An International, Multispecialty, Expert-Based Delphi Consensus Document on the Management of Patients with Asymptomatic and Symptomatic Carotid Stenosis.

A Consensus Statement Endorsed by the International Union of Angiology (I.U.A.)

Pier Luigi Antignani, MD, PhD, FIUA, EFAVF, FESVM, FRSM
Vascular Centre, Nuova Villa Claudia, Rome, Italy

J. Michael Bacharach
Department of Vascular Medicine and Endovascular Intervention, North Central Heart Institute and the Avera Heart Hospital, Sioux Falls, South Dakota, U.S.A.

Ales Blinc, MD, PhD
Department of Vascular Diseases, Division of Internal Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia
Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Martin M. Brown, MD
Stroke Research Centre, Department of Brain Repair and Rehabilitation, UCL Queen Square Institute of Neurology, University College London, London, UK

Richard P. Cambria, MD, FACS
Division of Vascular and Endovascular Surgery, St. Elizabeth's Medical Center, Boston, MA, U.S.A.

Laura Capoccia, MD, PhD
Vascular Surgery Division, Department of Surgery, SS. Filippo e Nicola Hospital, Avezzano, Italy

Seemant Chaturvedi, MD
Department of Neurology, University of Maryland School of Medicine, Baltimore, U.S.A.

Daniel G. Clair, MD, FACS
Department of Vascular Surgery, Vanderbilt University Medical Center, Nashville, TN, U.S.A.

Alan Dardik, MD, PhD, FACS, DFSVS, FAHA
Department of Surgery, Yale School of Medicine, New Haven, CT, U.S.A.

Alun H. Davies, MA, DM, FRCS
Department of Surgery and Cancer, Section of Vascular Surgery, Imperial College London, Charing Cross Hospital, London, UK

Gert J. de Borst, MD, PhD, EBSQVasc
Department of Vascular Surgery, University Medical Center Utrecht, Utrecht, The Netherlands

Vincenzo Di Lazzaro, MD
Department of Medicine and Surgery, Unit of Neurology, Neurophysiology, Neurobiology and Psychiatry, Universita Campus Bio-Medico di Roma, Roma, Italy
Fondazione Policlinico Universitario Campus Bio-Medico, Roma, Italy

Hans-Henning Eckstein, MD, PhD, FEBVS
Department for Vascular and Endovascular Surgery, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany

Gianluca Faggioli, MD, PhD
Vascular Surgery, University of Bologna "Alma Mater Studiorum", Policlinico S. Orsola Malpighi, Bologna, Italy

Jose Fernandes e Fernandes, MD, PhD, FACS, FRCS Eng, FESC, FEBVS
Faculty of Medicine, Lisbon Academic Medical Center, University of Lisbon, Portugal
Hospital da Luz Torres de Lisboa, Lisbon, Portugal

George Geroulakos, FRCS, DIC, PhD
Department of Vascular Surgery, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece

Peter Gloviczki, MD
Division of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN, U.S.A.

Guillaume Goudot, MD, PhD, FESC
Vascular medicine department, Georges Pompidou European hospital, APHP, Université Paris Cité, Paris, France

William A. Gray, MD, FSCAI
Lankenau Heart Institute, Wynnewood, Pennsylvania, U.S.A.

Arkadiusz Jawien, MD, PhD
Department of Vascular Surgery and Angiology, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

Mateja K. Jezovnik, MD, PhD
Department of Advanced Cardiopulmonary Therapies and Transplantation, The University of Texas Health Science Centre at Houston, Houston, Texas, U.S.A.

Stavros K. Kakkos, MD, MSc, PhD, RVT
Department of Vascular Surgery, University of Patras Medical School, Patras, Greece

Brajesh K. Lal, MD
Department of Vascular Surgery, University of Maryland School of Medicine, Baltimore
Department of Vascular Surgery, Baltimore VA Medical Center, Baltimore, U.S.A.
Department of Neurology, Mayo Clinic, Rochester, MN, U.S.A
.

Gaetano Lanza, MD, PhD
Vascular Surgery Department, IRCSS Multimedica Hospital, Castellanza, Italy

George S. Lavenson Jr., MD, FACS, SVS, WVS, SVU, RVT
Department of Surgery, Uniformed Services University, Bethesda, MD, U.S.A.

Carl J. Lavie, MD, FACC
John Ochsner Heart and Vascular Institute, Ochsner Clinical School, The University of Queensland School of Medicine, New Orleans, LA, U.S.A.

Christos D. Liapis, MD, FACS, FRCS, EBSQVasc
Athens Vascular Research Center, Athens, Greece

Ian M. Loftus, MD, FRCS
St. George's Vascular Institute, St. George's University London, London, UK

Sean Lyden, MD, FACS
Department of Vascular Surgery, The Cleveland Clinic, Cleveland, OH, U.S.A.

