CAS as measured with intraoperative transcranial Doppler.[23] TCAR was

Table 2. Continued

Procedure Data				Primary Outcome			Procedure Complications					
EPD	Technical Success n (%)	Local Anesthesia, n (%)	CEC	30-d Stroke, n (%)	30-d MI, n (%)	30-d Death, n (%)	CCA Dissection, n (%)	Flow Reversal Intolerance, n (%)	CNI, n (%)	Cervical Hematoma, n (%)	CEA Conversion, n (%)	Others, n (%)
ENROUTE	73 (97.3)	5 (6.7)	NR	3 (3.7)	0 (0)	2 (2.7)	1 (1.3)	NR	0 (0)	2 (2.6)	2 (2.6)	ACST: 1 (1.3)
ENROUTE	NR	6 (5)	NR	1 (1.2)	1 (1.2)	0 (0)	NR	1 (1.2)	NR	NR	NR	
ENROUTE	68 (90.6)	NR	Yes	1 (1.3)	0 (0)	0 (0)	4 (5.3)	5 (6.7)	2 (2.7)	NR	1 (1.3)	Major bleeding events: 2 (2.7); TF-CAS conversion: 3 (4)
ENROUTE	140 (99)	74 (53)	Yes	2 (1.4)	1 (0.7)	2 (1.4)	8 (5.7)	1 (0.7)	1 (0.7)	5 (3.5)	1 (0.7)	Puncture site stenosis: 1 (0.7)
Self-made	97 (100)	97 (100)	NR	5 (5.2)	3 (3.1)	0 (0)	NR	NR	NR	NR	3 (3.1) excluded from analysis	
Self-made	211 (96.3)	219 (100)	Yes	4 (1.8)	1 (0.5)	1 (0.5)	2 (0.9)	3 (1.4)	2 (0.9)	1 (0.5)	5 (2.3)	ACST: 1 (0.5)
Self-made	48 (100)	48 (100)	NR	1 (2.1)	1 (2.1)	0 (0)	0 (0)	4 (7.7) excluded from analysis	0 (0)	0 (0)	0 (0)	
Self-made	100 (97)	72 (70)	NR	2 (2)	0 (0)	0 (0)	5 (4.9)	3 (4)	0 (0)	2 (1.9)	4 (4)	
Self-made	60 (96.8)	62 (100)	Yes	2 (3.2)	0 (0)	0 (0)	1 (1.6)	1 (1.6)	NR	1 (1.6)	1 (1.6)	sICH: 1 (3.2)
Self-made	17 (100)	4 (23.5)	No	0 (0), in hospital	NR	0 (0), in hospital	NR	NR	NR	2 (11.8)	0 (0)	
Self-made	21 (100)	21 (100)	Yes	0 (0)	0 (0)	0 (0)	NR	0 (0)	NR	NR	NR	

ACST indicates acute carotid stent thrombosis; CCA, common carotid artery; CEA, carotid endarterectomy; CEC, clinical events committee; CNI, cranial nerve injury; EPD, embolic protection device; ICA, internal carotid artery; MI, myocardial infarction; NR, not reported; sICH, symptomatic intracranial hemorrhage; and TF-CAS, transfemoral carotid artery stenting.

Stroke

associated with a significant lower rate of embolization as compared with TF-CAS but not with CEA[23] (Table 3).

Subgroup Analysis—Symptomatic Patients

Subgroup analysis within symptomatic patients was possible in 6 studies.[13–16,20,25] None, however, reported the delay between the index event and revascularization. The PROOF trial (Protection System: First-In-Man) conducted a post hoc analysis but identified no trend due to lack of statistical power.[15]

Two studies comparing TCAR with TF-CAS[14,25] found no differences in rates of in-hospital stroke, myocardial infarction, and death. Symptomatic status was identified as a risk factor for new embolization on magnetic resonance imaging in the TF-CAS but not in the TCAR group. DW-MRI new asymptomatic ipsilateral ischemic infarcts were significantly less common after TCAR.[25] Finally, another study reported a reduced rate of in-hospital stroke/death after TCAR (1.6% versus 3.1%; $P<0.001$).[20]

TCAR was compared with CEA in 2 studies,[13,16] which reported no significant differences in primary outcomes in either study, although a trend toward worse outcomes following TCAR was identified in 1 study (30-day stroke, 2.4% versus 1.5%; $P=0.19$).[13]

Long-Term Outcome

One-year outcome analysis was reported in the ROADSTER trial[12]: 0.6% ipsilateral stroke and 4.2% mortality (all deaths unrelated to neurological events).

Comparative 1-year outcomes analysis between TCAR and CEA showed no difference in death/stroke (4.6% versus 6.8%; $P=0.32$).[16] Longer term data are currently absent.

DISCUSSION

In the present review, limited data from poor or moderate methodological quality studies were included. No study achieved high quality standards (Table 1). Available data were either derived from single-arm studies (Table 2) or from comparative analysis with historic controls (Table 3). Thus far, no randomized controlled trial compared TCAR with either CEA or TF-CAS.

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Table 3. Comparative Studies

Reference		n	Consecutive Patients	Demographic Data: Age, y (Mean±SD)	Demographic Data: Male Sex, n (%)	Neurologically Symptomatic Patients: n (%)	Neurologically Symptomatic Patients: Timing	High Risk for CEA Criteria: Contralateral ICA Occlusion, n (%)	High Risk for CEA Criteria: Restenosis After CEA, n (%)
TCAR vs TF-CAS									
Schermerhorn et al[20]	TCAR	5251	Yes	73.1±9.4	3346 (63.7)	2596 (49.4)	NR	NR	NR
	TF-CAS	6640		69.7±9.7	4308 (64.9)	4301 (64.8)	NR	NR	NR
	P Value			NS	0.023				
Malas et al[14]	TCAR	638	Yes	73.5±4.0	414 (64.9)	214 (33.5)	NR	NR	119 (18.7)
	TF-CAS	10 136		70±4.0	6534 (64.5)	4247 (41.9)	NR	NR	2730 (26.9)
	P Value			0.001		<0.01			<0.001
Leal et al[25]	TCAR	31	Yes	68.1±10.7	27 (87.1)	21 (67.7)	NR	NR	NR
	TF-CAS	33		67.2±10.1	31 (93.9)	23 (69.7)	NR	NR	NR
	P Value			>0.05	>0.05	>0.05			
Lin et al[29]	TCAR	31	Yes	NR	NR	18 (58.1)	NR	9 (29.0)	1 (3.2)
	TF-CAS	25		NR	NR	13 (54.2)	NR	0 (0)	2 (8.3)
TCAR vs CEA									
Schermerhorn et al[13]	TCAR	1182	Yes	73.3±3.8	745 (63)	378 (32)	NR	118 (10)	189 (16)
	CEA	10797		70.8±3.7	6478 (60)	2915 (27)	NR	432 (4.2)	205 (1.9)
	P Value			0.001	>0.05	0.001		<0.001	<0.001
Kashyap et al[16]	TCAR	292	Yes	71.1±8.7	192 (65.8)	103 (35.3)	NR	NR	NR
	CEA	371		70.7±8.5	221 (59.6)	143 (38.5)	NR	NR	NR
TCAR vs CEA vs TF-CAS									
Plessers et al[23]	TCAR	16	NR	71.3±9.5	13 (81.3)	8 (50)	NR	NR	NR
	CEA	10		65.7±4.3	6 (60)	6 (60)	NR	NR	NR
	TF-CAS	8		62.4±9.9	5 (62.5)	4 (50)	NR	NR	NR

(*Continued*)

Importantly, all published studies on the safety of the ENROUTE system published were company sponsored, with a declaration of interest for receiving grants from Silk Road Medical, Inc, by the first and last authors.

Three studies including data from the VQI TCAR Surveillance Project Registry compared (partly) the same cases with controls from different registries.[13,14,20] Of relevance, the most common exclusion criteria in the full text analysis was data duplication (Figure I in the Data Supplement). This observation should serve as a warning signal to journal editors. In addition, population heterogeneity including both symptomatic and asymptomatic patients or primary and redo procedures in the same analysis hampered our review.

Current guidelines emphasize the importance of performing carotid interventions as soon as possible after the onset of symptoms, especially within the first 7 to 14 days.[6] A recent meta-analysis of the 3 major randomized controlled trials on 30-day outcomes, stratified for delays to intervention, reported that CAS was associated with a 3-fold excess risk of stroke or death if performed within 7 days of the index event (compared with CEA) and a 2-fold excess risk when performed between 8 and 14 days.[33,34] Until now, no dedicated and powered analysis on the safety of TCAR versus CEA in (recently) symptomatic patients has been presented.

The omission of any published data regarding TCAR outcomes, stratified for delays to intervention in symptomatic patients, means that guidelines will continue to have to recommend CEA as the first-choice intervention in the early time period after onset of symptoms.

As TCAR was developed for deployment in high risk for CEA patients, it is surprising that only limited information about risk factors associated with TCAR is available. A single study was found on the impact of age on in-hospital outcomes, comparing TCAR with TF-CAS and CEA. TCAR was associated with a 72% reduction in stroke risk and 76% reduction in the risk of stroke/death/myocardial infarction compared with TF-CAS in patients ≥80 years of age. No difference was attained when TCAR was compared with CEA.[35]

With respect to outcome, reporting on in-hospital events only, instead of 30-day events, may cause underreporting

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Table 3. Continued

Procedure Data				Primary Outcome			Complications				
EPD	Technical Success, n (%)	Local Anesthesia, n (%)	CEC	30-d Stroke, n (%)	30-d MI, n (%)	30-d Death, n (%)	CCA Dissection, n (%)	Flow Reversal Intolerance, n (%)	CNI, n (%)	Access Site Hematoma, n (%)	CEA Conversion, n (%)
ENROUTE	5236 (99.7)[1]	NR	No	43 (1.3)[1]	7 (0.2)[1]	25 (0.8)[1]	NR	NR	NR	116 (3.5)[1]	NR
Distal filter	6599 (99.4)[1]	NR	No	83 (2.5)[1]	10 (0.3)[1]	48 (1.5)[1]	NR	NR	NR	125 (3.8)[1]	NR
				0.001	NS	0.007				NR	
ENROUTE	633 (99.2)	134 (21)	NR	12 (1.9), in hospital	6 (0.9), in hospital	6 (0.9), in hospital	NR	NR	NR	NR	NR
Distal filter	10082 (99.5)	8951 (88.5)	NR	334 (3.3), in hospital	34 (0.3), in hospital	133 (1.3), in hospital	NR	NR	NR	NR	NR
	>0.05	<0.001		0.04	>0.05	>0.05					
Self-made	NR	NR	NR	0 (0)	0 (0)	0 (0)	NR	NR	NR	NR	NR
Distal filter	NR	NR	NR	0 (0)	0 (0)	0 (0)	NR	NA	NR	NR	NR
Self-made	28 (90.3)	31 (100)	NR	0 (0)*	0 (0)*	0 (0)*	NR	0 (0)	NR	2 (6.5)	3 (9.7)
Distal filter	23 (92.0)	25 (100)	NR	0 (0)*	0 (0)*	0 (0)*	NR	NA	1 (4.0)	NA	0 (0)
ENROUTE	NR	236 (20)	NR	17 (1.4)	11 (0.9)	12 (1.1)	NR	NR	7 (0.6)	NR	NR
NA	NR	702 (6.5)	NR	130 (1.2)	43 (0.4)	65 (0.6)	NA	NA	194 (1.8)	NR	NR
		0.001		0.682	0.06	0.11			<0.001		
ENROUTE	292 (100)	18 (6.2)	No	3 (1)	2 (0.7)	1 (0.3)	0 (0)	NR	1 (0.3)	NR	NR
NA	371 (100)	12 (3.2)	No	4 (1.1)	2 (0.5)	3 (0.8)	NA	NA	11 (3)	NR	NR
ENROUTE	16 (100)	12 (75)	NR	0 (0)*	0 (0)*	0 (0)*	2 (12.5)	NR	0 (0)	NR	NR
NA	10 (100)	0 (0)	NR	0 (0)*	0 (0)*	0 (0)*	0 (0)	NA	1 (10)	NR	NA
Distal filter	8 (100)	7 (87.5)	NR	1 (12.5%), in hospital	0 (0)*	0 (0)*	0 (0)	NA	0 (0)	NR	NR

CCA indicates common carotid artery; CEA, carotid endarterectomy; CEC, clinical events committee; CNI, cranial nerve injury; EPD, embolic protection device; ICA, internal carotid artery; MI, myocardial infarction; NA, not applicable; NR, not reported; TCAR, transcarotid artery revascularization; and TF-CAS, transfemoral carotid artery stenting.
*Evaluation timing not reported.

of events.[14] Over one-quarter of perioperative strokes occur following discharge after both CAS and CEA.[36] Dissection during TCAR may lead to serious clinical consequences but was not uniformly reported[11] (Tables 2 and 3).

The lower risk for CNI with TCAR as compared with CEA, especially in redo procedures, has been emphasized. However, most CNIs are temporary with no clinical impact on patients' outcome at 12 months.[37,38] In this review, CNI was assessed at hospital discharge only, with temporary and permanent lesions not being appropriately distinguished.

Anatomic suitability and exclusion criteria for TCAR were also underreported. The rate of patients complying with ENROUTE Transcarotid Neuroprotection System (Silk Road Medical, Inc) instructions for use was lacking in all studies. A single retrospective analysis on suitability for TCAR reported compliance with instructions for use in 72% of patients in their cohort (n=112).[39] Another study reported failed eligibility for CEA due to a distal stenosis, of which 52 (56.5%) arteries met the eligibility criteria for TF-CAS and 72 (78.3%) for TCAR.[40]

Contraindications for flow reversal were not uniformly reported, even though in 1 study, flow reversal intolerance reached 20% of patients with contralateral occlusion.[28]

Although the ROADSTER multicenter trial presented promising 1-year outcomes,[12] longer follow-ups are clearly needed.

TCAR was developed to reduce the number of embolic complications associated with TF-CAS (by avoiding wire/catheter manipulation within the aortic arch). However, in an analysis of neurological events in the ICSS (International Carotid Stenting Study),[41] the most common pathophysiological mechanism (in one-third of the cohort) was hemodynamic. Also, cerebral hyperperfusion syndrome seems a rather neglected and underestimated mechanism of post-stenting stroke.[41]

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While TCAR could, in theory, reduce the risk of aortic arch manipulation–related embolic stroke, it cannot diminish the risk of hemodynamic stroke. Data on DW-MRI suggested that TCAR would reduce the risk for new lesion development.[25] However, no study has ever compared post-TCAR with post-CEA DW-MRI.

CONCLUSIONS

In the present review, we found limited data on the safety and efficacy of TCAR. Well-designed investigator-driven independent studies comparing TCAR with CEA in recently symptomatic patients are necessary to establish the true value of TCAR in carotid revascularization.

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CHAPTER 4

4.2 STRENGTHS AND OBVIOUS LIMITATIONS OF TRANSCERVICAL CAROTID ARTERY REVASCULARIZATION

CHAPTER 4

4.2 Strengths and Obvious Limitations of Transcervical Carotid Artery Revascularization

Letter to the editor published in *the Journal of Vascular Surgery*, indexed to PubMed/MEDLINE journal

- CiteScore of 6.5
- CiteScore Highest Percentile - Surgery - 95% (First Quartile)
- Journal Impact Factor of 4.860

Strengths and obvious limitations of transcervical carotid artery revascularization

We read with interest the article "An Updated Systematic Review and Meta-Analysis of Results of Transcervical Carotid Artery Stenting with Flow Reversal"[1] recently published in the *Journal of Vascular Surgery*. We believe that further critical analysis of the reported raw data is mandatory to clarify the deemed strengths and obvious limitations of transcervical carotid artery revascularization (TCAR).

The crude rates of technical success were indisputably high (98.25%) and the 30-day mortality and stroke rates remarkably low (0.48% and 0.71%, respectively). However, in their review, no analysis of the quality of the included studies was performed. Most data were derived from company-sponsored single-arm studies or comparative analyses with historical controls.[2-5] No randomized controlled trial comparing TCAR with either carotid endarterectomy (CEA) or transfemoral carotid artery stenting has been performed, and this was disregarded in the review by Paraskevas et al.[1]

Crude outcomes were obtained by merging symptomatic with asymptomatic patients without a differential analysis on the relative frequency of each status, only declaring that in one study the combined stroke, death, and myocardial infarction rate was 5.1% in symptomatic patients compared with 0% in the asymptomatic cohort.[6] Also, for the symptomatic patients, no data on the procedure delay from the index event were reported nor stated as a limitation of the available data. Because the phrase "high risk of stroke" mostly applies to recently symptomatic patients, the efficacy of novel endovascular techniques requires validation, especially for expedited interventions.[7]

Data on compliance with the instructions for use for the ENROUTE Transcarotid Neuroprotection System (Silk Road Medical, Inc, Sunnyvale, Calif) are lacking, as are data on the contraindications for flow reversal.

The authors correctly highlighted the obvious need for longer term data to establish the role of TCAR. However, we disagree that the reported primary 30-day procedural outcomes document unequivocally the value of TCAR, especially because no direct comparison with either transfemoral carotid artery stenting or CEA has ever been performed. We believe that independent randomized controlled trials comparing TCAR with CEA in recently symptomatic (<14 days) patients are required to establish the true place of TCAR in carotid revascularization.

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Reply

We thank Coelho and de Borst[1] for their interest in our work.[2] We agree with them that the available studies on transcervical carotid artery revascularization (TCAR) have not reported any data on the procedure delay from the

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CHAPTER 5

EFFECTIVENESS AND SAFETY OF DUAL-LAYER STENTS IN CAROTID ARTERY DISEASE: A SYSTEMATIC REVIEW

CHAPTER 5. Effectiveness and Safety of Dual-Layer Stents in Carotid Artery Disease: a Systematic Review

Systematic review and meta-analysis of the literature published in the *International Angiology*, indexed to PubMed/MEDLINE journal

- CiteScore of 3.9
- CiteScore Highest Percentile – Cardiology and Cardiovascular Medicine - 63% (Second Quartile)
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**Shared first-authorship*

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REVIEW
CAROTID DISEASE

EDITOR'S CHOICE

Effectiveness and safety of dual-layer stents in carotid artery disease: a systematic review

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ABSTRACT

Introduction: Carotid artery stenting (CAS) has emerged as a minimally invasive alternative to carotid endarterectomy (CEA) in atherosclerotic carotid artery disease, even though the risk for procedural stroke after CAS remains significantly higher. Recently, in order to reduce embolic cerebral events after CAS, a new generation of dual-layer stents (DLS) has been developed. This review aimed to perform a detailed analysis of the available evidence on safety and efficacy of DLS in both symptomatic and asymptomatic atherosclerotic carotid artery stenosis.