Armando Mansilha, MD, PhD, FIUA, FEBVS
Faculty of Medicine of the University of Porto, Porto, Portugal
Department of Angiology and Vascular Surgery, Hospital de S. Joao, Porto, Portugal

Ombretta Martinelli, MD, PhD
Faculty of Medicine, Sapienza University of Rome, Rome, Italy
Vascular Surgery Unit, "Umberto I." Hospital, Rome, Italy

Jon S. Matsumura, MD
Department of Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, U.S.A.

Gabor Menyhei, MD, PhD, EBSQVasc
Department of Vascular Surgery, University of Pecs, Pecs, Hungary

James F. Meschia, MD, FAHA, FAAN, FANA
Department of Neurology, Mayo Clinic, Jacksonville, FL, U.S.A.

Dimitri P. Mikhailidis, MD, FFPM, FRCP, FRCPath
Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London, UK

Antoine Millon, MD, PhD
Department of Vascular and Endovascular Surgery, Louis Pradel Hospital, Hospices Civil de Lyon, France

Piotr Musialek, MD, DPhil (Oxford), FESC
Jagiellonian University Department of Cardiac and Vascular Diseases, John Paul II Hospital, Krakow, Poland

Piotr Myrcha, MD, PhD, MBA
Department of General and Vascular Surgery, Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland

Andrew N. Nicolaides, MS, FRCS, PhD (Hons)
Vascular Screening and Diagnostic Center, Nicosia, Cyprus
University of Nicosia Medical School, Nicosia, Cyprus
Department of Vascular Surgery, Imperial College, London, UK

Kosmas I. Paraskevas, MD
Department of Vascular Surgery, Central Clinic of Athens, Athens, Greece

Sakil A. Parikh, MD, FSCAI
Division of Cardiology, Department of Medicine, New York-Presbyterian Hospital/ Columbia University Irving Medical Center, New York, NY, U.S.A.
Center for Interventional Cardiovascular Care and Division of Cardiology, Department of Medicine, Columbia University Irving Medical Center, New York, NY, U.S.A.

Rodolfo Pini, MD, PhD
Vascular Surgery, University of Bologna "Alma Mater Studiorum", Policlinico S. Orsola Malpighi, Bologna, Italy

Pavel Poredos, MD, PhD
Department of Vascular Diseases, University Medical Centre Ljubljana, Slovenia

Robert M. Proczka, MD, PhD
1st Department of Vascular Surgery, Medicover Hospital, Warsaw, Poland

Lazarski University Faculty of Medicine, Warsaw, Poland

Stefano Ricci, FRCPed
Neurology Department-Stroke Unit, Gubbio-Gualdo Tadino and Citta di Castello Hospitals, USL Umbria 1, Perugia, Italy

Jean-Baptiste Ricco, MD, PhD, FEBVS
Department of Vascular Surgery, University Hospital of Toulouse, Toulouse, France

Peter Arthur Ringleb, MD
Department of Neurology, Heidelberg University Hospital, Heidelberg, Germany

Gary Roubin, MD, PhD
Department of Cardiology, Cardiovascular Associates of the Southeast/ Brookwood, Baptist Medical Center, Birmingham, Ala, U.S.A.

Tatjana Rundek, MD, PhD
Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, U.S.A.

Luca Saba, MD
Department of Radiology, Azienda Ospedaliera Universitaria Di Cagliari, Cagliari, Italy

Ravish Sachar, MD, FACC
North Carolina Heart and Vascular Hospital, UNC-REX Healthcare, University of North Carolina, North Carolina, U.S.A.

Felix Schlachetzki, MD
Department of Neurology, University Hospital of Regensburg, Regensburg, Germany

Eric A. Secemsky, MD, MSc, RPVI, FACC, FAHA, FSCAI, FSVM
Smith Center for Outcomes Research, Division of Cardiology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, U.S.A.
Harvard Medical School, Boston, MA, U.S.A.

Mauro Silvestrini, MD
Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

Francesco Spinelli, MD, PhD
Vascular Surgery Division, Department of Medicine and Surgery, Campus Bio–Medico University of Rome, Rome, Italy

Francesco Stilo, MD, PhD
Vascular Surgery Division, Department of Medicine and Surgery, Campus Bio–Medico University of Rome, Rome, Italy

Sherif Sultan, MD, FRCS, FACS, PhD
Western Vascular Institute, Department of Vascular and Endovascular Surgery, University Hospital Galway, University of Galway, Ireland

Alexei Svetlikov, MD, PhD
Division of Vascular and Endovascular Surgery, North–Western Scientific Clinical Center of Federal Medical Biological Agency of Russia, St. Petersburg, Russia

Raffi Topakian, MD
Department of Neurology, Academic Teaching Hospital Wels-Grieskirchen, Wels, Austria

Christopher J. White MD, MACC, MSCAI
Department of Medicine and Cardiology, Ochsner Clinical School, University of Queensland, Brisbane, Australia
Department of Cardiology, The John Ochsner Heart and Vascular Institute, New Orleans, LA, U.S.A.

Clark J. Zeebregts, MD, PhD
Department of Surgery (Division of Vascular Surgery), University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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Author for correspondence:

Kosmas I. Paraskevas, MD

Department of Vascular Surgery, Central Clinic of Athens,

24, Alexander Papagou Street, Neo Irakleio14122,

Athens, Greece

E–mail: paraskevask@hotmail.com

Abstract (288 words)

Aim: Despite the publication of various national/international guidelines, several questions concerning the management of patients with asymptomatic (AsxCS) and symptomatic (SxCS) carotid stenosis remain unanswered. The aim of this international, multi-specialty, expert-based Delphi Consensus document was to address these issues to help clinicians in making decisions when guidelines are unclear.

Methods: Fourteen controversial topics were identified. A 3-round Delphi Consensus process was performed including 61 experts. The aim of Round 1 was to investigate the differing views and opinions about these unresolved topics. In Round 2, clarifications were asked from each participant on ≥1 question. In Round 3, the questionnaire was re-sent to all participants for their final vote. Consensus was reached when ≥75% of experts agreed on the preferred clinical response.

Results: Most experts agreed: (i) that the current periprocedural/in-hospital stroke/death thresholds for performing a carotid intervention should be lowered from 6 to 4% in SxCS and from 3 to 2% in AsxCS patients, (ii) that the time threshold for a patient being considered "recently symptomatic" should be reduced from the current definition of "6 months" to 3 months or less, (iii) that 80-99% AsxCS carries a higher risk of stroke compared with 60-79% AsxCS, (iv) that factors beyond the grade of stenosis and symptoms should be included to the indications for revascularization (e.g., plaque features of vulnerability and silent infarctions on brain CT scans), and, (v) that shunting should be used selectively, rather than always or never. Consensus could not be reached on the rest of the topics due to conflicting, inadequate, or controversial evidence.

Conclusions: The present international, multi-specialty expert-based Delphi Consensus document attempted to provide responses to several unanswered/unresolved issues. However, consensus could not be achieved on some topics, highlighting areas requiring future research.

Keywords: Asymptomatic carotid stenosis, Delphi Consensus, stroke, transient ischemic attack, symptomatic carotid stenosis

Introduction

In the last few years, several International Societies and Associations (e.g., the Society for Vascular Surgery [SVS],[1,2] the European Society for Vascular Surgery [ESVS],[3] the European Stroke Organisation (ESO),[4] the American Heart Association/American Stroke Association (AHA/ASA)[5] and others[6]) have released new, or have updated their earlier guidelines and recommendations regarding the management of patients with symptomatic (SxCS) and asymptomatic (AsxCS) carotid artery stenosis. Such Society Guidelines[1-6] are particularly useful because they guide everyday decision-making and clinical practice, thus helping clinicians to optimize the management of their patients.

Despite the release of various guidelines and recommendations,[1-6] several unanswered and unresolved issues remain. There is a number of reasons to explain the persistence of such unresolved issues, including the paucity of data, the lack of Level I Evidence (i.e., randomized controlled trials [RCTs]) to answer a particular question, or the publication of controversial results in the literature. As a result, clinicians and patients may often face situations in which the evidence to support a proposed intervention is sparse or doubtful.[7] However, even if the evidence is insufficient for evidence-based guidelines, a Delphi-based Trustworthy Consensus Statement can still be carried out.[7] It is expected that groups of experts can provide recommendations within the context of uncertainty, even if the evidence is considered insufficient.[8]

The aim of the present international, multi-specialty, expert-based Delphi Consensus document was to address the various unresolved issues regarding the management of patients with SxCS and AsxCS to help clinicians in their everyday decision-making. The rationale of gathering experts from different specialties was to avoid “surgical bias” or

"interventional cardiologist/radiologist bias". The objective was to produce recommendations, considering the views and opinions of representative experts with different areas of expertise involved in the management of patients with carotid stenosis.

Materials and Methods

An international, multi-specialty, expert-based Delphi Consensus document was prepared in accordance with the Conducting and Reporting Delphi Studies (CREDES) Checklist.[9] A total of 61 experts from the United States of America and Europe (Cyprus, France, Germany, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, Russia, Slovenia, and the United Kingdom) were invited to participate. Overall, 20 participants were from the U.S.A. and 41 from Europe. All participants had at least 20 years of relevant clinical experience in the management of patients with carotid artery stenosis and proof of relevant academic expertise, as documented by relevant publications. The experts included were Vascular Surgeons (n=35), Neurologists/Stroke Physicians (n=9), Interventional Cardiologists (n=8), Vascular Specialists/Angiologists (n=7) and Interventional Radiologists (n=2).

Following a search of the literature (PubMed/MedLine, Scopus and EMBASE) and after receiving feedback from the Delphi Consensus participants, a questionnaire consisting of 14 unresolved/unanswered questions was composed (**Figure 1**). A total of 3 Rounds were undertaken. The aim of Round 1 was to obtain a broad idea and to investigate the differing views and opinions regarding the various identified unresolved topics. In Round 2, clarifications were requested by the Delphi Consensus coordinator (K.I.P.) on ≥1 question from individual participants when the answers provided were not

clear enough or did not comply with the pre-specified standards. In Round 3, the questionnaire was re-sent to all participants for their final vote. Consensus was reached when ≥75% of experts agreed on the preferred response. All information was collected anonymously. No Delphi Consensus participant was identified or was made aware of the identity of the comments by the rest of the participants to avoid any potential bias. Only the Delphi Consensus coordinator was aware of the identity of each participant's comments.