Evidence acquisition: A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The primary endpoint was the 30-day rate of myocardial infarction (MI), stroke and death. Secondary outcomes included rate and timing of stent occlusion/restenosis.

Evidence synthesis: A total of 20 articles with 1193 patients were included. Thirty-day MI ranged from 0-5%, 30-day stroke ranged from 0-10.5% and 30-day mortality ranged from 0-10%. Stent occlusion rate ranged from 0-52.4%, the majority of which occurred intraprocedurally (N.=50; 61.7%), in emergency treated patients. The incidence of new ipsilateral cerebral ischemic lesions after CAS with DLS was reported in five studies, ranging from 5.5-37%.

Conclusions: Despite the theoretic advantage of reducing the risk for procedural embolic events when compared to conventional stents, high quality evidence is scarce. Also, safety issues regarding DLS in the emergency setting have been raised, particularly for thrombotic complications. Additional data from well-designed Randomized Controlled Trials are needed to assert the true value of DLS.

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Key words: Stroke; Carotid stenosis; Stents; Endarterectomy, carotid.

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Introduction

Atherosclerotic carotid artery stenosis is a major cause of stroke, accounting for 25% of all anterior circulation ischemic events.[1] Although carotid endarterectomy (CEA) is still considered the gold standard, carotid artery stenting (CAS) has emerged as a minimally invasive alternative, particularly in high surgical risk patients.[1] However, CAS has a higher risk of procedural stroke when compared to CEA,[2] even though long-term outcomes seem comparable for both techniques.[3]

Plaque protrusion through the stent struts is one of the main causes of cerebral embolization and seems to be influenced by stent design. Registry and randomized controlled trial (RCT) data have demonstrated free cell area and cell design influence procedural stroke risk with the highest complication rate for open cell types and increased free cell area.[4-6]

In order to minimize procedural cerebral ischemic events, a new generation of dual-layer stents (DLS) has been developed. There are three types of DLS currently available in Europe: the Casper-RX (Microvention; Tustin, CA, USA), the Roadsaver™ Carotid Stent System (Microvention; Tustin, CA, USA) and the CGuard™ Embolic Protection System (InspireMD; Winsen, Germany). The design of these new DLS basically includes a small pore-size micro-mesh layer which lies underneath the basic metallic stent structure, theoretically minimizing the possibility of micro-embolic events from the target lesion and consequently reducing rates of procedural stroke in patients undergoing CAS, while maintaining stent flexibility and conformability.[7] Despite the theoretic advantage when compared to conventional stents, practical proof of concept and high quality data are currently lacking.

The purpose of this systematic review was to perform a detailed analysis on the quality of the currently available evidence on safety and efficacy of DLS in both symptomatic and asymptomatic patients with atherosclerotic carotid artery stenosis.

Evidence acquisition

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. PubMed database was last accessed in April 2020, using the following query: ((Dual-Layer Stents) OR (Dual-Layer

TABLE I.—*Methodological Index for non-randomized studies score.*

	Runck *et al.*, 2019[9]	Yilmaz *et al.*, 2017[10]	Lamanna *et al.*, 2019[11]	Pfaff *et al.*, 2020[12]	Bartolini *et al.*, 2019[13]	Ierardi *et al.*, 2019[14]	Hopf-Jensen *et al.*, 2015[15]	Ozpeynirci *et al.*, 2020[16]	Bosiers *et al.*, 2016[17]
A clearly stated aim	2	2	2	2	2	2	2	1	2
Inclusion of consecutive patients	2	2	2	2	2	2	0	2	0
Prospective collection of data	0	0	0	0	0	0	2	0	2
Endpoints appropriate to the aim of the study	2	2	2	2	2	2	2	2	2
Unbiased assessment of the study endpoint	0	0	0	0	0	2	2	0	2
Follow-up period appropriate to the aim of the study	2	2	2	2	2	2	2	2	2
Loss to follow-up less than 5%	2	2	0	2	2	2	2	2	2
Prospective calculation of the study size	0	0	0	0	0	0	0	0	1
An adequate control group	NA	2	NA	NA	NA	NA	NA	NA	NA
Contemporary groups	NA	0	NA	NA	NA	NA	NA	NA	NA
Baseline equivalence of groups	NA	0	NA	NA	NA	NA	NA	NA	NA
Adequate statistical analyses	NA	2	NA	NA	NA	NA	NA	NA	NA
Total MINORS score	10	14	8	10	10	12	12	9	13
Maximum possible score	16	24	16	16	16	16	16	16	16
Quality assessment	M	P	P	M	M	M	M	M	M

NA: not applicable; P: poor; M: moderate; G: good.

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Carotid) OR (Dual-layer)) AND ((Carotid Artery Stenting) OR (Carotid Artery Revascularization) OR (Carotid artery) OR (Carotid stenosis)). Figure 1 shows literature screening and selection according to the PRISMA diagram.

The eligibility criteria included any publication on DLS in the context of atherosclerotic carotid artery disease. Concerning how recent this technology is, no time frames were established. Exclusion criteria were defined as follows: 1) case reports, case series with <5 patients, systematic reviews and meta-analyses; 2) articles published in a language other than Portuguese or English; and 3) procedures performed for non-atherosclerotic etiologies.

Data collected and analyzed included age, sex, cardiovascular risk factors, stent type, use of embolic protection devices, proportion of symptomatic patients and setting (emergent or non-emergent). In this review, primary endpoints were procedural (30-day) myocardial infarction (MI), stroke and death. Secondary outcomes included rate of stent occlusion/restenosis and timing since the carotid procedure.

The methodology of the studies and the risk of bias were systematically assessed using the Methodological Index for non-randomized studies (MINORS) score[8] (Table I).[9-28] A score ≤8 was considered poor, 9-14 moderate, and 15-16 good quality for non-comparative studies. Cutoff points were ≤14, 15-22, and 23-24, respectively, for comparative studies. Authorship of the studies was not masked from the reviewers.

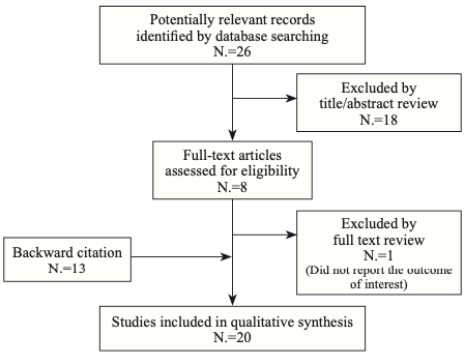

Figure 1.—Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Musialek *et al.*, 2016[18]	De Vries *et al.*, 2019[19]	Schofer *et al.*, 2015[20]	Nerla *et al.*, 2016[21]	Casana *et al.*, 2017[22]	Mutzenbach *et al.*, 2018[23]	Machnik *et al.*, 2017[24]	Diaz *et al.*, 2018[25]	Wissgot *et al.*, 2015[26]	Ruffino *et al.*, 2016[27]	Broussalis *et al.*, 2019[28]
2	1	2	2	2	2	2	2	2	2	2
2	2	2	2	2	2	0	0	0	2	2
2	0	2	2	0	2	0	0	0	2	0
2	2	2	2	2	2	2	2	2	2	2
2	0	2	2	1	2	0	0	0	2	2
2	2	2	2	2	2	2	2	2	2	2
2	0	2	2	2	2	2	2	2	2	0
0	0	1	0	0	0	0	0	0	0	0
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
14	7	15	14	11	14	8	8	8	14	10
16	16	16	16	16	16	16	16	16	16	16
M	P	G	M	M	M	P	P	P	M	M

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Neurologic symptomatic status was defined as a transient ischemic attack or minor disabling ischemic stroke in the previous 6 months in the carotid artery territory. Urgent procedures were defined as when the carotid intervention was performed <14 days after the index event and emergency procedures when performed in the first 24 hours after the event.

Evidence synthesis

A total of 20 articles with 1193 patients were included in the qualitative analysis. Regarding methodological quality assessment, a single comparative study was included classified as poor methodological quality (14 out of 24 points). The remaining studies were non-comparative, five of which were considered to have poor quality (N.=5; 26.3%), thirteen moderate (N.=13; 68.4%) and only one study good methodological quality (N.=1; 5.3%) (Table I).[9-28]

Six studies were prospective (with a total of 411 patients) and the remaining were retrospective (14 studies, with a total of 782 patients). Five hundred and ninety-three patients (49.7%) received a Casper-RX (Microvention; Tustin, CA, USA) stent, two of whom were treated with bilateral stenting. Three hundred and eighty-two patients (32%) received a Roadsaver™ (Microvention; Tustin, CA, USA) stent (including one patient submitted to bilateral CAS). The remaining patients (N.=218; 18.3%) received the CGuard™ system (InspireMD; Winsen, Germany), five of whom were submitted to bilateral stenting. A total of 1201 stents were deployed. Embolic protection devices (EPD's) were used in 727 (60.5%) procedures. Most patients (N.=729; 61.1%) were symptomatic, with 356 (48.8%) treated in an emergency setting (CAS performed within 24 hours). In most of the remaining cases, recency of symptoms regarding the index event was not reported, so they were classified as non-emergent (Table II).[9-28]

Patients' age ranged from 66 to 75.8 years and the majority of them were male (61.5-84%). Cardiovascular risk factors' prevalence, including hypertension, diabetes mellitus, dyslipidemia, coronary artery disease and smoking and the remaining demographic data of included patients are reported in Table III.[9-28]

Regarding primary endpoints, 30-day MI ranged from 0 to 5%, 30-day stroke ranged from 0% to 10.5% and 30-day

TABLE II.—*Information on included articles.*

Authors	Year of publication	Type of study	N.	Stent type	EPD (%)	Symptomatic (%)	Setting
Runck *et al.*[9]	2019	Retrospective	66	Casper RX	0	100	E
Yilmaz *et al.*[10]	2017	Retrospective	20	Casper RX	NR	100	E
Lamanna *et al.*[11]	2019	Retrospective	19 (20)	Casper RX	55	100	E
Pfaff *et al.*[12]	2020	Retrospective	160	Casper RX	NR	100	E
Bartolini *et al.*[13]	2019	Retrospective	21	Casper RX	0	100	E
Ierardi *et al.*[14]	2019	Retrospective	13	Roadsaver™	92.3	23	NE
Hopf-Jensen *et al.*[15]	2015	Prospective	7	Roadsaver™	0	100	E (29%) NE (71%)
Ozpeynirci *et al.*[16]	2020	Retrospective	28 (29)	Casper RX	0	100	E
Bosiers *et al.*[17]	2016	Prospective	100	Roadsaver™	58	31	NE
Musialek *et al.*[18]	2016	Prospective	101 (106)	CGuard™	100	55	E (9%) NE (91%)
De Vries *et al.*[19]	2019	Retrospective	54	Roadsaver™ (91%) CGuard™ (9%)	31	83	E (50%) NE (50%)
Schofer *et al.*[20]	2015	Prospective	30	CGuard™	100	33.3	NE
Nerla *et al.*[21]	2016	Prospective	150	Roadsaver™	100	29	NE
Casana *et al.*[22]	2017	Retrospective	82	CGuard™	NR	19	NE
Mutzenbach *et al.*[23]	2018	Retrospective	138	Casper RX	100	57.3	E (0.7%) NE (99.3%)
Machnik *et al.*[24]	2017	Retrospective	40 (41)	Roadsaver™	100	51.2	NE
Diaz *et al.*[25]	2018	Retrospective	19	Casper RX	100	73.7	NE
Wissgot *et al.*[26]	2015	Retrospective	12	Casper RX	100	100	NE
Ruffino *et al.*[27]	2016	Prospective	23	Roadsaver™	100	60.9	NE
Broussalis *et al.*[28]	2019	Retrospective	110	Casper RX	100	59.1	E (2.7%) NE (97.3%)

EPD: embolic protection device; E: emergent; NE: non-emergent; NR: not reported.

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TABLE III.—*Demographic data of included patients.*

Authors	N.	Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	Dyslipidemia (%)	CAD (%)	Smoke (%)
Runck *et al.*[9]	66	NR	71	82	27	65	21	NR
Yilmaz *et al.*[10]	20	69.9	NR	NR	NR	NR	NR	NR
Lamanna *et al.*[11]	19	69	68	74	5	26	NR	53
Pfaff *et al.*[12]	160	66	65	NR	NR	NR	NR	NR
Bartolini *et al.*[13]	21	71.3	61.9	71.4	14.3	90.5	NR	38.1
Ierardi *et al.*[14]	13	75.8	61.5	84.6	38.5	92.3	69.2	46.2
Hopf-Jensen *et al.*[15]	7	75	71.4	100	NR	NR	85.7	NR
Ozpeynirci *et al.*[16]	28	71.7	78.6	NR	NR	NR	NR	NR
Bosiers *et al.*[17]	100	73.4	70	80	31	74	32	67
Musialek *et al.*[18]	101	69	70	NR	41	NR	63	NR
De Vries *et al.*[19]	54	69	81	63	15	57	19	86
Schofer *et al.*[20]	30	71.6	63.4	83.3	23.3	90	26.7	13.4
Nerla *et al.*[21]	150	74	75	83	27	71	27	55
Casana *et al.*[22]	82	73.8	75	87	27	72	32	71
Mutzenbach *et al.*[23]	138	71	74.6	89.8	24.6	84.8	28.9	19.6
Machnik *et al.*[24]	40	67.8	77.5	95	32.5	97.5	42.5	77.5
Diaz *et al.*[25]	19	66	84	89	26	11	26	42
Wissgot *et al.*[26]	12	69	66.7	NR	NR	NR	NR	NR
Ruffino *et al.*[27]	23	74.3	82.6	96.6	47.8	69.6	56.5	30.4
Broussalis *et al.*[28]	110	71	78.2	NR	NR	NR	NR	NR

CAD: coronary artery disease; NR: not reported.

mortality ranged from 0% to 10%. Concerning secondary outcomes, stent occlusion rate ranged from 0 to 52.4%. Most stent occlusions occurred intraprocedurally (N.=50; 61.7%). Twenty-nine (35.8%) stent occlusions occurred within the first 30 days after the procedure. Beyond this, two occlusions were detected at 70 and 90 days postprocedural, respectively. It is noteworthy that the vast majority of stent occlusions occurred in an emergency setting. In total, 78 occlusions (96.3%) occurred in an emergency setting, 2 (2.5%) in a non-emergency setting and in a single occlusion the timing of the event was not reported. No in-stent restenosis was registered. The incidence of events according to the outcomes of interest is represented in Table IV.[9-28]

A comparative analysis between conventional single-layer stents and DLS was performed in one study. Yilmaz *et al.* analyzed the performance of both stents in an emergency setting, in patients with tandem lesions of the anterior circulation, showing a significantly higher rate of acute occlusion of DLS compared with single-layer stents (45% *vs*. 3.7%; P=0.001).[10]

Two cohorts published posteriorly data regarding long-term (12 month) outcomes. Nerla *et al.* reported one MI (0.67%), three deaths (2%) and no cerebrovascular events (0%). Three significant restenosis (2%) were recorded, defined as a peak systolic velocity (PSV) above 250 cm/s. All restenosis cases were asymptomatic, detected by Doppler ultrasound (DUS) and confirmed by angiography.[29] On the other hand, Bosiers *et al.* showed a 12-month stroke rate of 4.2% and a 12-month restenosis rate of 7.5%.[30]

Five studies also evaluated the presence of new ipsilateral cerebral ischemic lesions after CAS detected by diffusion-weighted magnetic resonance imaging (DW-MRI). Lesion incidence ranged from 5.5% to 37% in the perioperative period, showing spontaneous resolution in most cases at the postoperative period.[20, 22, 23, 27, 28] Average lesion volume was available in three studies (60%) ranging from 0.039 cm to 0.076 cm^3.[20, 22, 27]

Discussion

In the present review, limited data from poor to moderate methodological quality studies were included. A single study achieved high quality standards (Table I).[9-28] Thus far, no RCT compared CAS with DLS *versus* conventional stents.

Study heterogeneity is one of the main issues and accordingly, no statistical analysis could be performed. Five studies analysed CAS with DLS in patients in different settings (emergent and non-emergent). Also, recency of symptoms concerning the index event is frequently not reported in symptomatic patients in the non-emergent setting.

A comparative study focused on plaque protrusion analysis after CAS performed with a DLS (N.=9) and a con-

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TABLE IV.—*Incidence of events according to the outcomes of interest.*

Authors	N.	Stent occlusion N. (%)	Time to occlusion (days)	In-stent restenosis N. (%)	30-day MI N. (%)	30-day Stroke N. (%)	30-day Mortality N. (%)
Runck *et al.*[9]	66	14 (21)	Intraprocedural	NR	NR	NR	NR
		1 (1.5)	0				
		1 (1.5)	1				
Yilmaz *et al.*[10]	20	9 (45)	<3	NR	NR	NR	NR
Lamanna *et al.*[11]	19 (20)	1 (5)	0	NR	1 (5)	1 (5)	2 (10)
		2 (10)	30				
Pfaff *et al.*[12]	160	25 (15.6)	Intraprocedural	NR	NR	NR	NR
		8 (5)	<3				
Bartolini *et al.*[13]	21	11 (52.4)	Intraprocedural	NR	NR	0 (0)	NR
Ierardi *et al.*[14]	13	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)
Hopf-Jensen *et al.*[15]	7	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)
Ozpeynirci *et al.*[16]	28 (29)	1 (3.4)	1	NR	NR	NR	NR
Bosiers *et al.*[17]	100	0 (0)	-	0 (0)	1 (1)	1 (1)	1 (1)
Musialek *et al.*[18]	101 (106)	0 (0)	-	0 (0)	0 (0)	1 (0.9)	0 (0)
De Vries *et al.*[19]	54	1 (1.85)	0	NR	NR	NR	NR
		1 (1.85)	1				
		1 (1.85)	7				
		1 (1.85)	30				
		1 (1.85)	70				
Schofer *et al.*[20]	30	NR	-	NR	0 (0)	0 (0)	0 (0)
Nerla *et al.*[21]	150	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)
Casana *et al.*[22]	82	1 (1.2)	0	NR	NR	1 (1.2)	0 (0)
Mutzenbach *et al.*[23]	138	1 (0.7)	90	0 (0)	NR	0 (0)	0 (0)
Machnik *et al.*[24]	40 (41)	0 (0)	-	0 (0)	NR	1 (2.5)	NR
Diaz *et al.*[25]	19	1 (5.3)	25	0 (0)	NR	2 (10.5)	NR
Wissgot *et al.*[26]	12	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)
Ruffino *et al.*[27]	23	0 (0)	-	0 (0)	0 (0)	0 (0)	0 (0)
Broussalis *et al.*[28]	110	0 (0)	-	0 (0)	NR	0 (0)	0 (0)

MI: myocardial infarction; NR: not reported.

ventional stent (N.=37) using magnetic resonance imaging (MRI) and optical frequency domain imaging (OFDI). The mean plaque protrusion area was significantly smaller in the DLS group (mean area, 0.013±0.034 mm^2 *vs.* 0.057±0.09 mm^2; P=0.006). However, clinical effectiveness was not evaluated.[31]

Overall results seem promising with a low rate of major adverse events. Procedural stroke was established as inferior to 3% in most studies, even in emergency setting with two exceptions: 1) procedural risk of 5% in an emergency setting; and 2) procedural risk of 10.5% in a small cohort of 19 patients, which can (partly) explain the exceedingly high risk for procedural neurologic events.