The first draft of the Delphi Consensus document was prepared by K.I.P. and was sent to all participants for their feedback and comments. The manuscript was revised twice based on the comments and suggestions of the Delphi participants. All participants approved the final manuscript and provided their consent to proceed with its publication. Any potential conflict of interest of each participant was declared and is listed at the end of this manuscript.

Results

The responses of the 61 Delphi Consensus participants for each pre-identified topic are presented, analyzed, and discussed below. All 61 participants provided answers to all 14 questions. When possible, the responses were in a pre-specified 7-answer format (**Yes – Probably Yes – Possibly Yes – Uncertain/Unknown/Unproven/No opinion – Possibly No – Probably No – No**). The response "**Uncertain/Unknown/Unproven/No opinion**" included one or more of the following:

a. the Consensus participant does not have a (definitive) opinion or does not have enough experience about this question (e.g., a Neurologist may not know if the best type of patch is Dacron, polytetrafluoroethylene [PTFE], or autologous vein),
b. the evidence supporting a particular question is controversial, conflicting, or inadequate, or
c. there is no Level I evidence from RCTs to provide enough evidence, either to support or to refute a particular question.

1. **Should the periprocedural/in-hospital stroke/death thresholds for performing carotid endarterectomy (CEA)/carotid artery stenting (CAS) in SxCS (<6%) and AsxCS (<3%) patients be reduced to 4% for SxCS and to 2% for AsxCS patients, as proposed by the 2020 German-Austrian[6] and the 2021 ESO[4] guidelines?**

Several studies and registries published after 2010 have demonstrated lower perioperative/in-hospital stroke/death rates for patients undergoing CEA/CAS compared with earlier studies. For example, a report of CEA (n=48,185) and CAS (n=4,602) outcomes from 9 countries (Australia, Denmark, Finland, Norway, Sweden, Switzerland, Hungary, Italy and the UK) demonstrated that the combined stroke and death rate was 0.9% in AsxCS and 2.3% in SxCS patients.[10] In AsxCS patients, stroke/death rates were 0.5% in Italy, 0.9% in Australia, 1.6% in Switzerland and 1.8% in the UK.[10] In contrast, Norway (2.5%) and Sweden (2.7%) reported the highest stroke/death rates, but these were still below the accepted threshold for intervention in AsxCS patients (<3%).[10] In contrast, for SxCS patients all countries reported death/stroke rates <4%, with Italy

reporting the lowest (0.9%) and Norway the highest rates (3.8%).[10] Similarly, another registry from the UK presenting the outcomes of 23,235 recently SxCS patients undergoing CEA, reported a combined 30-day stroke/death rate of 2.31% (95% confidence interval [CI]: 2.11-2.50).[11]

An analysis of all elective CEAs (n=142,074) and CAS procedures (n=13,086) in Germany between 2009 and 2014 demonstrated that the combined risk of in-hospital periprocedural stroke or death for AsxCS patients was 1.4% for CEA and 1.7%, for CAS.[12] For SxCS patients, in-hospital the periprocedural stroke/death risk was 2.5% for CEA and 3.7% for CAS.[12] Based on these results, the 2020 German-Austrian[6] and subsequently the 2021 ESO[4] guidelines lowered the threshold for in-hospital stroke/death rates from 3 to 2% for AsxCS patients and from 6 to 4% for recently symptomatic patients.

Most of the Delphi Consensus document participants (54 of 61; 88.6%) thought that the periprocedural stroke/death thresholds for performing CEA/CAS in both SxCS and AsxCS patients should be lowered from the current ones (**Table 1**). Due to improvements in surgical and endovascular skills/techniques, these lower thresholds (2% for AsxCS and 4% for SxCS patients) probably represent more reasonable thresholds nowadays.

2. Are new ischemic brain lesions after CEA or CAS associated with long-term cognitive impairment?

Several reports have indicated a high incidence of microemboli to the brain after both CEA and CAS.[13-17] Diffusion-weighted imaging (DWI) has been used to compare the incidence of new ischemic lesions after CAS/CAS. A 2008 systematic review including

32 studies (1,363 CAS; 754 CEA procedures) demonstrated that the incidence of any DWI lesion was significantly higher after CAS than after CEA (37 *vs.* 10%, respectively; p<0.01).[18] A >6-fold higher incidence of DWI lesions with CAS compared with CEA was obtained in a meta-analysis focusing on studies that directly compared the incidence of new DWI lesions after either CEA or CAS (odds ratio [OR]: 6.1; 95% CI: 4.19-8.87; p<0.01).[18] The use of cerebral protection devices reduced the incidence of new ipsilateral DWI lesions after CAS compared with non-use (33% *vs.* 45%, respectively; p<0.01).[18] The use of closed-cell stents also reduced the incidence of DWI lesions after CAS compared with open-cell designed stents (31% *vs*. 51%, respectively; p<0.01).[18] Of interest, a significantly higher incidence of new ipsilateral DWI lesions was demonstrated in CEA procedures where shunt use was obligatory compared with selective shunt usage (16% *vs*. 6%, respectively; p<0.01).[18]

Despite the higher number of new ischemic brain lesions after CAS than after CEA, a substudy of the largest RCT comparing CAS with CEA in SxCS patients, the International Carotid Stenting Study (ICSS), failed to show a difference in cognitive function after the 2 procedures.[19] Others have supported that ischemic brain lesions seen on DWI after CAS may be a marker of increased risk for recurrent cerebrovascular events.[20] It was suggested that patients with periprocedural DWI lesions might benefit from more aggressive and prolonged antiplatelet therapy after CAS.[20] Regarding the novel TransCarotid Artery Revascularization (TCAR) procedure, there is some evidence of fewer DWI lesions after TCAR compared with transfemoral CAS due to the reversal of blood flow.[21] It was suggested that TCAR provides cerebral embolic protection similar to that seen with CEA.[21]

The uncertainty in the clinical significance of silent cerebral emboli after carotid interventions is reflected in the responses of the Delphi Consensus participants (**Table 2**). Notwithstanding a possible effect of new silent cerebral lesions after CEA/CAS/TCAR on cognitive dysfunction, all necessary precautions (e.g., filters, cerebral protection devices, and more recently, flow reversal) should be taken to ensure maximum protection against silent ischemic brain lesions after carotid procedures.

3. Does severe AsxCS cause cognitive impairment and can carotid interventions either reverse or prevent cognitive decline?

The association between AsxCS with cognitive impairment is a highly controversial topic. Several studies have demonstrated a significant association between severe AsxCS and progressive cognitive decline.[22-25] A 2021 systematic review including 35 cross-sectional and longitudinal studies demonstrated that >90% of studies (33/35) reported an association between AsxCS and ≥1 test showing impaired cognitive function.[26] However, it was argued that a 'significant association' does not necessarily mean a 'causal relationship'.[26] Several pathophysiological mechanisms were identified by which AsxCS might cause cognitive impairment, including silent cerebral infarction, reduced cerebrovascular reserve, involvement in the pathophysiology of white matter hyperintensities or lacunar infarction, or via a combination of these methods.[26]

A more recent systematic review including 49 studies similarly demonstrated an association between AsxCS and progressive cognitive deterioration.[27] This systematic review suggested that the most likely mechanisms involved in the cognitive decline observed in AsxCS patients are probably cerebral hypoperfusion and/or silent cerebral

embolization.[27] Irrespective of the implicated pathomechanisms, it was concluded that patients with severe AsxCS are at increased risk of developing a progressive decline in several aspects of their cognitive function, including global cognition, memory and executive function.[27]

Whether or not carotid interventions can reverse any cognitive decline is another controversial topic. Several studies have demonstrated a beneficial effect of CEA/CAS on cognitive dysfunction, with some neurocognitive domains showing improvement post-procedurally.[28-30] Other studies, however, have reported mixed results or no significant change after either procedure.[31-33] A recent systematic review on the topic failed to demonstrate convincing evidence supporting intervention in AsxCS patients to reverse/prevent cognitive decline.[34] According to the 2023 ESVS carotid guidelines,[3] carotid interventions are not recommended for the prevention or improvement of cognitive impairment in AsxCS patients until new research clearly identifies AsxCS patient subgroups at risk for developing cognitive impairment, which is then improved by carotid interventions. The controversial results reported in the various studies in the literature and the uncertainty about a possible effect of carotid interventions on cognitive function in AsxCS patients are also reflected in the heterogeneity of the responses of the Delphi Consensus participants (**Table 3**). Thus, the Delphi participants could not reach a consensus on this topic.

4. Is completion duplex ultrasound or angiography useful to lower the risk of postoperative stroke after CEA?

The usefulness of completion duplex ultrasound or angiography in reducing the risk of postoperative stroke after CEA is another controversial issue. A study from Germany including 142,074 elective CEAs from 2009 to 2014 demonstrated an independent association between lower risks of stroke/death with intraoperative completion studies by duplex ultrasound (relative risk [RR]: 0.74; 95% CI: 0.63-0.88; p=0.001) or angiography (RR: 0.80; 95% CI: 0.71-0.90; p<0.001).[35] In contrast, other studies argued against the necessity of routine completion imaging, supporting that routine completion imaging does not improve perioperative outcomes.[36-38] Consequently, the 2022 SVS carotid guidelines concluded that there is insufficient evidence to recommend routine use of completion imaging after CEA.[2]