In the emergency setting, thrombotic complications occurred in an exceedingly high number of patients, reaching 52.4% in a retrospective study.[13] In fact, over 95% of DLS occlusions occurred in emergency treated patients. A likely explanation for acute DLS occlusion may be the increased burden of thrombogenic material in the second micromesh layer in emergency cohorts not previously prepared with dual antiplatelet therapy.[10]

Mazurek *et al.* performed an analysis from the PARADIGM study (which was included in our analysis), dividing study population in two groups: HCCS (highly calcific carotid stenosis) and non-HCCS patients. The purpose of this analysis was to evaluate the feasibility of a new DLS in the treatment of highly calcified lesions, which have been very challenging in endovascular management. They reported normal in-stent velocities and no adverse clinical events in the HCCS group, suggesting that DLS can be an alternative to CEA in the treatment of this type of lesions.[32]

DLS were developed to reduce the number of embolic complications associated with CAS (by avoiding embolization through the stent struts). However, a subset analysis of the International Carotid Stenting Study (ICSS) RCT, showed that the most common pathophysiological mechanism (in one-third of the cohort) was hemodynamic.[33]

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While, in theory, DLS can reduce the risk of embolization, they cannot reduce the risk for hemodynamic procedural stroke. Neuroimaging studies, in particular DW-MRI could give valuable information regarding silent cerebral embolization during CAS, although clinical significance of asymptomatic ischemic brain lesions remains elusive.[34]

Current guidelines emphasize the importance of performing carotid interventions as soon as possible after the onset of symptoms, especially within the first 7-14 days.[1] The omission of any published data regarding outcomes stratified for delays to intervention in non-emergent symptomatic patients, combined with anecdotal reports of high rate of acute stent thrombosis in the emergent setting, means that guidelines will continue to have to recommend CEA as the first choice intervention in the early time period after the onset of symptoms.

Conclusions

In conclusion, DLS have been appraised as an alternative to conventional stents with the potential advantage of reducing the risk for procedural embolic neurologic events. However, safety issues regarding its use in an emergency setting have been raised, particularly the risk for acute stent occlusion. Additional data, preferably from well-designed investigator driven independent RCT's, is needed to assert the true value of DLS in CAS.

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CARDIOVASCULAR SCIENCES
at Faculdade de Medicina da Universidade do Porto

CHAPTER 6

OVERVIEW OF EVIDENCE ON RISK FACTORS AND EARLY MANAGEMENT OF ACUTE CAROTID STENT THROMBOSIS DURING THE LAST TWO DECADES

CHAPTER 6. Overview of Evidence on Risk Factors and Early Management of Acute Carotid Stent Thrombosis During the Last Two Decades

Systematic review and meta-analysis of the literature published in *the Journal of Vascular Surgery*, indexed to PubMed/MEDLINE journal

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Overview of evidence on risk factors and early management of acute carotid stent thrombosis during the last two decades

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ABSTRACT

Objective: Acute carotid stent thrombosis (ACST) occurring in the first hours after the procedure is an exceedingly rare complication of carotid artery stenting, but it is potentially devastating. This review aimed to evaluate current literature, identifying all reported cases during the last two decades, with the final purpose of reporting predictive factors and early management.

Methods: A systematic review and meta-analysis was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Results: A total of 464 potentially relevant articles were selected. After review of records at title and abstract level, 29 articles with 60 patients were included. Twelve studies reported on ACST incidence rate in their cohorts, ranging from 0.36% to as high as 33%. In considering etiology, antiplatelet noncompliance or resistance is the most frequently reported risk factor. Emergency procedures seemed to be associated with greater risk for ACST, reaching 5.6% to 33% incidence. Dual-layer stents were also associated with greater risk (45% vs 3.7%; $P = .0001$; odds ratio, 21.3). Use of an overlapping stent as a bailout procedure because of dissection, malposition, or long lesions was correlated with increased risk (7.3% vs 0.002%), as were long stenotic lesions (22.9 ± 6.83 mm vs 14.2 ± 6.42 mm; $P = .0034$) and stent length (3.8 ± 0.4 cm vs 2.8 ± 0.86 cm; $P = .0055$). ACST was associated with neurologic status deterioration in 56.7% of cases. Time to symptoms or ACST diagnosis had a median of 1.5 hours, with 30% occurring intraprocedurally. In asymptomatic ACST, conservative management was unanimous. Endovascular treatment was the most common approach to intraprocedural ACST. Surgical options included carotid endarterectomy with stent explantation (n = 9), which was also a bailout after failed endovascular treatment in two cases.

Conclusions: ACST incidence is higher in emergent, neurologically unstable patients. Antiplatelet noncompliance, antiplatelet resistance, long stenotic lesions, use of more than one stent, and dual-layer stents are also associated with increased risk. The decision as to the best approach depends on whether ACST occurs intraprocedurally or afterward, the development of neurologic status deterioration, and the center's experience. However, additional studies must be undertaken to better define optimal management. (J Vasc Surg 2019;69:952-64.)

Keywords: Carotid stenosis; Carotid artery disease; Stents; Carotid artery thrombosis

Carotid artery stenting (CAS) is an alternative, in selected patients, to carotid endarterectomy (CEA) for the management of atherosclerotic carotid disease.[1] Stent thrombosis can be classified as early (<30 days), late (>30 days), and very late (>12 months), with early thrombosis being subclassified as acute (<24 hours) and subacute (1-30 days).[2]

Acute carotid stent thrombosis (ACST) is an exceedingly rare complication of CAS, but it can have devastating consequences.[3] The incidence of stroke directly attributable to ACST is unclear; it can occur as a direct consequence of stent thrombosis or as an indirect complication of distal embolization.[4] Data regarding potential causes, early management, and outcome are scarce.[5]

Data from the literature state that ACST after CAS is very rare, with a reported incidence of 0.5% to 0.8%.[6] However, a follow-up study of ACST using serial computed tomography angiography revealed an early in-stent thrombosis rate, among 23 cases of CAS, of 43.5%. The early in-stent thrombosis disappeared within 12 weeks, in most cases, as a result of endogenous fibrinolysis.[7] The preferential location for hypodense thrombus deposits in the acute and subacute period after CAS matches the site of turbulent or reversed flow in the carotid artery, evidencing that changes in flow dynamics affect thrombus development. Risk factors for in-stent thrombosis after CAS included long stenotic lesions and patients with long stents deployed across the carotid bifurcation.[7]

ACST management and outcome after successful rescue remain largely unknown.[8] In fact, no data about

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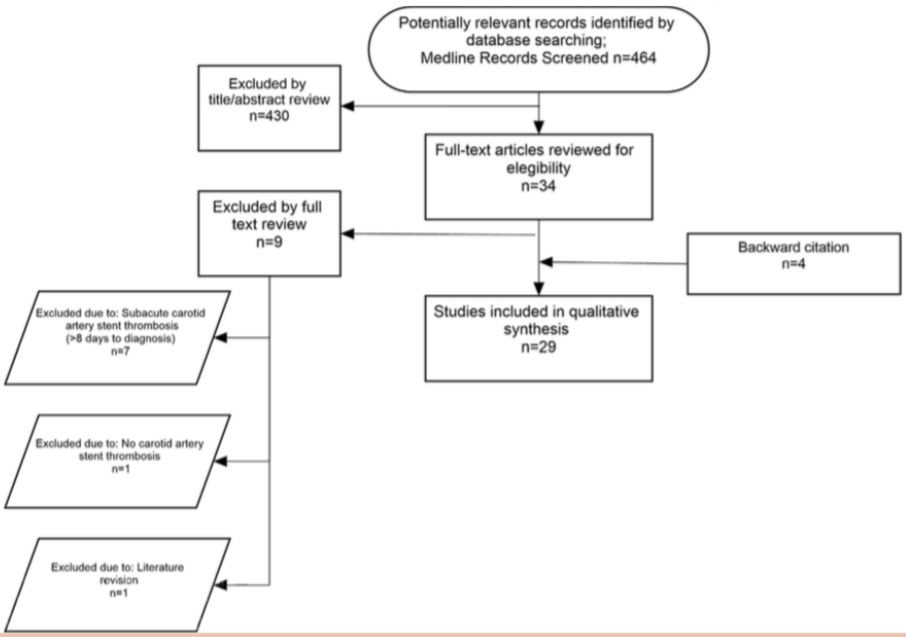

Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram summarizing literature screening process.

experience with the ideal strategy for revascularization after ACST have been published, and no randomized controlled trials (RCTs) have ever addressed the treatment of acute ischemic stroke caused by ACST. The European Society for Vascular Surgery updated its atherosclerotic carotid artery disease management guidelines, stating that thrombolysis should be considered and intravenous abciximab may be effective, but provided no specific approach.[1] Regardless of the treatment approach, ACST may lead to serious neurologic consequences and death. Procedure-related complications, operator-related causes, and patient-related risk factors are all potential culprits in ACST etiology.[6]

The purpose of this review was to evaluate the current literature on ACST, identifying all reported cases of ACST during the last two decades with the final purpose of reporting predictive factors and early management.

METHODS

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[9] The literature search was last updated in January 2018. A total of 464 results were retrieved using the MEDLINE database and the following query: (acute[All Fields] AND carotid[All Fields] AND ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields] AND ("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields])) OR ((("carotid"[All Fields] AND "artery"[All Fields]) OR "carotid artery"[All Fields] OR "carotid arteries"[MeSH Terms] OR ("carotid"[All Fields] AND "arteries"[All Fields]) OR "carotid arteries"[All Fields] OR ("carotid"[All Fields] AND "artery"[All Fields])) AND ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stenting"[All Fields])) AND (acute[All Fields] AND ("thrombosis"[MeSH Terms] OR "thrombosis"[All Fields]))) OR (acute[All Fields] AND carotid[All Fields] AND ("stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields]) AND ("occlusion"[All Fields]). The conduction of the search as proposed is demonstrated in Fig 1 by a Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

The eligibility criteria included any publication reporting ACST cases occurring within the first hours from the procedure (up to 8 days). Exclusion criteria included articles published in a language other than Portuguese, English, or Spanish and publications before the year 2000.

Two reviewers initially screened the identified studies. Further assessment of articles that potentially met inclusion criteria was performed using the full text (Fig 1). Data collected and analyzed included rate of stent thrombosis (in CAS cohorts), age, sex, stenosis grade,

Table I. Information on included articles

Article	Year of publication	No.	Type of study	Incidence rate for ACST, % (n/N)
Moulakakis and Lazaris[13]	2018	2	Case series	–
Moulakakis et al[43]	2017	4	Case series	0.59 (4/674)
Cvjetko et al[44]	2017	2	Case series	–
Miyakoshi et al[42]	2017	1	Case report	–
Yilmaz et al[10]	2017	10	Case series	21.3 (10/47) 45 (9/20) in subgroup analysis for dual-layer stent
Deguchi et al[17]	2016	1	Case report	33 (1/3)
Koklu et al[22]	2015	4	Case series	2.1 (4/192)
Steglich-Arnholm et al[33]	2015	8	Case series	17 (8/47)
Sorkin et al[31]	2015	1	Case report	–
Lockau et al[15]	2015	3	Case series	16.2 (n = 6)
Heck et al[14]	2015	1	Case report	5.6 (1/18)
Munich et al[18]	2014	1	Case report	–
Soize et al[45]	2014	1	Case report	–
Kim et al[11]	2013	3	Case series	–
Kanemaru et al[12]	2013	1	Case report	–
Markatis et al[21]	2012	1	Case report	–
Choi et al[40]	2012	1	Case report	–
Stotts et al[37]	2012	1	Case report	–
Iancu et al[6]	2010	1	Case report	–
Dhall et al[38]	2010	1	Case report	–
Seo et al[4]	2008	1	Case report	
Masuo et al[8]	2006	1	Case report	0.36 (1/307)
Setacci et al[19]	2005	3	Case series	0.5 (3/562)
Kurisu et al[46]	2004	1	Case report	–
Steiner-Boker et al[36]	2004	1	Case report	–
Bush et al[41]	2003	1	Case report	–
Owens et al[5]	2002	1	Case report	–
Chaturvedi et al[47]	2001	2	Case series	–
Tong et al[35]	2000	1	Case report	–
	Total	60		

ACST, Acute carotid stent thrombosis.

contralateral stenosis grade, criteria for CAS, type of stent, antiplatelet therapy and anticoagulation before stenting, potential intraoperative complications, neurologic status deterioration after ACST, time to stent occlusion (hours), type of ACST treatment, symptomatic intracranial hemorrhage (sICH), and neurologic outcome. An attempt was made to contact authors when information was missing. An e-mail was sent to the main author of seven manuscripts and we received three responses, all citing national data protection laws preventing them from sharing patients' data without specific permission. Authorship of the studies was not masked from the reviewers.

RESULTS

A total of 464 potentially relevant articles were initially selected. After review of the records at title or abstract level, 34 articles were read in full and 25 were judged eligible for inclusion. Backward citation led to the inclusion of four additional articles (Fig 1). A total of 29 articles with 60 patients were included. A total of 10 articles were cases series, and the remaining (n = 19) were case reports. A total of 12 studies presented an estimated incidence rate for their cohorts.

The incidence rate for ACST in cohorts ranged from 0.36% to as high as 33%. In four series, all patients presented with neurologic deterioration, and in the remaining series (n = 5), patients' symptoms were not specified. Moulakakis et al reported the largest cohort (n = 674) with a total of four cases of ACST, reaching an incidence rate of 0.59%. In emergency settings, ACST ranged from 5.6% to 33%, with one cohort reporting 45% ACST in a subgroup submitted to dual-layer stenting (Table I).

Table II. Demographic data of included patients

Article	Year of publication	No.	Age, years	Male sex	Stenosis grade, %	Side	Criteria for CAS	Stent
Moulakakis and Lazaris[13]	2018	2	66	Yes	90	Right	Asymptomatic	Xact[a]
			72	Yes		Right	Asymptomatic	Xact
Moulakakis et al[43]	2017	4	66	Yes	80	Left	Symptomatic	Xact
			67	Yes	90	Right	Symptomatic	Xact
			74	Yes	80	Left	Symptomatic	Xact
			73	No	60	Left	Symptomatic	Xact
Cvjetko et al[44]	2017	2	68	No	70	Right	Asymptomatic	Xact
			80	Yes	70	Left	Asymptomatic	MER[b]
Miyakoshi et al[42]	2017	1	84	Yes		Right	Symptomatic	Precise[c]
Yilmaz et al[10]	2017	10					Emergent (tandem occlusion)	Casper[d] (9)
Deguchi et al[17]	2016	1	71	Yes	100	Right	Emergent (tandem occlusion)	Wallstent[e]
Koklu et al[22]	2015	4	74	Yes	98	Right	Symptomatic	Xact
			73	Yes	95	Left	Symptomatic	Sinus[f]
			75	Yes	95	Left	Symptomatic	Sinus
			64	Yes	90	Left	Symptomatic	Cristallo[g]
Steglich-Arnholm et al[33]	2015	8					Emergent (tandem occlusion)	Wallstent
Sorkin et al[31]	2015	1	57	No	100	Left	Emergent (tandem occlusion)	Xpert[h] (1) + Xact (2)
Lockau et al[15]	2015	3					Emergent (tandem occlusion)	
Heck et al[14]	2015	1					Emergent (tandem occlusion)	
Munich et al[18]	2014	1	70		90	Left	Symptomatic	Precise
Soize et al[45]	2014	1					Emergent (tandem occlusion)	Wallstent
Kim et al[11]	2013	3	73	Yes				Wallstent
			75	Yes	90	Left	Symptomatic	Wallstent
			51	Yes				Wallstent
Kanemaru et al[12]	2013	1	77	Yes	90	Right	Symptomatic	Wallstent
Markatis et al[21]	2012	1	67	Yes	Preocclusive	Left		Acculink[i]
Choi et al[40]	2012	1	69	Yes	83	Right	Symptomatic	
Stotts et al[37]	2012	1	70	No	70	Right	Symptomatic	Precise
Iancu et al[6]	2010	1	65	Yes	80	Right	Symptomatic	Inflow
Dhall et al[38]	2010	1	62	Yes	90	Left	Symptomatic	Precise
Seo et al[4]	2008	1	64	Yes	85	Left	Asymptomatic	SMART[j]
Masuo et al[8]	2006	1	71	Yes		Left	Symptomatic	SMARTer[k]
Setacci et al[19]	2005	3	82	Yes			Symptomatic	Wallstent
			78	Yes	85	Left	Symptomatic	Wallstent
			72	Yes		Right	Symptomatic	Wallstent
Kurisu et al[46]	2004	1	72	Yes			Asymptomatic	
Steiner-Boker et al[36]	2004	1	64	No	90	Right	Asymptomatic	Wallstent
Bush et al[41]	2003	1	68	Yes	90	Right	Symptomatic	Dynalink[i]
Owens et al[5]	2002	1	65	Yes	70	Left	Asymptomatic	
Chaturvedi et al[47]	2001	2	63	No		Left	Symptomatic	
			57	Yes		Left	Symptomatic	

(Continued on next page)

Table II. Continued.