On the contrary, a recent systematic review and meta-analysis including 34 studies on intraoperative completion studies following CEA using angiography (n=53,218), intraoperative duplex ultrasound (n=20,020), flowmetry (n=16,812) and angioscopy (n=2,291) reached opposite conclusions.[39] This meta-analysis demonstrated that the performance of completion angiography was associated with lower rates of stroke (RR: 0.47; 95% CI: 0.36-0.62; p<0.0001) and stroke or death (RR: 0.76; 95% CI: 0.70-0.83; p<0.0001).[39] Similarly, the performance of intraoperative completion duplex ultrasound was associated with lower rates of stroke (RR: 0.56; 95% CI: 0.43-0.73; p<0.0001) and stroke or death (RR: 0.83; 95% CI: 0.74-0.93; p=0.0018), whereas angioscopy showed a significant association with lower stroke rates (RR: 0.48; 95% CI: 0.033-0.68; p=0.0001), but had no effect on the combined stroke or death rate.[39] Based largely on these results,

the 2023 ESVS carotid guidelines recommended that for patients undergoing CEA, intraoperative completion imaging with angiography, duplex ultrasound or angioscopy should be considered in order to reduce the risk of perioperative stroke (Class IIa; Level of Evidence: B).[3]

Around 60% of the Delphi Consensus participants supported that completion imaging (mainly in the form of duplex ultrasound) should definitely (29 of 61; 47.4%) or should probably/possibly (8 of 61; 13.2%) be performed to check the results of CEA as it may be useful to reduce the risk of stroke after CEA (**Table 4**).

5. Is dual antiplatelet therapy (DAPT) before and during CEA safe and effective in decreasing perioperative thromboembolic complications?

Antiplatelet agents play a key role in the management of patients with AsxCS and SxCS. Although there is no solid evidence to support a benefit of aspirin for AsxCS in terms of reducing stroke rates, the U.S. Preventive Services Task Force recommends initiating low-dose aspirin for primary prevention of cardiovascular disease (CVD) in adults aged 50-59 years who have a ≥10% 10-year CVD risk, are not at increased bleeding risk, have a life expectancy of ≥10 years and are willing to take low-dose aspirin daily for ≥10 years.[40] In contrast, for adults with a ≥10% 10-year CVD risk aged 60-69 years, the decision to initiate low-dose aspirin should be individualized, whereas the evidence for adults <50 or ≥70 years is insufficient.[40]

On the other hand, there is considerable evidence to support DAPT for secondary stroke prevention. In the multicenter (n=114 center) randomized, double-blind, placebo-controlled Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular

events (CHANCE) trial,[41] 5170 patients were randomized to aspirin plus clopidogrel or aspirin alone within 24h of a high-risk transient ischemic attack (TIA) or minor stroke. A stroke occurred in 8.2% of patients in the aspirin + clopidogrel group, compared with 11.7% of patients who took aspirin alone (hazard ratio [HR]: 0.68; 95% CI: 0.57-0.81; p<0.001).[41] Moderate or severe hemorrhage occurred in 7 patients (0.3%) in the clopidogrel-aspirin group and 8 (0.3%) in the aspirin group (p=0.73), while the rate of hemorrhagic stroke was 0.3% in each group.[41]

A meta-analysis including 8 RCTs (n=20,728 patients) comparing aspirin + clopidogrel *vs.* aspirin or clopidogrel alone as secondary prevention of stroke or TIA of arterial origin demonstrated that short-term (≤3 months) combination therapy was associated with a 31% reduction in the risk of stroke recurrence (RR: 0.69; 95% CI: 0.59-0.81; p<0.01), without increasing the risk of hemorrhagic stroke (RR: 1.23; 95% CI: 0.50-3.04; p=0.65) and major bleeding events (RR: 2.17; 95% CI: 0.18-25.71; p=0.54).[42] These RCTs, however, excluded patients that underwent carotid revascularization. Furthermore, short-term combination therapy was associated with a significantly lower risk of major vascular events (RR: 0.70; 95% CI: 0.69-0.82; p<0.01).[42] In contrast, long-term (≥1 year) treatment with aspirin + clopidogrel did not decrease the risk of stroke recurrence (RR: 0.92; 95% CI: 0.83-1.03, p=0.15), but was associated with a significantly higher risk of hemorrhagic stroke (RR: 1.67; 95% CI: 1.10-2.56; p=0.02) and major bleeding events (RR: 1.90; 95% CI: 1.46-2.48; p<0.01).[42] Additionally, long-term combination therapy failed to reduce the risk of major vascular events (RR: 0.92; 95% CI: 0.84-1.03; p=0.09).[42]

A study including all patients who had undergone transfemoral CAS (n=18,570) or TCAR (n=25,459) in the Vascular Quality Initiative database between 2016-2021 demonstrated that compared with DAPT, no antiplatelet therapy (RR: 2.0; 95% CI: 1.2-3.3) or aspirin monotherapy (RR: 2.2; 95% CI: 1.5-3.1) were associated with higher stroke/death rates after transfemoral CAS/TCAR and should be discouraged as unsafe practice.[43] On the other hand, P2Y12 inhibitor monotherapy (e.g., clopidogrel, ticlopidine, ticagrelor or prasugrel) was associated with similar rates of stroke/death compared with DAPT with aspirin plus P2Y12 inhibitor (for TCAR, RR: 0.98; 95% CI: 0.54-1.8; for transfemoral CAS, RR: 0.99; 95% CI: 0.58-1.7).[43]

Although DAPT seems beneficial over antiplatelet monotherapy for patients undergoing transfemoral CAS or TCAR, this may not apply to patients undergoing CEA. A recent systematic review and meta-analysis of perioperative outcomes of CEA on DAPT *vs.* aspirin monotherapy (n=11 studies; 47,411 patients; 14,345 on DAPT; 33,066 receiving only aspirin) demonstrated no difference in the rates of perioperative stroke (OR: 0.87; 95% CI: 0.72-1.05) and TIA (OR: 0.78; 95% CI: 0.52-1.17) in the DAPT compared with the aspirin monotherapy group.[44] However, DAPT was associated with a nearly 2.8-fold increased risk of neck hematoma (OR: 2.79; 95% CI: 1.87-4.18) and a nearly 2-fold increased risk of reoperation for bleeding (OR: 1.98; 05% CI: 1.77-2.23) compared with aspirin monotherapy.[44] The authors concluded that "***this suggests that the risks of performing CEA on DAPT outweigh the benefits, even in patients with symptomatic carotid stenosis***".[44] These results were verified in other large independent studies.[45,46] A national registry analysis including >12,000 patients with AsxCS/SxCS undergoing CEA showed that the effectiveness and safety of DAPT did not differ from

those of single antiplatelet therapy.[47] It was concluded that DAPT should be started immediately after a cerebrovascular event and should be continued until 30 days after CEA, followed by single antiplatelet therapy.[47] Along the same lines, a recent international, multispecialty, expert review and position statement concluded that a short course (<3 months) of DAPT should be initiated within 24h of a cerebrovascular event in patients with carotid artery stenosis to reduce the risk of recurrent events.[48] A similar recommendation was provided in the 2021 AHA/ASA Guidelines.[5] In patients undergoing TCAR or transfemoral CAS, patients should continue with DAPT for 1 month after which a P2Y12 inhibitor monotherapy should be continued.[48]

As a result of the conflicting data from the literature, a consensus on this topic could not be reached among the Delphi participants (**Table 5**).

6. **Is carotid restenosis after CEA a contra-indication for re-do CEA and (if revascularization is necessary) an indication for CAS?**

Due to conflicting data from multicentre RCTs,[49-51] the optimal management of restenosis after CEA is another controversial topic. Some RCTs (e.g., the Carotid and Vertebral Artery Transluminal Angioplasty Study [CAVATAS][49] and the Stent-Protected Angioplasty versus Carotid Endarterectomy [SPACE][50] study) reported higher incidence of restenosis after endovascular treatment compared with CEA. However, this did not translate into a higher incidence of recurrent ipsilateral cerebrovascular events. In contrast, the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) reported a similar incidence of restenosis after CAS and CEA (6.0 *vs.* 6.3%, respectively; HR: 0.90; 95% CI: 0.63-1.29; p=0.58).[51]

Data from population-based studies demonstrate similar stroke/death rates between re-do CEA and CAS after prior ipsilateral CEA.[52,53] However, re-do CEA carries a higher stroke/death/myocardial infarction risk for both SxCS and AsxCS patients compared with patients undergoing primary CEA.[52] Furthermore, re-do CEA may be associated with higher mortality rates compared with CAS, especially in patients with multiple comorbidities.[53]

A 2017 meta-analysis including prospective data from 11 RCTs demonstrated that the weighted incidence of >70% restenosis was 5.8% after CEA (11 RCTs; 4,249 patients) and 10% after CAS (5 RCTs; 2,716 patients).[54] However, CAS patients with untreated AsxCS >70% restenosis had a mere 0.8% late ipsilateral stroke rate over 50 months of follow-up.[54] In contrast, over a mean follow-up of 37 months, 13 of 141 CEA patients with >70% restenosis or occlusion suffered a late ipsilateral stroke compared with 33 of 2,669 patients who did not have a >70% restenosis or occlusion (9.2 *vs.* 1.2%, respectively; OR: 9.02; 95% CI: 4.70-17.28; p<0.0001).[54] Another individual patient-data meta-analysis including 1,132 restenosis patients treated in 13 studies (653 patients treated by CAS; 479 patients treated by CEA) demonstrated similar perioperative stroke/death rates with the 2 procedures (2.3 *vs.* 2.7%, respectively; adjusted OR: 0.8; 95% CI: 0.4-1.8).[55] However, re-do CEA was associated with a 5.5% risk of cranial nerve injury.[55]

The 2023 ESVS Guidelines recommended that for CEA patients with an asymptomatic 70-99% restenosis, reintervention may be considered following a multidisciplinary team review (Class IIb; Level of Evidence: A).[3] According to the 2022 SVS carotid guidelines,[2] early recurrent stenosis after CEA can be managed conservatively unless it is

symptomatic, progressive or causes ≥80% luminal stenosis. In contrast, late recurrent stenosis after CEA should be considered for reintervention with similar parameters as primary CEA in both symptomatic and asymptomatic cases.[2] Reintervention for recurrent stenosis after CEA can involve either redo CEA or CAS, based on the individual patient, clinical scenario, and relevant anatomy.[2]

The responses of the Delphi Consensus participants are presented in **Table 6**. Approximately half of the participants (29 of 61; 47.6%) did not think that carotid restenosis is an absolute contraindication for re-do CEA . However, they advised that in patients with recurrent carotid stenosis, CAS may be preferable due to the increased rates of cranial nerve injury and the presence of neck scarring ("hostile neck"). CAS in these patients appears to be a more attractive option and may thus be preferable in most patients requiring a re-intervention.