Article	Year of publication	No.	Age, years	Male sex	Stenosis grade, %	Side	Criteria for CAS	Stent
Tong et al[35]	2000	1	44	Yes	70		Asymptomatic	Symphony[e]
	Total	60	68.73± 8.03	83.3% (n = 30)				

CAS, Carotid artery stenosis.
[a]Abbot Vascular, Abbot Park, Ill.
[b]Balton, Warsaw Poland.
[c]Cordis Endovascular, Warren, NJ.
[d]MicroVention, Tustin, Calif.
[e]Boston Scientific, Natick, Mass.
[f]Sinus-Carotid-Conical-RX stent, OptiMed, Ettlingen, Germany.
[g]Cristallo Ideale SE stent, Invatec, Roncadelle, Italy.
[h]Xpert Biliary Stent, Abbot Vascular, Abbot Park, Ill.
[i]RX Acculink Stent System, Abbott Vascular, Rungis Cedex, France.
[j]Cordis, Miami, Fla.
[k]Johnson & Johnson, Miami, Fla.
[l]Guidant, Indianapolis, Ind.

The mean age was 68.73 ± 8.03 years, and 83.3% were male. The left internal carotid artery (ICA) was affected in 57.6%. Carotid artery stenosis was >70% in all reported cases, with two cases of complete occlusion (in the setting of emergent tandem occlusions; Table II).

In considering the initial clinical criteria for CAS in our review of ACST (N = 60 patients), 8 patients were asymptomatic (13.3%), 35 (58.3%) were symptomatic, and 17 (28.3%) were treated in an emergency setting with simultaneous intracranial thrombectomy (Table II).

The assumed pathophysiologic cause of ACST was pursued, even though it remained unclear in the majority of cases (n = 39 [65%]). In 2 cases (3.3%), ACST was presumed to be associated with inherent or acquired thrombotic disorders (malignant disease and heparin-induced thrombocytopenia thrombosis); in 7 cases (11.7%), antiplatelet noncompliance; in 3 cases (5%), antiplatelet resistance; in 3 cases (5%), carotid artery dissection; in 4 cases (6.7%), atherosclerotic plaque protrusion; and in 2 cases (3.3%), long lesions corrected with two carotid stents (Table III).

In technical considerations, the type of stent used may influence the outcome. The carotid Wallstent (Boston Scientific, Natick, Mass) was the most commonly used stent in 18 patients (30%), followed by Xact (Abbot Vascular, Abbot Park, Ill) in 8 patients (13.3%) and Precise carotid stent (Cordis Endovascular, Warren, NJ) in 3 patients (5%; Table II). In a report of ACST in the setting of emergency CAS with intracranial thrombectomy, the dual-layer stent Casper RX (MicroVention, Tustin, Calif) was reported to have a significantly higher rate of acute occlusion (45% vs 3.7%; odds ratio, 21.3; $P = .0001$).[10]

Thirty-four patients (57%) presented with neurologic deterioration. Time to symptoms of neurologic deterioration or ACST diagnosis was a median of 1.5 hours (range, 0-192 hours). Eighteen cases (30%) were intraprocedural (Table III).

Conservative management with anticoagulation alone was decided on in three cases (5%). Systemic intravenous thrombolysis alone was the treatment approach in two patients (3.3%) and facilitated thrombolysis in three patients (5%). In one case (1.7%), in-stent percutaneous transluminal angioplasty (PTA) and thrombolysis led to ICA rupture, and salvage treatment with CEA was successful (Table IV).

Endovascular treatment was the most common approach in intraprocedural ACST (n = 18 [30%]). A total of 10 patients (17%) were submitted to mechanical thrombectomy with or without concomitant facilitated thrombolysis. In one case (1.7%), stent-in-stent was subsequently performed after thrombectomy; in another case, stent-in-stent was the initial approach (1.7%; Table IV).

Surgical options included CEA with stent explantation (n = 9) with or without additional distal Fogarty thrombectomy, mechanical thrombectomy of embolus (n = 1), and superficial temporal artery-middle cerebral artery bypass (n = 1). CEA was used as a salvage treatment after failed endovascular treatment in two cases (Table IV).

As for outcome, we counted three deaths in this review, one due to sICH, one due to massive stroke, and one due to serious reperfusion injury in a patient treated in an emergency setting. In 22 patients (36.7%), there was early improvement with full neurologic recovery or mild deficits (modified Rankin scale score <2). In 21 patients (35%), there was no early improvement of deficits. Data are absent on outcome in the remaining 14 cases (23.3%; Table IV).

DISCUSSION

ACST is a rare cause of ICA flow arrest during CAS with distal filter protection, but it may have the most catastrophic consequences.[11] Data on ACST management come mainly from case reports and small case series. No RCTs have ever been published. Therefore, guidelines

Table III. Data on pathophysiologic causes of and neurologic status deterioration with acute carotid stent thrombosis (ACST)

Article	Year of publication	No.	Assumed cause	Neurologic status deterioration	Symptoms	Time to symptoms or diagnosis, hours
Moulakakisand Lazaris[13]	2018	2	Plaque protrusion	Yes	Left hemiparesis	0.5
			NS	Yes	TIA	1
Moulakakis et al[43]	2017	4	Deployment of two stents	Yes	Right hemiparesis and aphasia	72
			ICA dissection	Yes	Left hemiparesis	1
			Deployment of two stents	Yes	Right hemiparesis and aphasia	2
			ICA dissection with second stent deployment and malignant disease	Yes	Right arm paresis	72
Cvjetko et al[44]	2017	2	Antiplatelet noncompliance	Yes	Right hemiplegia and aphasia	1.5
			Antiplatelet noncompliance	Yes	TIA (24 hours); evolved to right hemiplegia and aphasia	24
Miyakoshi et al[42]	2017	1	Plaque protrusion	No	NA	48
Yilmaz et al[10]	2017	10	NS	No (9) Yes (1)	Hemiparesis (1)	<72
Deguchi et al[17]	2016	1	NS	No	NA	<96
Koklu et al[22]	2015	4	Antiplatelet resistance	NS	NA	3
			Antiplatelet resistance	NS	NA	4
			Antiplatelet resistance	NS	NA	3
			Antiplatelet noncompliance	NS	NA	192
Steglich-Arnholm et al[33]	2015	8	NS	Yes (8)	NS	0 (intraprocedural)
Sorkin et al[31]	2015	1	NS	Yes	NS	0 (intraprocedural)
Lockau et al[15]	2015	3	NS	NS	NS	0 (intraprocedural)
			NS	NS	NS	0 (intraprocedural)
			NS	NS	NS	0 (intraprocedural)
Heck et al[14]	2015	1	NS	No	NA	<48
Munich et al[18]	2014	1	NS	NS	NS	0 (intraprocedural)
Soize et al[45]	2014	1	Plaque protrusion	NS	NS	0 (intraprocedural)
Kim et al[11]	2013	3	NS	No	NA	0 (intraprocedural)
			NS	Yes	Global aphasia	0 (intraprocedural)
			NS	Yes	Drowsy mentality and hemiparesis	0 (intraprocedural)
Kanemaru et al[12]	2013	1	Malignant disease	No	NA	<144
Markatis et al[21]	2012	1	Antiplatelet noncompliance	Yes	Mild weakness in the right arm	24
Choi et al[40]	2012	1	NS	Yes	Hemiparesis, dysarthria, and left facial palsy	144
Stotts et al[37]	2012	1	HITT	Yes	Left arm paresis	0 (intraprocedural)
Iancu et al[6]	2010	1	ICA dissection	Yes	Hemiplegia	0 (intraprocedural)
Dhall et al[38]	2010	1	NS	Yes	NS	0 (intraprocedural)
Seo et al[4]	2008	1	NS	No	NA	0 (intraprocedural)
Masuo et al[8]	2006	1	NS	Yes	Right hemiparesis and motor aphasia	72

(Continued on next page)

Table III. Continued.

Article	Year of publication	No.	Assumed cause	Neurologic status deterioration	Symptoms	Time to symptoms or diagnosis, hours
Setacci et al[19]	2005	3	Plaque protrusion	Yes	Crescendo TIA	48
			Antiplatelet noncompliance and thrombocythemia	Yes	Severe neurologic deficit and decreased conscious	92
			Cardiac embolism	Yes	Left hemiplegia	2
Kurisu et al[46]	2004	1	NS	Yes	NS	168
Steiner-Boker et al[36]	2004	1	NS	Yes	Left facial paresis and dysarthria	0 (intraprocedural)
Bush et al[41]	2003	1	NS	Yes	Seizures and hemiparesis	0.25
Owens et al[9]	2002	1	NS	NS	Right arm weakness	0 (intraprocedural)
Chaturvedi et al[47]	2001	2	No dual antiplatelet treatment (isolated AAS)	Yes	Right hemiplegia and aphasia	0 (intraprocedural)
			No antiplatelet treatment	Yes	Right-sided weakness	96
Tong et al[35]	2000	1	NS	No	NA	0 (intraprocedural)
	Total	60				1.5 (range, 0-192)

AAS, Acute aortic syndrome; *HITT*, heparin-induced thrombocytopenia thrombosis; *ICA*, internal carotid artery; *NA*, not applicable; *NS*, not specified; *TIA*, transient ischemic attack.

in providing a structured approach and a strategy for ACST management are still missing. A great heterogeneity of included articles with regard to the treatment strategy is clear.

CAS may be performed in asymptomatic patients or symptomatic patients (stroke or transient ischemic attack <6 months ago) or as an early procedure in a neurologically unstable patient associated or not with intracranial thrombectomy or thrombolysis. In this systematic review concerning clinical criteria for initial CAS, most patients were symptomatic or treated in an emergency setting (Table II).

Analysis of the included articles reveals an astonishing variability in the incidence rate of ACST in CAS cohorts. This finding may in part be due to variability in post-stenting surveillance, evidenced by the fact that some series report only symptomatic cases of ACST. In patients with multiple risk factors, examination with Doppler ultrasound at least twice in the first week after CAS has been recommended.[12] It may also be due to the fact that some studies include CAS only in the emergency or symptomatic setting, whereas others include asymptomatic patients. In elective cases, incidence rate variability was notably lower and ranged from 0.36% to as high as 2.1%[13] (Table I). In emergent procedures, ACST ranged from 5.6% to 33%, suggesting an increased risk for ACST in an emergent setting[10,14-17] (Table I).

Even though recent literature stresses the differences between coronary and cerebrovascular territories, emphasizing the need to stop extrapolating data between territories, risk factors seemed to overlap in this systematic review. Emergent procedures, in particular in-tandem occlusions with simultaneous intracranial thrombectomy, had an unacceptably high rate of ACST in some series, reaching 45% of cases.[10]

Causes of this potentially catastrophic complication are usually subdivided into local and systemic causes. The systemic causes include inadequate antiplatelet treatment and hypercoagulable state. Local causes include vessel dissection, severe plaque protrusion, early stent restenosis, stent under expansion, and other technical concerns, such as stent kinking or coiling, long stenotic lesions, increased stent length, use of a second overlapping stent as bailout, and type of carotid stent.[6] Furthermore, stent deployment and PTA rupture the luminal plaque, exposing thrombogenic factors, which can lead to thrombotic events both locally within the stent and remotely at the distal protection device.[18] Hypercoagulable state is a rare but described cause of postprocedural ACST occurring hours to several days after the procedure.[19] Malignant disease, heparin-induced thrombocytopenia thrombosis, and thrombocythemia have been described as potential causes (Table III).

Failure to administer proper antiplatelet therapy is systematically identified as the most important, potentially preventable cause of ACST.[1] As previously stated, acute in-stent thrombosis and distal protection device occlusion may primarily be due to platelet aggregation after plaque rupture.[20] Therefore, it is recommended to start dual antiplatelet therapy with aspirin 300 mg initially

Table IV. Data on treatment and outcome of acute carotid stent thrombosis (ACST)

Article	Year of publication	No.	Treatment	Outcome	mRS
Moulakakis and Lazaris[13]	2018	2	CEA	Complete resolution of symptoms in <4 hours	0
			CEA	Uneventful recovery	0
Moulakakiset al[43]	2017	4	Isolated anticoagulation	Expressive aphasia	2
			Eversion CEA after ineffective thrombectomy	Mild residual aphasia	1
			Thrombolysis, thrombectomy, and stent-in-stent	Residual arm paresis	2
			Isolated anticoagulation	No deficits at 30 months	0
Cvjetko et al[44]	2017	2	CEA (direct closure)	NS	1
			CEA and Fogarty thrombectomy	NS	3
Miyakoshi et al[42]	2017	1	Stent-in-stent and anticoagulation	NS	3
Yilmaz et al[10]	2017	10	NS	NS	4.0 ± 1.9 (9 patients with dual-layer stents)
Deguchi et al[17]	2016	1	Isolated anticoagulation	NS	2
Koklu et al[22]	2015	4	NS	NS	NS
Steglich-Arnholm et al[33]	2015	8	Glycoprotein IIb/IIIa receptor antagonists (7); no treatment (1)	Early improvement (1); no early improvement (6; including the patient not submitted to treatment); death—reperfusion injury (1)	
Sorkin et al[31]	2015	1	Facilitated thrombolysis	No neurologic deficits at 30 days	0
Lockau et al[15]	2015	3	Thrombectomy	Successful thrombectomy	NS
			Thrombectomy	Unsuccessful thrombectomy	NS
			Thrombectomy	Unsuccessful thrombectomy	NS
Munich et al[18]	2014	1	Thrombectomy and glycoprotein IIb/IIIa receptor antagonists	No new neurologic deficits	NS
Heck et al[14]	2015	1	NS	NS	NS
Soize et al[45]	2014	1	NS	NS	NS
Kim et al[11]	2013	3	Thrombectomy	NS	NS
			Thrombectomy	NS	NS
			Thrombectomy	NS	NS
Kanemaru et al[12]	2013	1	Glycoprotein IIb/IIIa receptor antagonists and anticoagulation	Shrinkage of the in-stent thrombosis with complete resolution by 11 weeks	0
Markatis et al[21]	2012	1	CEA and Fogarty thrombectomy	Minor numbness in three fingers	1
Choi et al[40]	2012	1	Superficial temporal artery-middle cerebral artery bypass	NS	3

(Continued on next page)

Table IV. Continued.

Article	Year of publication	No.	Treatment	Outcome	mRS
Stotts et al[37]	2012	1	Facilitated thrombolysis	NS	1
Iancu et al[6]	2010	1	Thrombolysis	NS	0
Dhall et al[38]	2010	1	Facilitated thrombolysis and thrombectomy	Clinical improvement	1
Seo et al[4]	2008	1	Glycoprotein IIb/IIIa receptor antagonists and anticoagulation	NS	0
Masuo et al[8]	2006	1	In-stent PTA	Mild right hemiparesis	1
Setacci et al[19]	2005	3	CEA	Full neurologic recovery	0
			CEA	Gradual improvement	0
			Fogarty thrombectomy	NS	0
Kurisu et al[46]	2004	1	Thrombolysis and stent-in-stent	NS	1
Steiner-Boker et al[36]	2004	1	Facilitated thrombolysis	NS	0
Bush et al[41]	2003	1	Glycoprotein IIb/IIIa receptor antagonists and thrombectomy	Clinical improvement by 2 weeks	0
Owens et al[5]	2002	1	In-stent PTA and thrombolysis led to ICA rupture; treatment with CEA	Fine motor deficits	1
Chaturvedi et al[47]	2001	2	Thrombolysis	Hemorrhagic stroke and death	NA
			No treatment	Massive stroke and death	NA
Tong et al[35]	2000	1	Glycoprotein IIb/IIIa receptor antagonists	NS	0
	Total	60			

CEA, Carotid endarterectomy; *mRS*, modified Rankin scale; *NA*, not applicable; *NS*, not specified; *PTA*, percutaneous transluminal angioplasty.

for up to 14 days, followed by 75 mg daily if the patient is not already taking aspirin and clopidogrel (75 mg daily) starting 3 days before CAS. Both should be continued for at least 1 month, followed by clopidogrel thereafter. In the acute setting, loading doses of both clopidogrel and aspirin as well as continuous intravenous administration of a third antiaggregant (glycoprotein IIb/IIIa inhibitor) are usually administered. Before the procedure, 5000 units of unfractionated heparin (UFH) is usually administered intravenously.[1,19,21]

Aspirin resistance has been defined clinically as development of thrombotic and vascular events despite suitable therapy. Clopidogrel resistance has been defined as continued activity of platelet $P2Y_{12}$ receptors even under appropriate therapy.[22] The association between aspirin or clopidogrel resistance and poor outcome or ACST is well established.[23,24] In this study, three patients (5%) were assumed to have ACST due to antiplatelet agent resistance. Fifi et al[25] reported 5.2% aspirin resistance and 36.5% clopidogrel resistance among 96 patients who underwent CAS. Recent data, however, recommend against routine testing for clopidogrel and aspirin resistance as RCTs have failed to demonstrate the benefit of platelet function monitoring to adjust therapy.[26] It is noteworthy that less drug resistance may be encountered with newer antiplatelet agents, such as ticagrelor and prasugrel, because of reduced enzymatic polymorphisms.[27]

Direct oral anticoagulants, such as rivaroxaban and dabigatran, are an alternative to vitamin K antagonists. Unlike vitamin K antagonists, direct oral anticoagulants do not require routine international normalized ratio monitoring, have more favorable pharmacologic properties, and are being increasingly pursued for their beneficial profile in peripheral artery disease. However, no data are currently available on direct oral anticoagulants for CAS.[28]

Technical intraprocedural complications including dissection, atheroma plaque prolapse, kinking, and coiling of the distal ICA segment can result in ACST. In this systematic review, technical intraprocedural complications were responsible for nine ACST cases (15%). This may be underestimated because causes of ACST remained unclear in the majority of cases (n = 39 [65%]).

Among ICA thrombosis mechanisms, distal embolic protection device (EPD) occlusion during CAS was the

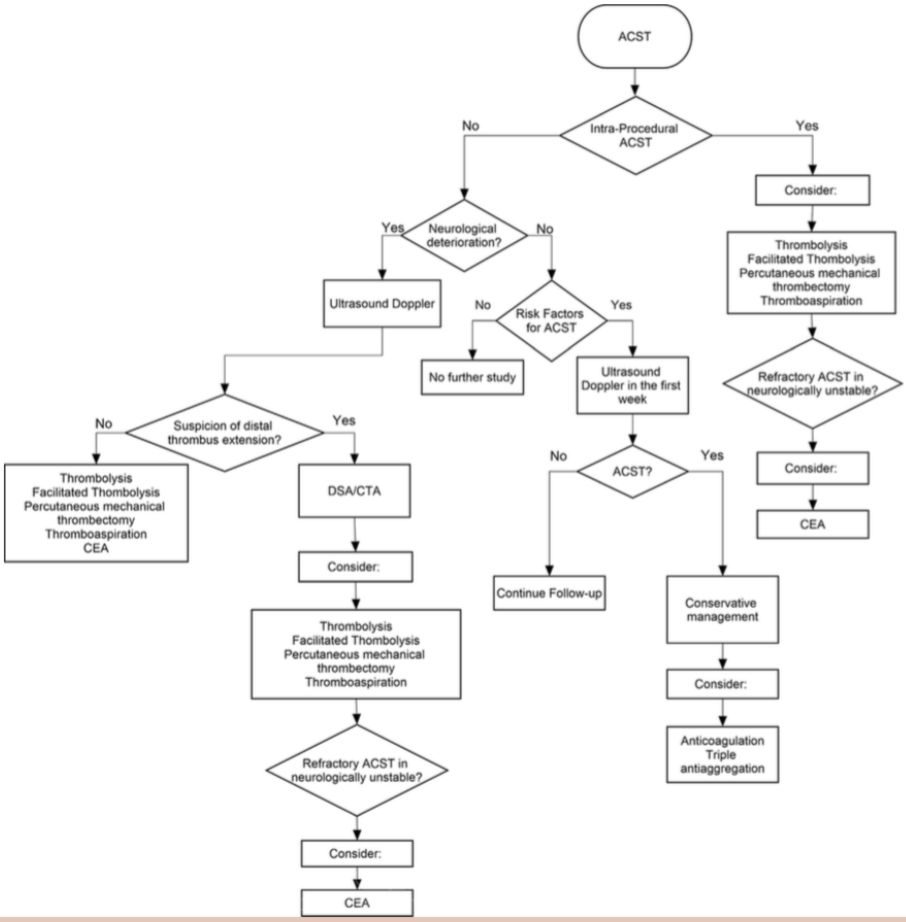

Fig 2. Proposed management algorithm for acute carotid stent thrombosis (*ACST*). *CEA*, Carotid endarterectomy; *CTA*, computed tomography angiography; *DSA*, digital subtraction angiography.

most frequent cause. It is admitted that EPD occlusion and carotid stent thrombosis are sequential events as they share etiologic mechanisms.[29] Intraprocedural carotid stent thrombosis due to EPD thrombosis has been described in four patients (6.7%; Table III).[11,30]

Resorting to a second overlapping stent as a bailout after dissection or malposition or as a result of long lesions was associated with increased risk of thrombosis (3/41 [7.3%] vs 1/633 [0.002%]; $P < .05$).[13,31] Long stenotic lesions (22.9 ± 6.83 mm vs 14.2 ± 6.42 mm; $P = .0034$) and stent length (3.8 ± 0.4 cm vs 2.8 ± 0.86 cm; $P = .0055$) were described as risk factors for in-stent thrombosis.[7]

The type of carotid stent influences the rate of complications. Postprocedural complication rates are higher in open-cell stents compared with closed-cell stents.[32] The influence of stent cell design on cerebral embolism after CAS is not well understood, but closed-cell stent designs provide greater vascular wall coverage and may better prevent debris dislodgment during CAS compared with open-cell stent designs.[32]

A new generation of carotid artery stents has been introduced that uses a second micromesh layer for more thorough prevention of debris dislodgment and plaque protrusion. However, in a recent report of ACST in the setting of emergency carotid stenting with

intracranial thrombectomy, dual-layer stents were reported to have a significantly higher rate of acute occlusion (45% vs 3.7%; $P = .0001$; odds ratio, 21.3).[10] In another study, Steglich-Arnholm et al[33] reported a rate of ACST of 9% in the setting of emergency CAS with intracranial thrombectomy. Interestingly, in 2 of 47 cases, dual-layer stents (Casper RX) were used, but reports are missing about which type of stents occluded in this series.

Several possible approaches to ACST management are described in the literature. The decision as to the best approach depends on whether the ACST occurs intraprocedurally or afterward, the presence or absence of neurologic status deterioration, and the center's experience. To plan an approach, when a neurologic deficit is diagnosed in the early post-CAS period, a prompt carotid Doppler ultrasound evaluation should be performed. When the findings of this examination are normal or when distal extension of thrombosis is undetermined, a second-level study (angiography or computed tomography angiography) should be performed.[3]

Peri-interventional carotid stent thrombosis ideally requires fast reperfusion therapy to limit the time of ischemia, reperfusion injury, and associated sICH.[34] For cases of severe neurologic state deterioration, an urgent revascularization procedure should be decided on. The dilemma arises when the patient is in a stable state with minor signs of neurologic deficit.[21] This is particularly true considering that all revascularization alternatives raise concerns for distal embolization of thrombus and for sICH. Based on all these considerations, an improved algorithm for management was delineated for an approach to patients (Fig 2).[2]

Anticoagulation alone was used as an approach to ACST in two patients (3.3%), one with no neurologic status deterioration and one with mild symptoms. It was an adjuvant therapy in most cases (Table IV). Early thrombus disaggregation, termed dethrombosis, by use of the glycoprotein IIb/IIIa inhibitor abciximab administered intravenously or intra-arterially has been reported to recanalize acutely occluded stents.[3,35] An intravenous infusion of tirofiban has also been used as a rescue for intraprocedural ACST.[4] Systemic intravenous thrombolysis alone was used in two patients (5%), complicated with sICH in one case, but stent recanalization was achieved in the other case (Table IV). It is frequently used as an adjuvant to endovascular thrombectomy or in combination with glycoprotein IIb/IIIa receptor antagonists (facilitated thrombolysis). The combined therapeutic regimen consisting of dethrombosis (glycoprotein IIb/IIIa inhibitors) and fibrinolysis, termed facilitated thrombolysis, improves recanalization rates.[36] Each targets different phases of thrombus formation, making concomitant use relevant to revascularization.[3] This approach was used in four cases (6.7%), being effective in all reported cases, with no complications[31,37,38] (Table IV). It seems especially helpful in hyperacute carotid stent thrombosis.[31]

The management of ACST may require emergent definite surgical repair, particularly when neurologic status deterioration ensues.[19] Transfer of experience from acute thrombosis management after CEA suggests including this procedure, with or without concomitant thrombectomy, in the ACST management armamentarium.[19] CEA was performed in nine patients (15%). There are some concerns about CEA in this setting. First, surgical preparation and exploration are laborious and time-consuming, delaying carotid revascularization. Second, emergency surgery performed under dual antiplatelet therapy and anticoagulation is associated with higher hemorrhagic morbidity. Third, in an acute post-CAS setting, surgical exploration is associated with greater risk for cranial nerve damage, associated with local hematoma or inflammatory reaction and the more extensive ICA dissection necessary to permit safe stent explantation.[11] However, stent removal and CEA were effective in recanalization and neurologic status improvement in all reported cases, even as a bailout (Table IV).

Superficial temporal artery-middle cerebral artery bypass anastomosis is described as an alternative option for symptomatic patients with ACST, providing symptom and imaging improvement on follow-up, especially when intra-arterial thrombolysis is not possible.[39,40] A single case is described in this review with an acceptable outcome (modified Rankin scale score of 3; Table IV).

The literature remains sparse about how effective and reliable endovascular treatment strategies are. Mechanical thrombectomy was used in 10 patients (16.7%), being effective in stent revascularization in nine cases (the remaining case was submitted to CEA; Table IV).

Munich et al[18] described successful thromboaspiration of hyperacute intraprocedural carotid stent thrombosis refractory to intravenous administration of abciximab.[8] Kim et al[11] described three cases of successful thromboaspiration. Dhall et al[38] described successful simultaneous direct thrombosuction with the guiding sheath with facilitated thrombolysis for intraprocedural ACST.

Percutaneous mechanical thrombectomy (AngioJet Rheolytic Thrombectomy System; Possis Medical Inc, Minneapolis, Minn) was used in a hyperacute carotid stent thrombosis in combination with abciximab with good outcome.[41] Thrombectomy with the Penumbra reperfusion catheter (Penumbra Inc, Alameda, Calif) was first used for recanalization of acute intracranial large arterial vessels, but it has potential for ACST. Caution is warranted, however, if ACST is caused by severe plaque protrusion.[11]

In-stent PTA performed under distal protection without additional placement of stent was described in one case successfully.[8] Stent-in-stent was performed in another case. After the second CAS, oral cilostazol was added for triple antiplatelet therapy, but as the in-stent thrombosis increased further, continuous infusion of UFH was started. The lesion did not progress further, and after 14 days of continuous UFH, regression of the plaque was confirmed.[42]

The long-term outcome after successful rescue of ACST is currently unclear. Most studies report short-term follow-up, usually with no imaging follow-up (Table IV).

The main limitations of the included studies were as follows: no prespecification of selection criteria for the study population, small population size in most studies, and varying imaging follow-up criteria for CAS. Risk of bias of publication must be emphasized as underreporting of this complication is likely to occur and was considered the main limitation to this study by the authors.

CONCLUSIONS

The decision as to the best approach depends on whether ACST occurs intraprocedurally or afterward, the development of neurologic status deterioration, and the center's experience. In asymptomatic ACST, conservative management was unanimous.

In patients with neurologic deterioration, surgical management was effective in achieving ICA recanalization. However, concerns exist about delayed revascularization because of laborious surgical dissection and increased risk for cranial nerve damage. Endovascular treatment including thrombectomy, thromboaspiration, PTA, and stent-in-stent could be applied quickly during the procedure, but long-term efficacy is still debatable. A role for thrombolysis and facilitated thrombolysis is still to be determined.

Prognosis after ACST depends on several critical considerations, including initial clinical presentation, which expresses the ischemic brain damage; timely diagnosis of the event; and rapid revascularization of the ischemic penumbra area. Expeditious revascularization of ischemic penumbra areas is key as delayed recanalization can be associated with impaired neurologic recovery.[43] Still, additional studies must be undertaken to better define optimal management.

AUTHOR CONTRIBUTIONS

Conception and design: APC, ML, AC
Analysis and interpretation: APC, ML, CN, RG, AC
Data collection: APC, JC, RA, NC, AS
Writing the article: APC, CN, RG, AC
Critical revision of the article: APC, ML, CN, RG, JC, RA, NC, AS, AC
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CARDIOVASCULAR SCIENCES
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CHAPTER 7

A DELPHI CONSENSUS STUDY ON LIVING WITH CAROTID ARTERY DISEASE – PATIENT REPORTED OUTCOME MEASURES

CHAPTER 7. A Delphi Consensus Study on Living with Carotid Artery Disease – Patient Reported Outcome Measures

Systematic review and meta-analysis of the literature submitted for publication and under review process in *The European Journal of Vascular and Endovascular Surgery*, indexed to PubMed/MEDLINE journal

- CiteScore of 7.1
- CiteScore Highest Percentile - Surgery - 96% (First Quartile)
- Journal Impact Factor of 6.428

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A Delphi Consensus Study on Living with Carotid Artery Disease – Patient Reported Outcome Measures

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Abstract:	Introduction Currently, evidence is lacking for disease-specific patient reported outcome measure (PROM) for use in carotid artery disease. This study aimed to obtain expert consensus on the most important items to include in a PROM designed to capture the impact of carotid artery stenosis on overall health and health-related quality-of-life (HRQOL). Methods A three round modified Delphi consensus study was performed. A mixed expert Delphi panel of doctors and patients (as patients are experts in their own disease) was implemented. The aim was to obtain pre-defined consensus on items in four pre-defined domains: generic, quality-of-life, symptom-related and treatment-related. Consensus was reached in rounds 2 and 3 with >70% agreement. Results The experts agreed on 24 items (out of 50) on the four pre-defined domains. The final items were distributed as follows: five in the Generic, six in the Quality-of-life, six in the Symptom and seven in the Treatment-related domain. Interestingly, comparing the items that reached consensus in our study, with the generic and disease-specific PROMs previously used in carotid artery disease investigation, the only constant items were: “difficulty with walking” and “ability to perform daily activities” included in the “Symptom Domain”. The items that reached expert consensus in this study included three additional domains with emphasis given to the impact of the diagnosis, treatment and follow-up on patient´s life and to fear/concern "about the future and “about severe stroke”. In the “Treatment Domain” emphasis was also attained on the side-effects, long-term patient satisfaction and on the information provided regarding treatment options. Discussion As hard clinical outcomes become increasingly rare, comparison between different approaches to carotid artery disease becomes increasingly difficult. The consensus reached provides insight into patient and clinical expert opinion regarding the most

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A Delphi Consensus Study on Living with Carotid Artery Disease – Patient Reported Outcome Measures

Running Title: Patient Reported Outcome Measures on Carotid Artery Disease

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What does this study/review add to the existing literature and how will it influence future clinical practice

Resorting to a modified Delphi Methodology, a mixed expert panel of doctors and patients was assembled, aiming to obtain consensus on the most important items to include in a patient reported outcome measure (PROM) designed to capture the impact of atherosclerotic carotid artery stenosis and its treatment on overall health and health-related quality-of-life. The result was a questionnaire comprising dimensions previously unexplored in disease-specific PROMs and providing a fresh perception of patient and clinical expert opinion. In both clinical and investigational settings, its prospective application, after appropriate external validation, could provide valuable data on the impact of different management options.

Abstract

Introduction

Currently, evidence is lacking for disease-specific patient reported outcome measures (PROM) for use in atherosclerotic carotid artery stenosis (either symptomatic or asymptomatic). This study aimed to obtain expert consensus on the most important items to include in a PROM designed to capture the impact of atherosclerotic carotid artery stenosis on overall health and health-related quality-of-life (HRQOL).

Methods

A three round modified Delphi consensus study was performed. A mixed expert Delphi panel of doctors (international panel of vascular surgeons and neurologists dedicated to this pathology) and patients (either symptomatic or asymptomatic patients meeting criteria for carotid artery revascularization) was implemented. The aim was to obtain pre-defined consensus on items in four pre-defined domains: generic, quality-of-life, symptom-related and treatment-related. Consensus was reached in rounds 2 and 3 with >70% expert agreement.

Results

The experts agreed on 23 items (out of 49) on the four pre-defined domains. The final items were distributed as follows: five in the Generic, six in the Quality-of-life, six in the Symptom and six in the Treatment-related domain.

Interestingly, comparing the items that reached consensus in our study, with the generic and disease-specific PROMs previously used in carotid artery disease investigation, the only constant items were: “difficulty with walking” and “ability to perform daily activities” included in the “Symptom Domain”.

Considering the items that reached expert consensus in the additional domains, emphasis was given to the impact of the diagnosis, treatment and follow-up on patient´s life and to fear/concern "about the future and “about severe stroke”. In the “Treatment Domain” emphasis was also attained on the side-effects, long-term patient satisfaction and on the information provided regarding treatment options.

Discussion

As hard clinical outcomes become increasingly rare, comparison between different approaches to carotid artery disease becomes increasingly difficult. The consensus reached provides a newly defined disease-specific PROM that warrants independent validation in specific populations in the future.

Key-Words

Patient Reported Outcome Measures [MeSH]; Carotid Stenosis [MeSH]; Stent [MeSH]; Endarterectomy, Carotid [MeSH]; Quality of life [MeSH];

Introduction

Carotid artery revascularization with either carotid artery stenting (CAS) or carotid endarterectomy (CEA) is performed for secondary or tertiary prevention of stroke and related disability and complications in patients with atherosclerotic carotid artery stenosis, either symptomatic or asymptomatic, respectively. (1)

Several secondary and potential surrogate outcomes have been considered for balancing the benefit of intervention which is classically analysed using procedural (30-day) stroke, death and myocardial infarction (MI) as primary outcomes. For instance, the possible contribution of diffusion weighted-magnetic resonance imaging (DW-MRI) lesions after CEA/CAS for recurrent stroke or cognitive decline have been studied and are currently a matter of debate. (1)

On the other hand, the benefits of supplementing objective clinical outcome data with a well-developed, valid, consistent, reliable and responsive patient reported outcome measure (PROM) could help provide more targeted data on health-related quality of life (HRQOL), treatment efficacy, procedural *minor*/*major* complications and treatment satisfaction. (2, 3)

PROMs are questionnaires completed by patients in relation to their health and daily functioning and can be categorised as generic, disease-specific or dimensional-specific (measure the effect of an intervention on a specific concept e.g. anxiety). Generic PROMs can be used in a variety of conditions and allow comparison across different patient groups. In contrast, disease-specific PROMs are specific to symptoms and/or treatments associated with a particular disease or condition.

Currently, evidence is lacking for disease-specific PROM for use in atherosclerotic carotid artery stenosis, either in asymptomatic patients for clinical decision (isolated best medical treatment (BMT) or associated to CEA or CAS) or in symptomatic patients undergoing carotid artery revascularisation (CEA versus CAS) (3) Thus, they are not routinely used in either clinical or investigational fields. The development and validation of a new PROM for this setting is warranted in order to supplement traditional clinical outcomes, capture changes in health status and quality of life and subsequently support treatment decisions. (2)

The aim of this study was to obtain expert consensus on the most important items to include in a PROM designed to capture the impact of atherosclerotic carotid artery

stenosis and its associated treatments on the health and HRQOL from the patients' perspective. Given the emphasis on the patient and the importance of their involvement on the development of PROMs, both doctors and patients were included as experts.

Methods

Questionnaire development and design follows the modified Delphi methodology.(4)

Patient Expert Selection:

To capture patient´s perspective, patients were included as experts during all stages of PROM development in a ratio of one patient expert per one medical expert and their inputs were valued and weighted equally. Patients diagnosed with carotid artery stenosis in the year of 2019 in the Angiology and Vascular Surgery Department of Centro Hospitalar de Vila Nova de Gaia e Espinho (CHVNG/E) were retrospectively identified using the Duplex Ultrasound records and patients that met the inclusion criteria (as follows) were randomly invited to participate. Random selection was performed using the "Select Cases" function from the IBM® SPSS® software.

The inclusion criteria were defined as follows: Patients must be willing to participate and be in full use of their cognitive abilities. Evidence of extra-cranial carotid stenosis >50%, if symptomatic (history of stroke/transient ischemic attack (TIA) in the past 6 months) or >70% if asymptomatic, using the NASCET methodology. (5) Treatment could include: best medical treatment (BMT) alone or associated to either CAS or CEA (under both general and local anaesthesia). Patients with either no complications or minor/major complications could be included, provided they understand and are able to answer the questions.

The following exclusion criteria were defined: (1) CEA/CAS performed for recurrent carotid artery stenosis or for (2) Carotid artery dissection or radiation angiopathy; (3) Dementia or other pathologies conditioning loss of cognitive function limiting the ability to understand and answer the questions.

A written informed consent was provided to the patients notifying participation was voluntary, anonymous and that they could withdraw consent at any time, as defined by the Declaration of Helsinki. (6) "One-on-one" telephone interviews were performed to collect each patient expert´s perspective anonymously and to permit them to rank each

item in the Likert scale as independently as possible. In the second and third round, patient experts were provided with an overview of the results as well as their own answers in the previous rounds before there were asked to re-rate the items. (Figure 1)

Medical Expert Selection:

Medical experts were also included, both vascular surgeons and neurologists. The international expert panel invited to participate included vascular surgery experts from the European Union of Medical Specialists (UEMS) Council Board of Vascular Surgery, the European Society of Vascular Surgery Council and the International Angiology Editorial Board. An extended invitation was addressed to each Vascular Surgery expert´s multidisciplinary team senior neurologist(s). Medical experts were invited to participate by email, and all communication was generated by email. Surveys were performed using an online survey service, Google Forms. All correspondence was anonymous. After the email with background information, experts received an invitation to participate and complete the first round of this Delphi study within four weeks. After two weeks a kind reminder to complete the survey was sent by email. One week thereafter, one final reminder was sent. To provide feedback after each round, experts received an overview of the overall results as well as their own answers in the previous round and were asked to complete the subsequent round.

Delphi Phases

In the first phase of Delphi, “Item Generation”, a literature search was performed on the existing qualitative research on patient´s perspective on carotid artery stenosis and carotid artery revascularization, namely from pre-existing quality of life questionnaires used in clinical trials. (7-9) Based on the existing data, several items (n=18) were organized in four domains: generic, quality-of-life related, symptom-related and treatment-related. Regarding each item, the experts were asked to classify it regarding relevance using a 5-point Likert Scale (1: Strongly agree; 2: Agree; 3: Neutral; 4: Disagree; 5: Strongly disagree). Opposite to other Delphi studies, a neutral opinion from the experts was allowed given the specificities of the expert panel (by including patients as experts). In the first round “Item Generation”, a free text response was available within each domain enquiring experts about additional items they considered relevant as well as

other comments and suggestions. Free text responses were taken into account by the research team and were included in the subsequent round.

Based on the first round, the preliminary questionnaire was updated and each item was either excluded or maintained on the following rounds, based on predefined levels of consensus. In the second and third rounds, experts were provided with their previous answers as well as the general group results in a controlled feedback process and were asked to re-assess each item. Items were either excluded, included or no consensus was achieved.

Definition of consensus:

Fleiss' kappa (k) is a statistical measure of inter-rater reliability and k>0.80 is defined as almost perfect agreement. Using a 5-item Likert Scale in a qualitative research, obtaining perfect agreement is virtually impossible. Therefore, we defined the following criteria for consensus: range of >70% of experts rating an item as 1-2 (totally agree/agree). (10, 11) This level of agreement was considered appropriate in previous Delphi studies and is aligned with the recommended quality indicators for a Delphi study. (11-13)

Stability of answers in the distribution of responses was also considered. (11) In the first round (Item Generation) no question was definitely included even if they reached pre-defined level of consensus. Criteria for dropping items at each round: if rated 4-5 (Likert Scale) by >30% of the expert group or if rated 1-2 (Likert Scale) by <50% of the expert group. The remaining items (not included/not dropped) were included in the following round(s) for further assessment.

Criteria for ending the Delphi Study

Delphi studies could be considered complete when pre-defined consensus is achieved or after a pre-defined number of rounds. Given the number of items posed to the experts, it would be unlikely to reach consensus in all items. Therefore, we pre-defined a total of three rounds. (14)

Data analysis

All comments were read and summarized by the first author (AC). Afterwards, this summary was reviewed by the coordinating research team (GJB and AM) to confirm its accuracy and subsequently used in the next rounds of questions.

Statistical analysis was performed with the use of SPSS®, version 27.0. Categorical variables were presented as frequencies and percentages. All reported p values were two-tailed, with a p value of 0.05 indicating statistical significance.

Statistical analysis was performed to determine the impact of several characteristics on the Likert categorization using the Kruskal-Wallis test for categorical (ordinal) variables. Fleiss´ kappa was calculated to determine overall consensus. Discriminative analysis of agreement between patient and medical experts as well as between symptomatic and asymptomatic medical experts was attained in order to analyse significant difference in perspectives between these groups.

Results

Demographic/Sample Characteristics

An international panel of 80 medical experts were invited to participate (69 vascular surgeons and 11 neurologists) and 43 accepted to participate (33 vascular surgeons and 10 neurologists). The included medical experts presented different nationalities (from 15 different countries) with the consequent heterogeneous backgrounds. (Online Supplement – Table 1) Thereafter, a random selection of 40 patients was invited to participate and a total of 29 patients accepted (12 (41.4%) patients were symptomatic and 17 (58.6%) were asymptomatic). All patients were submitted to CEA and inclusion in this study occurred after the CEA. The Second Round was completed by 38 medical experts and 20 patient experts, with a dropout rate of 20.8% (11.6% in the medical and 34.5% in the patient expert group). The Third Round was completed by 37 medical experts and 18 patient experts, with a dropout rate of 3.5% (2.6% in the medical and 5.3% in the patient expert group). An organogram of the methodology and included experts is present in Figure 1.

The first Delphi round was sent out in June 2020 and the last Delphi round was completed in December 2021.

First Delphi Round

Table 1 resumes the results of First Round. Two general comments were consistent amongst experts and were uptaken in the second round: Classifications of -3 to +3 or 1 to 10 in the questionnaires included too many possible classifications and -2 to +2 or 1 to 5, respectively, were considered better suited. Two questions were initially posed to regarding Generic Domain and both were maintained with a majority (>50%) of experts agreeing/totally agreeing with both items. (Table 1) Three additional items were suggested by the experts (Table 2). In the Quality of Life Domain, three initial items were maintained and the remaining four items were dropped. (Table 1) Six additional items were suggested by the experts (Table 2). In the Symptom Domain, all five initial items were maintained (Table 1) and ten additional items were suggested (Table 2). A suggestion was made to alter the third question from the symptom domain from "personal care" to "personal hygiene and getting dressed" to reduce ambiguity. Finally, in the Treatment Domain, all four initial items were maintained (Table 1) and four additional items were suggested (Table 2).

Discriminative analysis of consensus between medical experts and patient experts was attained. Disagreement between experts was analyzed resorting to the Kruskal-Wallis test and it occurred mainly in the Symptom Domain (Online supplement – Table 2): two questions (out of 7) in the Quality of Life Domain, four (out of five) in the Symptom Domain and two (out of four) in the Treatment Domain. Discriminative analysis of consensus between symptomatic and asymptomatic patient experts was performed (Online supplement – Table 3) with no significant differences between both groups with one exception in the quality of life domain.

Second Delphi Round

Table 3 resumes the results of the second round. In the Generic Domain, agreement was achieved in one item (Likert 1-2 in 77.8% of experts; Fleiss Kappa 0.61). (Table 3) Stability of answers from round 1 to 2 was <50% with up to one-third of experts skewing towards the majority. (Table 4)

In the Quality of Life Domain, agreement was achieved in five items (Likert 1-2 in 69.2-82.5% of experts; Fleiss Kappa 0.51-0.68), (Table 3) of which three were original items from round 1 with a stability of answers of 47.4-67.4% and up to one-third of experts

skewing towards the majority. (Table 4) Four items transited to the third round.

In the Symptom Domain, agreement was achieved in three items, three items were dropped and the remaining nine transited to the third round. (Table 3) Stability of answers from round 1 to 2 was 45.6-75.4% with 15.8-26.3% skewing towards the majority. (Table 4)

In the Treatment Domain, agreement was achieved in five items, two items were dropped and the remaining four passed through to the following rounds. (Table 3) Stability of answers from round 1 to 2 was 41.8-61.8% with 20.0-29.1% skewing towards the majority. (Table 4)

Discriminative analysis of consensus between medical experts and patient experts was attained and disagreement occurred again mainly in the Symptom Domain (14 out of 15 questions) but also in three questions (out of 9) from the Quality of Life Domain (Online supplement – Table 4). Discriminative analysis of consensus between symptomatic and asymptomatic patient experts was performed (Online supplement – Table 5) with no significant differences between groups with the exception of two questions in the Generic domain (concerning the impact of BMT and carotid revascularization on their quality of life) and one question in the Quality-of-Life Domain regarding the impact of carotid stenosis on usual daily activities.

Third (Last) Delphi Round

The third and last round is resumed in Table 5. Agreement was reached for all four questions in the generic domain, one in the quality of life domain, three in the symptom domain and one in the treatment-related domain. The remaining items were either dropped or no agreement was achieved. (Table 5) Stability of answers from round 2 to 3 ranged from 41.5-64.2%, 60.4-73.6%, 32.1-83% and 47.2-64.2% in the Generic, Quality of Life, Symptom and Treatment Domains, respectively, with globally 11.4-35.8% skewing towards the majority. (Table 4)

Discriminative analysis of consensus between medical experts and patient experts was attained and disagreement occurred in three (out of four) questions in the Generic Domain, three (out of four) questions in the Quality of Life Domain, seven (out of 10) questions in the Symptom Domain and four (out of five) questions in the Treatment Domain (Online supplement – Table 6). Discriminative analysis of consensus between

symptomatic and asymptomatic patient experts was performed (Online supplement – Table 7) with no significant differences between both groups with the exception of one questions in the Generic domain and one question in the Quality-of-Life Domain regarding the impact of carotid stenosis on usual daily activities.

Final Questionnaire

Agreement was definitely reached for a total of five items in the Generic domain, six in the quality-of-life domain, six in the symptoms domain and six in the treatment-related domain. Table 6 resumes the final questionnaire with the items for which agreement between experts was reached.

No agreement was reached for three in the quality of life domain, six in the symptoms domain and four in the treatment-related domain. A total of 13 questions were definitely excluded by the experts (four in the quality of life domain, six in the symptoms domain and three in the treatment-related domain). (Tables 1,3 and 4)

Discussion

Assessment of overall health and HRQOL can contribute to the development of better and more efficient standards in the care and management of stroke and carotid artery disease. Overall health and HRQOL assessment can provide valuable data on quality of care, especially as comparison between different treatment approaches to carotid artery disease (BMT/CEA/CAS) becomes increasingly challenging based solely on the hard clinical outcomes which are becoming ever more rare. (3, 15)

PROMs are taking a progressively more central position in the assessment of medical conditions. Accordingly, the United Kingdom National Institute for Health and Clinical Excellence (NICE) guidelines support their application in different settings of technologic appraisal. (16)

PROMs should be assessed at the onset of the disease, after treatment and periodically in the long-term and they should be able to detect intra-individual changes. (17) PROMs must also determine which health outcomes are the most relevant for patients in a comprehensible and understandable manner.

Multiple studies have assessed HRQOL after CEA using different instruments, with varying results. Several single-center studies have reported no decrement in self-reported

HRQOL at 6 months after CEA (18-20) and results were sustained at 8 to 11 years (21). Other uncontrolled studies have reported significant improvement in HRQOL after CEA (22), but at least one study described significant worsening of health status after CEA (23).

Using the generic PROM Short-Form 36 (SF-36), patients with symptomatic carotid disease reported significantly lower scores in physical, social, emotional, and mental functioning as compared to the general population. Progression of the disease reduced physical functioning but did not affect other domains of HRQOL. (9) SF-36 was found more suitable for evaluating HRQOL in patients in the chronic phase after a stroke than in the acute stage. (24)

Comparative HRQOL after CEA versus CAS has been reported in several studies, most notably in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) and Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPHIRE) trials. (8, 25) In these two trials, SF-36 was applied and in addition to the generic PROM, six disease-specific modified Likert scales designed specifically for comparison of CAS versus CEA were used. The first three questions assessed the level of difficulty each patient experienced with walking, eating/swallowing, and driving. The next three questions evaluated how often patients were bothered by headaches, neck pain, and leg pain during the previous week. Two additional questions were introduced in CREST (but not in SAPHIRE) to rate their level of pain (0–10 scale) and to estimate the number of times pain medications were needed over the past week. (8, 25) These disease-specific PROMs evaluated a limited dimension of quality-of-life (functional status and pain) and their development, validity and responsiveness were unclear. These trials included both symptomatic and asymptomatic patients but the assessed items were arguably more oriented for the evaluation of revascularization in symptomatic patients. (24)

Literature data suggest less impairment during the early recovery period after CAS as compared with CEA, but these differences are time-limited and restricted to highly sensitive, disease-specific outcomes and physical role limitations. (7, 8)

In CREST, patients undergoing CAS had better health-related quality-of-life during the first month after revascularization compared to patients undergoing CEA. These benefits were most pronounced for measures of overall physical function and pain. In addition,

disease-specific measures demonstrated that limitations related to ambulation and leg discomfort were more common after CAS, whereas limitations related to eating and neck discomfort were more common after CEA. All of these differences between CAS and CEA were modest in magnitude and were no longer present at one-year follow-up. (7)

In SAPPHIRE, patients reported fewer symptoms and less impairment of physical function at the two-week visit when undergoing CAS versus CEA, but these differences were no longer apparent at one-month follow-up. (8)

On the other hand, exploratory analyses of the impact of periprocedural events on health status revealed a strong and consistent impairment of HRQOL at one-year among those patients who experienced a periprocedural stroke when compared with those who did not. Surprisingly, health status at one-year was influenced by the occurrence of periprocedural stroke, but not by either MI or cranial nerve palsy. (7)

Nowadays there are several unanswered questions in carotid artery revascularization. Does CEA/CAS improve overall health and HRQOL in asymptomatic patients? Does overall health and HRQOL depend on the surgical technique (CEA versus CAS) in both symptomatic and asymptomatic patients? Are there predictors of overall health and HRQOL in stroke patients treated with CEA/CAS? We believe the developed questionnaire portrays the most important and relevant questions on overall health and HRQOL for patients with carotid artery disease. It includes a total of 23 questions with an answer in a 5 or 6 points scale, involving four domains.

Interestingly, comparing the items that reached consensus in our study, with the disease-specific questionnaires used in CREST and SAPHIRE, the only constant item is “difficulty in walking”. In the latter two questionnaires, a lot of emphasis is given to pain (“headache”, “neck pain”, “leg pain”, “pain” and “pain medication”) while in this study “pain” was not suggested by any expert and was not included in the final questionnaire. Regarding the Symptom Domain, consensus was reached on items related to specific functions (walking, speaking and hand function) as well as independency, mental performance and ability to perform daily activities. (Table 6)

Comparing our final questionnaire with the most used generic PROM (SF-36), the constant items were “walking” and “ability to perform daily activities” (specified in SF-36 as “bathing/dressing” and “lifting/carrying groceries”). (Table 6) The final questionnaire that reached expert consensus included additional dimensions apart from the “Symptom

Domain", which is the only domain explored by the other cited questionnaires. In the Generic Domain, emphasis is given to the impact of the diagnosis, treatment and follow-up. In the Quality-of-Life domain emphasis is given to "fear/concern about the future" and "fear/concern about severe stroke". In the "Treatment Domain" emphasis is on the side-effects of treatment and long-term satisfaction of treatment but also on the information provided regarding treatment options. (Table 6) The consensus reached in this questionnaire reveals experts value dimensions of the impact of the disease and of the treatment that were previously unexplored.

There are several limitations to this manuscript. First, it portrays a list of items that seem relevant but still require external validation for specific populations. Patient inclusion was unicentric portraying a specific population and the clinical practice of a single Vascular Surgery Department and as a consequence no included patient expert was submitted to CAS which may limit validity in this subset of patients. Also and unfortunately, due to differential dropout between groups in the Delphi rounds, the final number of experts was very different in the final round (18 patient experts and 37 medical experts), which inevitably means medical experts opinion had the most weight on the final decision to include/drop items.

Discriminative analysis of agreement between patient and medical experts revealed significant differences between their opinions. A plausible explanation is the difficulty of asymptomatic and/or symptomatic patients in evaluating a symptom/complication they did not experience. Indeed, a careful analysis of their answers reveals patient experts were more likely to classify an item as neutral (Likert 3), while medical experts were more assertive in agreeing/disagreeing. A paradigmatic example was the item in the symptomatic domain in round two analysing the importance of the difficulty in eating/swallowing: one patient strongly agreed with the item while the remaining classified the item as Likert 3. We can hypothesize that a single patient experienced that symptom and therefore strongly agreed with its importance while the remaining did not have an opinion. (Table 4 – Online Supplement) This does not mean their input is less valuable than medical experts. Indeed, they contributed very significantly to the Item Generation stage, stating their perceptions very clearly.

The discriminative analysis between symptomatic and asymptomatic patient experts surprisingly revealed residual difference between them on all rounds. (Table 3, 5 and 7 –

Online Supplement) This may be due to the low number of patients on both groups. Also, the inclusion of symptomatic patients with minor symptoms and of asymptomatic patients with history of stroke more than 6 months ago could have softened the differences between these two very dissimilar groups. It is noteworthy the small number of individuals in each group limited definite conclusions from discriminative analysis.

Pilot testing and external validation of the questionnaire for different groups are warranted as the prospective next course of action. Afterwards, inclusion of the validated PROM at pre-defined timings (including baseline) in RCTs on carotid revascularization could introduce valuable and clinically relevant data regarding differences in overall health and HRQOL between different approaches. In a clinical setting, obtaining these PROM data could facilitate treatment selection. It could also facilitate informing patients regarding the risks and benefits of alternative approaches to carotid revascularization and lead to a more patient-centered decision making.

In conclusion, the consensus reached provides insight into patient and clinical expert opinion regarding the most important items to include in a disease-specific PROM for patients with atherosclerotic carotid artery stenosis. Routine application of a PROM in either clinical practice or in clinical trials could help answer the main questions in carotid artery revascularization nowadays: Which asymptomatic patients benefit from intervention? How should we intervene (CEA/CAS) in both asymptomatic and symptomatic patients.

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Disclosures

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Ethical Requirements

- **Patients´ informed consent** was obtained and willing patients signed a Consent Form designed according to the Declaration of Helsinki.
- **Individual self-determination** and **autonomy** was safeguarded. Patients were informed that they could withdraw their consent at any time.
- **Data confidentiality** was guaranteed by coding each expert questionnaire with a serial number, only knowledgeable to the Principal Investigator. No expert personal data or any other data that could allow expert identification will be published.
- **Indemnification for damages** – N/A
- **Continuation of treatment** – N/A

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Table 1

Question	Likert (1-5)					Rated 1-2 (%)	Rated 4-5 (%)	Fleiss Kappa	Decision
	1	2	3	4	5				
Generic Domain									
If I did not have carotid stenosis my life would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable)	25 (34.7)	22 (30.6)	16 (22.2)	3 (4.2)	6 (8.3)	65.3	12.5	0.58	**Maintain**
If I had not been submitted to carotid artery revascularization my life would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable)	25 (41.0)	17 (27.9)	10 (16.4)	3 (4.9)	6 (9.8)	58.3	12.5	0.42	**Maintain**
Quality of Life Domain									
In general I would classify my quality of life as (Classify from 1-10, being 1 the worst you can imagine and 10 the best you can imagine)	41 (56.9)	15 (20.8)	6 (8.3)	6 (8.3)	4 (5.6)	77.7	13.9	0.77	**Maintain**
If I did not have carotid stenosis my fear/concern about the future would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	30 (41.7)	20 (27.8)	12 (16.7)	5 (6.9)	5 (6.9)	69.5	11.2	0.66	**Maintain**
If I had not been submitted to carotid artery revascularization my fear/concern about the future would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	24 (39.3)	16 (26.2)	12 (19.7)	7 (11.5)	2 (3.3)	55.5	12.5	0.45	**Maintain**
If I did not have carotid stenosis my family life would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	14 (19.4)	20 (27.8)	32 (44.4)	0 (0)	6 (8.3)	47.2	8.3	0.49	**Drop**
If I had not been submitted to carotid artery revascularization my family life would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	10 (16.1)	20 (32.3)	24 (38.7)	4 (6.5)	4 (6.5)	41.7	11.2	0.35	**Drop**
If I did not have carotid stenosis my ability to perform physical activities would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	18 (25.4)	17 (23.9)	29 (40.8)	2 (2.8)	5 (7.0)	48.6	9.7	0.49	**Drop**
If I had not been submitted to carotid artery revascularization my ability to perform physical activities would be (Classify from -3 to +3: -3 a lot worse; -2 worse; -1 a little worse; 0 the same; 1 a little better; 2 better; 3 a lot better; alternatively, you can answer not applicable):	11 (17.7)	20 (32.3)	23 (37.1)	4 (6.5)	4 (6.5)	43.1	11.2	0.37	**Drop**
Symptom Domain									
Classify your degree of difficulty walking (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	37 (51.4)	17 (23.6)	10 (13.9)	2 (2.8)	6 (8.3)	75.0	11.1	0.75	**Maintain**
Classify your degree of difficulty eating/swallowing (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	32 (44.4)	10 (13.9)	23 (31.9)	0 (0)	7 (9.7)	58.3	9.7	0.58	**Maintain**
Classify your degree of difficulty in Personal Care (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	39 (54.2)	8 (11.1)	20 (27.8)	1 (1.4)	4 (5.6)	65.3	7.0	0.66	**Maintain**
Classify your degree of difficulty in your Daily Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	35 (48.6)	12 (16.7)	2 (2.8)	10 (13.9)	5 (6.9)	65.3	9.7	0.65	**Maintain**
Classify your degree of difficulty in your Work Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	35 (48.6)	13 (18.1)	10 (13.9)	10 (13.9)	4 (5.6)	66.7	19.5	0.66	**Maintain**
Treatment Domain									

How bothered are you by the side effects of the treatment for your illness? (Classify from 1-10, being 1 the worst you can imagine and 10 the best you can imagine)	32 (44.4)	22 (30.6)	10 (13.9)	2 (2.8)	4 (5.5)	75.0	8.4	0.74	**Maintain**
How bothersome do/did you find the treatment for your illness? (Classify from 1-10, being 1 the worst you can imagine and 10 the best you can imagine)	35 (48.6)	13 (18.1)	16 (22.2)	3 (4.2)	3 (4.2)	66.7	8.4	0.64	**Maintain**
How satisfied are you with the impact of your personal opinion in the treatment choice? (Classify from 1-10, being 1 the worst you can imagine and 10 the best you can imagine)	23 (31.9)	17 (23.6)	21 (29.2)	4 (5.6)	5 (6.9)	55.5	12.5	0.50	**Maintain**
How satisfied are you with the information that was given to you regarding your treatment options? (Classify from 1-10, being 1 the worst you can imagine and 10 the best you can imagine)	38 (52.8)	6 (8.3)	19 (26.4)	2 (2.8)	5 (6.9)	61.1	9.7	0.59	**Maintain**

Table 2

Generic Domain
▪ If I had not been submitted to carotid Doppler Ultrasound screening my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable) ▪ If I had not been started on best medical therapy after the diagnosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable) ▪ If I did not have to keep a periodic follow-up of my carotid revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
Quality of Life Domain
▪ I fear my carotid stenosis will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable) ▪ I fear my carotid surgery will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable) ▪ My life is now better than before the carotid operation (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable) ▪ Carotid stenosis has changed my usual daily activities (social, working, physical activities) (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable) ▪ If I did not have carotid stenosis my fear/concern about the severe stroke would be (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable) ▪ If I had not been submitted to carotid surgery my fear/concern about the severe stroke would be (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable)
Symptom Domain
▪ Classify your degree of of difficulty in speaking (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your voice after carotid revascularization (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify your degree of of difficulty in hand function (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify your degree of difficulty in social interactions (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your independency (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your mental performance/memory (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your perception of your anxiety (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your feeling of sadness(from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your feeling of apathy (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A) ▪ Classify the degree of impact in your quality of sleep (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)
Treatment Domain
▪ How satisfied are you with the impact of treatment of your QoL? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine) ▪ How satisfied are you with the impact of treatment of your social life? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine) ▪ How satisfied are you with the financial impact of treatment (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)

- Would you recommend carotid revascularization as a good treatment option (Classify from 1-5, being 1 I would not recommend and 5 would strongly recommend)

How would you classify the impact of treatment on fear/anxiety (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How satisfied are you with the information that was given to you regarding the possible treatment complications? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How bothersome do/did you find the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How satisfied are you with the long-term quality of life results of treatment? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)

Table 3

Question	Likert (1-5) n(%)			Fleiss Kappa	Agreement
	1-2	3	4-5		
Generic Domain					
If I had not been started on best medical therapy after the diagnosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	49 (77.8%)	6 (9.5%)	2 (3.2%)	0.61	**Agreement**
If I did not have carotid stenosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	40 (63.5%)	14 (22.2%)	3 (4.8%)	0.45	No Agreement
If I had not been submitted to carotid artery revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	42 (66.7%)	11 (17.5%)	4 (6.3%)	0.47	No Agreement
If I had not been submitted to carotid Doppler Ultrasound screening my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	39 (61.9%)	14 (22.2%)	4 (6.3%)	0.43	No Agreement
If I did not have to keep a periodic follow-up of my carotid revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	37 (58.7%)	16 (25.4%)	4 6.3%)	0.40	No Agreement
Quality of Life Domain					
In general, I would classify my quality of life as (Classify from 1-5, being 5 the best you can imagine and 1 the worst you can imagine)	52 (82.5%)	2 (3.1%)	3 (4.8%)	0.68	**Agreement**
If I had not been submitted to carotid artery revascularization my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	47 (74.6%)	9 (14.3%)	1 (1.6%)	0.57	**Agreement**
My life is now better than before the carotid operation (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	44 (69.8%)	10 (15.9%)	3 (4.8%)	0.51	**Agreement**
If I did not have carotid stenosis my fear/concern about the severe stroke would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	45 (71.4%)	9 (14.3%)	3 (4.8%)	0.52	**Agreement**
If I had not been submitted to carotid surgery my fear/concern about the severe stroke would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	46 (73.0%)	9 (14.3%)	2 (3.2%)	0.55	**Agreement**
If I did not have carotid stenosis my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	42 (66.7%)	12 (19.1%)	3 (4.8%)	0.47	No Agreement
I fear my carotid stenosis will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	36 (57.1%)	19 (30.2%)	2 (3.2%)	0.41	No Agreement
I fear my carotid surgery will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	33 (52.4%)	20 (31.7%)	4 (6.3%)	0.37	No Agreement

Carotid stenosis has changed my usual daily activities (social, working, physical activities) (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	40 (63.5%)	14 (22.2%)	3 (4.8%)	0.45	No Agreement
Symptom-related Domain					
Classify your degree of difficulty walking (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	47 (74.6%)	8 (12.7%)	2 (3.2%)	0.57	**Agreement**
Classify the degree of impact in your independency (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	46 (73.0%)	10 (15.9%)	1 (1.6%)	0.67	**Agreement**
Classify the degree of impact in your mental performance/memory (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	44 (77%)	12 (19.2%)	2 (3.5%)	0.62	**Agreement**
Classify your degree of difficulty eating/swallowing (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	33 (52.4%)	8 (12.7%)	2 (3.2%)	0.28	No agreement
Classify your degree of difficulty in personal hygiene and getting dressed (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	39 (61.9%)	18 (28.6%)	0 (0%)	0.46	No agreement
Classify your degree of difficulty in your Daily Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	42 (66.7%)	15 (23.8%)	0 (0%)	0.49	No agreement
Classify your degree of difficulty in your Work Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	40 (63.5%)	9 (14.3%)	8 (12.7%)	0.43	No agreement
Classify your degree of difficulty in speaking (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer not applicable)	42 (66.7%)	14 (22.2%)	1 (1.6%)	0.49	No agreement
Classify the degree of impact in your voice after carotid revascularization (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	37 (58.7%)	19 (30.2%)	1 (1.6%)	0.43	No agreement
Classify your degree of difficulty in hand function (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	40 (63.5%)	16 (25.4%)	1 (1.6%)	0.46	No agreement
Classify your degree of difficulty in social interactions (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	33 (52.4%)	23 (36.5%)	1 (1.6%	0.39	No agreement
Classify the degree of impact in your feeling of sadness (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	32 (50.8%)	21 (33.3%)	4 (6.3%)	0.36	No agreement
Classify the degree of impact in your perception of your anxiety (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	30 (47.6%)	25 (39.7%)	2 (3.2%)	0.37	**Drop**
Classify the degree of impact in your feeling of apathy (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	26 (41.3%)	25 (39.7%)	6 (9.5%)	0.33	**Drop**
Classify the degree of impact in your quality of sleep (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	30 (47.6%)	25 (39.7%)	2 (3.2%)	0.38	**Drop**
Treatment- related Domain					
How bothered are you by the side effects of the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	47 (74.6%)	7 (11.1%)	3 (4.8%)	0.56	**Agreement**
How bothersome do/did you find the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	44 (69.8%)	10 (15.9%)	3 (4.8%)	0.51	**Agreement**
How satisfied are you with the impact of treatment of your QoL? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	44 (69.8%)	10 (15.9%)	3 (4.8%)	0.51	**Agreement**
How satisfied are you with the information that was given to you regarding the possible treatment complications? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	48 (76.2%)	7 (11.1%)	2 (3.2%)	0.59	**Agreement**
	44 (69.8%)	9 (14.3%)	4 (6.3%)	0.50	**Agreement**
How satisfied are you with the long-term quality of life results of treatment? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	48 (76.2%)	7 (11.1%)	2 (3.2%)	0.59	**Agreement**
How satisfied are you with the impact of your personal opinion in the treatment choice? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	34 (53.9%)	19 (30.2%)	4 (6.3%)	0.38	No Agreement

How satisfied are you with the information that was given to you regarding your treatment options? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	38 (60.3%)	16 (25.3%)	3 (4.8%)	0.42	No Agreement
How satisfied are you with the impact of treatment of your social life? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	37 (58.7%)	17 (27.0%)	3 (4.8%)	0.41	No Agreement
Would you recommend carotid revascularization as a good treatment option (Classify from 1-5, being 1 I would not recommend and 5 I would strongly recommend)	42 (66.7%)	7 (11.1%)	8 (12.7%)	0.46	No Agreement
How satisfied are you with the financial impact of treatment (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	17 (27.0%)	32 (50.8%)	8 (12.7%)	0.34	**Drop**
How would you classify the impact of treatment on fear/anxiety (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	29 (46.0%)	22 (34.9%)	6 (9.5%)	0.33	**Drop**

Table 4

Question	**STABILITY Classification 1-5**		**Final Decision**
	ROUND 1-2	**ROUND 2-3**	
Generic Domain			
If I did not have carotid stenosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	Answer Stability: 28 (49.1%) Skewed towards majority: 16 (28.1%)	Answer Stability: 34 (64%) Skewed towards majority: 10 (18.9%)	**Agreement**
If I had not been submitted to carotid artery revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	Answer Stability: 16 (34.8%) Skewed towards majority: 14 (30.4%)	Answer Stability: 34 (64.2%) Skewed towards majority: 19 (35.8%)	**Agreement**
If I had not been submitted to carotid Doppler Ultrasound screening my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	NA	Answer Stability: 23 (43.4%) Skewed towards majority: 11 (20.8%)	**Agreement**
If I had not been started on best medical therapy after the diagnosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	NA	NA	**Agreement**
If I did not have to keep a periodic follow-up of my carotid revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	NA	Answer Stability: 22 (41.5%) Skewed towards majority: 19 (35.8%)	**Agreement**
Quality of Life Domain			
In general I would classify my quality of life as (Classify from 1-5, being 5 the best you can imagine and 1 the worst you can imagine)	Answer Stability: 27 (47.4%) Skewed towards majority: 11 (28.1%)	NA	**Agreement**
If I had not been submitted to carotid artery revascularization my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	Answer Stability: 31 (67.4%) Skewed towards majority: 13 (28.3%)	**NA**	**Agreement**
If I did not have carotid stenosis my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	Answer Stability: 35 (61.4%) Skewed towards majority: 18 (31.6%)	NA	No Agreement
I fear my carotid stenosis will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	NA	Answer Stability: 32 (60.4%) Skewed towards majority: 20 (37.7%)	No Agreement
I fear my carotid surgery will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	NA	Answer Stability: 39 (73.6%) Skewed towards majority: 16 (30.2%)	No Agreement
Symptom-related Domain			

Classify your degree of difficulty walking (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	Answer Stability: 36 (63.2%) Skewed towards majority: 15 (26.3%)	**NA**	**Agreement**
Classify your degree of difficulty in your Daily Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	Answer Stability: 41 (71.9%) Skewed towards majority: 12 (21.1%)	Answer Stability: 44 (83.0%) Skewed towards majority: 10 (18.9%)	**Agreement**
Classify your degree of difficulty in speaking (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer not applicable)	NA	Answer Stability: 39 (73.6%) Skewed towards majority: 10 (18.0%)	**Agreement**
Classify your degree of difficulty in hand function (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	NA	Answer Stability: 34 (64.2%) Skewed towards majority: 18 (33.9%)	**Agreement**
Classify your degree of difficulty eating/swallowing (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	Answer Stability: 27 (47.4%) Skewed towards majority: 11 (19.3%)	Answer Stability: 40 (75.5%) Skewed towards majority: 7 (13.2%)	No agreement
Classify your degree of difficulty in personal hygiene and getting dressed (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	Answer Stability: 43 (75.4%) Skewed towards majority: 9 (15.8%)	Answer Stability: 37 (69.8%) Skewed towards majority: 9 (16.9%)	No agreement
Classify your degree of difficulty in your Work Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	Answer Stability: 26 (45.6%) Skewed towards majority: 14 (24.6%)	Answer Stability: 29 (54.7%) Skewed towards majority: 13 (24.5%)	No agreement
Classify the degree of impact in your voice after carotid revascularization (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	NA	Answer Stability: 21 (39.6%) Skewed towards majority: 9 (16.9%)	No agreement
Classify your degree of difficulty in social interactions (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	NA	Answer Stability: 17 (32.1%) Skewed towards majority: 6 (11.3%)	No agreement
Classify the degree of impact in your feeling of sadness (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	NA	Answer Stability: 21 (39.6%) Skewed towards majority: 8 (15.1%)	No agreement
Treatment- related Domain			
How bothered are you by the side effects of the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	Answer Stability: 34 (61.8%) Skewed towards majority: 16 (29.1%)	**NA**	**Agreement**
How bothersome do/did you find the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	Answer Stability: 34 (61.8%) Skewed towards majority: 13 (23.6%)	**NA**	**Agreement**
Would you recommend carotid revascularization as a good treatment option (Classify from 1-5, being 1 I would not recommend and 5 I would strongly recommend)	NA	Answer Stability: 34 (64.2%) Skewed towards majority: 17 (32.1%)	**Agreement**
How satisfied are you with the impact of your personal opinion in the treatment choice? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	Answer Stability: 23 (41.8%) Skewed towards majority: 14 (25.5%)	Answer Stability: 28 (52.8%) Skewed towards majority: 13 (24.5%)	No Agreement
How satisfied are you with the information that was given to you regarding your treatment options? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	Answer Stability: 28 (50.9%) Skewed towards majority: 11 (20.0%)	Answer Stability: 26 (49.1%) Skewed towards majority: 9 (16.9%)	No Agreement
How satisfied are you with the impact of treatment of your social life? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	NA	Answer Stability: 25 (47.2%) Skewed towards majority: 13 (24.5%)	No Agreement

Table 5

Question	Likert (1-5) n(%)			Fleiss Kappa	Agreement
	1-2	3	4-5		
Generic Domain					
If I did not have carotid stenosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	43 (78.2%)	11 (20.0%)	1 (1.8%)	0.65	**Agreement**
If I had not been submitted to carotid artery revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	48 (87.3)	7 (12.7%)	1 (1.8%)	0.77	**Agreement**
If I had not been submitted to carotid Doppler Ultrasound screening my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	38 (69.1%)	10 (18.2%)	7 (12.7%)	0.52	**Agreement**
If I did not have to keep a periodic follow-up of my carotid revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	41 (74.5%)	11 (20%)	2 (3.6%)	0.59	**Agreement**
Quality of Life Domain					
If I did not have carotid stenosis my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)	44 (80%)	8 (14.5%)	3 (5.5%)	0.66	**Agreement**
I fear my carotid stenosis will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	33 (60%)	19 (34.5%)	3 (5.5%)	0.37	No Agreement
I fear my carotid surgery will affect my ability to continue my job/professional career (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	31 (56.4%)	23 (41.8%)	1 (1.8%)	0.49	No Agreement
Carotid stenosis has changed my usual daily activities (social, working, physical activities) (from 1 to 5, from 1 “strongly agree” to 5 being “strongly disagree”, alternatively you can answer not applicable)	37 (67.3%)	16 (29%)	2 (3.6%)	0.53	No Agreement
Symptom-related Domain					
Classify your degree of difficulty in your Daily Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	38 (69%)	17 (31%)	0 (0%)	0.57	**Agreement**
Classify your degree of difficulty in speaking (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer not applicable)	40 (72.7%)	14 (25.5%)	1 (1.8%)	0.59	**Agreement**
Classify your degree of difficulty in hand function (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	41 (74.5%)	13 (23.6%)	1 (1.8%)	0.60	**Agreement**
Classify your degree of difficulty in personal hygiene and getting dressed (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	32 (58.2%)	20 (36.4%)	2 (3.6%)	0.46	No agreement
Classify your degree of difficulty in your Work Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	37 (67%)	11 (20%)	7 (12.7%)	0.50	No agreement
Classify the degree of impact in your voice after carotid revascularization (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	35 (63.6%)	19 (34.5%)	1 (1.8%)	0.52	No agreement
Classify your degree of difficulty eating/swallowing (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)	25 (45.5%)	29 (52.7%)	1 (1.8%)	0.48	**Drop**
Classify your degree of difficulty in social interactions (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	26 (47.3%)	27 (49.1%)	2 (3.6%)	0.46	**Drop**
Classify the degree of impact in your feeling of sadness (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	16 (29.1%)	36 (65.6%)	3 (5.5%)	0.51	**Drop**

Classify the degree of impact in your quality of sleep (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)	18 (32.7%)	31 (56.4%)	6 (10.9%)	0.43	**Drop**
Treatment- related Domain					
Would you recommend carotid revascularization as a good treatment option (Classify from 1-5, being 1 I would not recommend and 5 I would strongly recommend)	48 (87.3%)	5 (9.1%)	3 (5.5%)	0.77	**Agreement**
How satisfied are you with the impact of your personal opinion in the treatment choice? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	29 (52.7%)	25 (45.5%)	1 (1.8%)	0.48	No Agreement
How satisfied are you with the information that was given to you regarding your treatment options? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	36 (65.5%)	17 (30.9%)	2 (3.6%)	0.52	No Agreement
How satisfied are you with the impact of treatment of your social life? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	36 (65.5%)	17 (30.9%)	2 (3.6%)	0.52	No Agreement
How would you classify the impact of treatment on fear/anxiety (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)	22 (40%)	27 (49.1%)	6 (10.9%)	0.40	**Drop**

Table 6

Question
Generic Domain
If I had not been started on best medical therapy after the diagnosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I did not have carotid stenosis my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I had not been submitted to carotid artery revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I had not been submitted to carotid Doppler Ultrasound screening my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I did not have to keep a periodic follow-up of my carotid revascularization my life would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
Quality of Life Domain
In general I would classify my quality of life as (Classify from 1-5, being 5 the best you can imagine and 1 the worst you can imagine)
If I had not been submitted to carotid artery revascularization my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
My life is now better than before the carotid operation (from 1 to 5, from 1 “strongly disagree” to 5 being “strongly agree”, alternatively you can answer not applicable)
If I did not have carotid stenosis my fear/concern about the severe stroke would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I had not been submitted to carotid surgery my fear/concern about the severe stroke would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
If I did not have carotid stenosis my fear/concern about the future would be (Classify from -2 to +2: -2 a lot worse; -1 worse; 0 the same; 1 better; 2 a lot better; alternatively, you can answer not applicable)
Symptom-related Domain
Classify your degree of difficulty walking (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)
Classify the degree of impact in your independency (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)
Classify the degree of impact in your mental performance/memory (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)
Classify your degree of difficulty in your Daily Activities (from 1 to 5 with 1 being the worst degree of difficulty; alternatively, you can answer not applicable)
Classify your degree of difficulty in speaking (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer not applicable)
Classify your degree of difficulty in hand function (from 1 to 5, with 1 being the worst degree of difficulty, alternatively you can answer N/A)
Treatment-related Domain
How bothered are you by the side effects of the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)

How bothersome do/did you find the treatment for your illness? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How satisfied are you with the impact of treatment of your QoL? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How satisfied are you with the information that was given to you regarding the possible treatment complications? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
How satisfied are you with the long-term quality of life results of treatment? (Classify from 1-5, being 1 the worst you can imagine and 5 the best you can imagine)
Would you recommend carotid revascularization as a good treatment option (Classify from 1-5, being 1 I would not recommend and 5 I would strongly recommend)

Legends

Figure 1. Organogram of Delphi Methodology

Table 1. Resume of expert´s answers and level of agreement in the First Delphi Round

Table 2. Additional items suggested by the experts in the First Delphi Round

Table 3. Resume of expert´s answers and level of agreement in the Second Delphi Round

Table 4. Stability of expert´s answers throughout the Delphi Rounds

Table 5. Resume of expert´s answers and level of agreement in the Third Delphi Round

Table 6. Final PROM developed according to expert consensus

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DISCUSSION

DISCUSSION

PART I – Carotid Intervention in the Acute Phase

In the last decade, treatment for acute stroke has been revolutionized with the introduction of intracranial thrombectomy (IT) which established itself as the new standard of care in treating large-vessel anterior circulation ischemic stroke, with five large volume randomized controlled trials (RCT) demonstrating its superiority over isolated intravenous thrombolysis (IVT). (12-16) Patients with tandem lesions of the carotid bifurcation and intracranial circulation are particularly challenging. The proximal lesion hampers distal access and controversy about simultaneous emergency CAS ensues. Therefore, expanding our knowledge in this particular field is of paramount importance. In **Chapter 1** the authors explored the dichotomy between IT with and without simultaneous CAS. In the meta-analysis there was no clinical benefit from emergency CAS, with significantly increased time to intracranial recanalization and exposure to potential hazardous consequences from symptomatic intracranial haemorrhage (sICH) and acute carotid stent thrombosis (ACST). However, included studies were low quality and observational. Therefore, the timing and relative role of endovascular versus surgical revascularization of the extracranial carotid artery in this setting remained to be determined.

The results from two recent registries have been published, comparing IT with or without synchronous CAS (17, 18). In both publications, emergent CAS during neurothrombectomy was achieved with similar risk of sICH and procedural mortality compared to no stenting. Clinical outcomes attained by the modified Rankin scale (mRs) were superior in the synchronous CAS group. However, selection bias was raised as an issue with both publications and controversy still stands.

In **Chapter 2**, the authors focused on the optimal timing for carotid intervention (CEA/CAS). The outcomes procedural stroke, death and MI were compared in patients submitted to CEA or CAS within two versus 3-14 days of the index event and within seven versus 8-14 days of the index event. Also, outcomes after CEA versus CAS were compared within each time frame. This systematic review and meta-analysis presented the

following conclusions: (1) description of timing of intervention delay regarding the index event was not universal; (2) CEA was safer than CAS when performed within two or seven days of the index event; (3) considering absolute rates of 30-day stroke, mortality, and death/stroke, CEA performed within two days of the index event complied with the accepted thresholds in international guidelines and (4) the ideal timing for performing CAS (when indicated against CEA) was not yet defined.

The underlying matter in intervention timing is the dichotomy between the risk of recurrent events versus the risk of procedural events. Recurrency has been estimated to reach 26% in the first 14 days after the index event (19) and a national audit has shown a reduction in recurrences from 25% to 18% with the decrease in the median waiting time for CEA from 13 to 7 days. (20) However, a multicentric retrospective analysis of prospective data published in 2021 has showcased a significant reduction in the rates of recurrent stroke (<4% in a median follow up of 11 days) (21) which was mainly attributed to BMT optimization. The publication concluded that the time frame of 14 days was adequate and that very early intervention (<2 days) was unnecessary. Selection bias by only including patients considered fit for surgery and possible underreporting of events were discussed issues with the publication. Therefore, additional studies are necessary to ascertain the real incidence of recurrent events under state of the art BMT. Also, description of timing of intervention after the index event should become standard in RCT and other large volume studies.

PART II – Carotid Artery Revascularization: CEA versus CAS

The duality between CEA and CAS is a never ending subject of controversy and research. On one hand, procedural stroke is the main major complication of carotid revascularization and clinical research has focused on (1) reducing its incidence and (2) comparing it after CEA versus CAS. With time, this complication has become increasingly rare with a consequent reduction in the accepted threshold from 3% procedural stroke to 2% in-hospital stroke in asymptomatic patients and from 6% procedural stroke to 4% in-hospital stroke in symptomatic patients in the European Stroke Organization (ESO) guidelines. (22) Comparing the risk of procedural stroke after CEA/CAS, the risk was still

higher after CAS for both disabling and non-disabling stroke. In order to further reduce the risk of procedural stroke, understanding the mechanisms of procedural events is, therefore, crucial.

On the other hand, several secondary and potential surrogate outcomes have been considered for balancing the benefit of intervention which is classically analysed using procedural (30-day) stroke, death and myocardial infarction (MI) as primary outcomes. The possible contribution of diffusion weighted-magnetic resonance imaging (DW-MRI) lesions after CEA/CAS for recurrent stroke or cognitive decline has been studied and is currently a matter of debate. (3) Patient Reported Outcome Measures (PROM) have also been studied as a way to study the impact of carotid artery stenosis on overall health and health-related quality of life (HRQOL).

Understanding the mechanisms of procedural events and the subsequent technical developments

In **Part II** the authors focused on the physiopathologic mechanisms and on technical developments of two procedural events: procedural stroke and acute carotid stent thrombosis (ACST).

Despite a considerable body of evidence concerning the occurrence of procedural stroke after CEA and CAS in the literature, comprehensive analysis of its mechanism are surprisingly scarce. Understanding the mechanisms of procedural stroke could: (1) assist in balancing the choice for revascularization versus conservative therapy; (2) assist in choosing either open or endo techniques; and (3) assist in taking appropriate periprocedural measures to further reduce procedural stroke rate. In **Chapter 3** the authors focused on analysing the main mechanisms of procedural stroke and in the development of procedural stroke reporting standards to facilitate future clinical investigation. The basic mechanisms underlying procedural stroke are heterogeneous but can be broadly classified in four categories: (1) embolic (either cardioembolic or athero-embolic), (2) internal carotid artery (ICA) occlusion, (3) hemodynamic (hypo or hyperperfusion) and (4) haemorrhagic. Recent technical advances in CAS have focused on reducing the risk for procedural stroke, mainly by reducing the risk for athero-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. Also, the development of transcarotid artery revascularization (TCAR) is a perfect example of how the understanding of the physiopathological mechanism of stroke after TFCAS has led to further refinement of the stenting technique, hereby avoiding aortic arch manipulation during carotid access and reducing the risk of embolism related to target lesion traversal. These two technical developments are thoroughly analysed in Chapters 4 and 5.

In Chapter 4, a systematic review on the safety and efficacy of TCAR was performed. There are several theoretical advantages of TCAR: (1) it is designed to avoid aortic arch manipulation and concomitant athero-embolic procedural stroke; (2) the neurocerebral protection system is already in place when ICA lesion traversal is started, diminishing the risk of carotid-embolic events; (3) minimal carotid approach reduces the risk of cranial nerve injury (versus CEA). Although evidence is promising, we currently lack high quality data. Also, analysis of data stratified by delay from index neurologic event is unavailable which hinders analysis of safety in recently symptomatic patients.

In Chapter 5, we focussed on the safety and effectiveness of Dual-Layer Stents (DLS). Again, a theorical advantage is advocated by reducing the risk of atheroembolism after plaque protrusion through the stent struts. Similarly to TCAR, high quality data are scarce and RCT´s comparing DLS to conventional stents are warranted. Also, safety issues regarding DLS in the emergency setting have been raised, particularly for thrombotic complications due to reduced stent flexibility.

Even though technical developments of CAS have mainly focused on reducing the risk of athero-embolic complications, procedural stroke may also occur due to ACST and this complication was analyzed in Chapter 6. ACST seemed to be an exceedingly rare complication after CAS that could nonetheless lead to catastrophic consequences. (23) The incidence of stroke attributable to ACST is currently unclear, as it could be assumed to be a direct result of stent thrombosis or an indirect result of distal embolization. Also, guidelines providing a structured approach and strategy for management after ACST are unavailable. In Chapter 6, the authors provided a detailed analysis of ACST

physiopathologic mechanisms as well as proposed a structured approach to management.

Patient Reported Outcome Measures (PROM)

Several secondary and potential surrogate outcomes have been considered for balancing the benefit of carotid intervention which is classically analysed using procedural (30-day) stroke, death and MI as primary outcomes.

The benefits of supplementing objective clinical outcome data with a well-developed, valid, consistent, reliable and responsive disease-specific PROM could help provide more targeted data on HRQOL, treatment efficacy, procedural *minor*/*major* complications and treatment satisfaction. In Chapter 7, the authors resorted to the Delphi methodology, including both patient and medical experts in carotid artery disease, to identify the most relevant items in four pre-defined domains: generic, quality-of-life, symptom and treatment-related.

The result was a questionnaire comprising dimensions previously unexplored in generic and disease-specific PROMs and providing a fresh insight into patient and clinical expert opinion. Comparing the items that reached consensus in our study, with the disease-specific and generic PROMs previously used in carotid artery disease investigation, the only constant items were: “difficulty with walking” and “ability to perform daily activities”, respectively. In the symptom domain of this PROM, consensus was reached on items related to both specific functions (walking, speaking and hand function) as well as independency, mental performance and ability to perform daily activities.

In the remaining three domains, emphasis was given to the impact of the diagnosis, treatment and follow-up on patient´s life, to fear/concern "about the future and “about severe stroke” as well as to side-effects, long-term patient satisfaction and to the quality of information provided regarding treatment options.

Pilot testing and external validation of the questionnaire are definitely warranted. Afterwards, the authors believe the inclusion of the validated PROM at pre-defined

timings (including baseline) in RCTs on carotid revascularization could introduce valuable and clinically relevant data and lead to a more patient-centered decision making.

Future Perspectives

As extensively discussed in this chapter, several unresolved issues in managing carotid artery disease still ensue. There is hope that ongoing RCT´s can help in answering these questions.

Regarding emergent CAS in tandem lesion, the Thrombectomy In TANdem Occlusion (TITAN) RCT (NCT 03978988) is currently recruiting, aiming to compare thrombectomy alone with thrombectomy associated to emergent CAS in patients with tandem lesions. Primary outcomes include modified treatment in cerebral ischemia (mTICI) and National Institutes of Health Stroke Scales (NIHSS) scores at 24 hours and the RCT is estimated to be completed in 2024.

With BMT improvement, recent RCTs have focused on comparing BMT alone with BMT associated to carotid revascularization (CEA/CAS) in either asymptomatic and symptomatic patients.

Stent Protected Angioplasty versus Carotid Endarterectomy-2 (SPACE-2) randomized asymptomatic patients to a three arm study: BMT alone versus CEA plus BMT versus CAS plus BMT, but it was prematurely interrupted due to slow recruitment. Inability to convince patients and many non-trial clinicians of the merits of BMT alone and economic restrains were considered the main culprits.

As unfortunate as SPACE-2 was in evaluating how BMT complements CEA/CAS in the modern era, hope is focused on the remaining ongoing trials. The second Carotid Revascularization versus Stenting Trial (CREST-2) started randomizing asymptomatic patients to CEA plus BMT versus BMT alone and CAS plus BMT versus BMT alone, while the second ECST trial (ECST-2) includes a BMT alone versus BMT plus carotid revascularization (either CEA or CAS) arm for both symptomatic and asymptomatic patients. The RCT ACTRIS (Asymptomatic Severe Atherosclerotic Carotid Artery Stenosis

at Higher than Average Risk of Ipsilateral Stroke) will compare BMT alone and BMT plus CEA in asymptomatic patients who exhibit one or more features suggestive of them being at higher risk of suffering a late ipsilateral stroke.

Although these studies may shed some light in the debate CEA/CAS versus updated BMT, the methodologies are very similar to studies published in the last decades. We believe investigation on carotid artery disease should diverge from analyzing solely procedural (30-day) stroke, death and MI in the same pre-defined groups: BMT, CEA or CAS in either symptomatic or asymptomatic patients. Investigation should also focus on the impact of intervention timing, on the physiopathology of procedural stroke and other outcomes, on the independent evaluation of technological developments and on diversifying the studied outcomes on both short (30-day) and long-term, in order to obtain distinctive and relevant results from clinical investigation.

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“Eu sou eu e a minha circunstância”

José Ortega y Gasset

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v.referência	v.comunicação	n.referência	data
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assunto

Provas de Doutoramento

Informo V. Exª. que, por meu despacho de 2022.09.01, proferido no âmbito de delegação reitoral, nomeei o júri proposto para as provas de doutoramento em Ciências Cardiovasculares, requeridas por V. Exª., com a seguinte constituição:

Presidente: Doutor Joaquim Adelino Correia Ferreira Leite Moreira, Professor Catedrático da Faculdade de Medicina da Universidade do Porto

Vogais:

- Doutor Mauro Gargiulo, Professor Catedrático da Universidade de Bolonha, Italy;

- Doutor Luís Mendes Pedro, Professor Associado com Agregação da Universidade de Lisboa;

- Doutor Frederico Bastos Gonçalves, Professor Auxiliar Convidado da Universidade Nova de Lisboa;

- Doutora Raquel Ângela Silva Soares Lino, Professora Catedrática da Faculdade de Medicina da Universidade do Porto;

- Doutor José Carlos de Magalhães Silva Cardoso, Professor Catedrático da Faculdade de Medicina da Universidade do Porto;

- Doutor Armando Amilcar Pires Mansilha Rodrigues de Almeida, Professor Catedrático Convidado da Faculdade de Medicina da Universidade do Porto;

- Doutora Elsa Irene Peixoto Azevedo Silva, Professora Associada Convidada da Faculdade de Medicina da Universidade do Porto.

Com os melhores cumprimentos,

A Vice-Reitora,

(Profª. Doutora Fátima Vieira)

(1/6)/PV

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FMUP FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

CAROTID ARTERY ATHEROSCLEROTIC DISEASE: TIMING OF INTERVENTION, PROCEDURAL OUTCOMES AND PATIENT REPORTED OUTCOME MEASURES

Andreia Pires Coelho

2022