7. Can TCAR be performed safely in the first 7-14 days after symptom onset with procedural risks similar to CEA?

TCAR has quickly gained ground as a hybrid revascularization technique combining the benefits of transfemoral CAS (less invasive nature, avoidance of cranial nerve injury) and at the same time avoiding many of CAS drawbacks (e.g., avoidance of aortic arch).[56-62] A recent report showed that TCAR is increasingly performed in the U.S. over the last years and has surpassed transfemoral CAS.[56] Several reports have demonstrated that TCAR is associated with similar stroke/death rates with CEA in both symptomatic and asymptomatic patients.[57-62] However, TCAR has the advantage of avoiding cranial nerve injuries and is associated with a lower risk of postoperative MI compared with CEA.[59,60]

Furthermore, TCAR is associated with lower stroke/death rates compared with transfemoral CAS.[62]

All current guidelines (i.e., the 2021 AHA/ASA,[5] the 2022 SVS,[1,2] the 2023 ESVS,[3] the 2021 ESO[4] and the German-Austrian[6] guidelines) provide a strong recommendation for CEA in patients with carotid stenosis within 14 days of a neurologic event (TIA or minor stroke). A recent article used data from the SVS Vascular Quality Initiative database between January 2016 and December 2020 to compare 30-day outcomes of symptomatic patients who had undergone TCAR (n=1,282) or CEA (n=13,249) within 14 days of a stroke or TIA.[63] After 1:1 propensity matching, 728 pairs were included for analysis.[63] The primary composite outcome of stroke, death or MI was more frequent in patients undergoing TCAR compared with CEA (4.7 *vs.* 2.6%, respectively; p=0.04). This was driven by a higher rate of postoperative ipsilateral stroke in the TCAR compared with the CEA group (3.8 *vs.* 1.8%, respectively; p=0.005), whereas no differences were found in terms of death (0.7 *vs.* 0.8%, respectively; p=0.8) or MI (0.8 *vs.* 1%, respectively; p=0.7). Furthermore, performing TCAR within 48h of a stroke episode was an independent predictor of postoperative stroke or TIA (OR 5.4; 95% CI: 1.8-16). However, this increased risk of postoperative stroke or TIA was not found when performing TCAR within 48 hours of a TIA episode.[63] Verification of these preliminary results in larger studies is necessary before any definite conclusions can be drawn.

The responses of the 61 experts regarding the suitability of TCAR to be performed within 7-14 days of a recent cerebrovascular event are shown in **Table 7**. Approximately half of the Delphi participants (32 of 61; 52.5%) voted that it is not yet known/certain/proven if TCAR can be performed safely in the first 7-14h after symptom

onset with procedural risks similar to CEA. This is an area that requires additional research.

8. Should the time threshold for a patient being defined as 'recently symptomatic' be reduced from the current definition of '6 months'?

Early RCTs recruiting "recently symptomatic patients", like the European Carotid Surgery Trial (ECST)[64] or the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[65] defined "recently symptomatic" patients as those having suffered an ipsilateral TIA or non-disabling stroke within 180 days before study entry. A pooled data analysis from the ECST and NASCET, however, demonstrated that the benefit from surgery was greatest in men, patients ≥75 years and those randomized within 2 weeks after their last ischemic event, and it fell rapidly with increasing delay.[66] As a result, all current guidelines strongly recommend CEA within 2 weeks of a recent cerebrovascular event (TIA or minor stroke).[1-6] This suggests that the definition of "recently symptomatic patients" as those having suffered a cerebrovascular event within the last 180 days may be inappropriate.

The responses of the 61 Delphi Consensus participants can be seen in **Table 8**. Overall, >80% of the study participants (50 of 61; 82.0%) thought that the time threshold for patients to be defined as "recently symptomatic" should be reduced from the current definition of "6 months". Of those, 31/50 participants (62.0%) responded that the 'recently symptomatic' period should be reduced to 3 months and another 8/50 (16.0%) thought that it should be reduced to '4 weeks/1 month'. The remaining 11/50 (22.0%)

participants did not have a strong opinion about what the time threshold for a patient being defined as "recently symptomatic" should be reduced to.

9. Is local/regional anesthesia better than general anesthesia in patients undergoing CEA?

Some surgeons are more comfortable performing CEA under general anesthesia, whereas others prefer local/regional anesthesia to be able to interact with the patient. The General versus Local Anaesthesia (GALA) trial was a multicentre RCT randomly assigning 3,526 patients with SxCS or AsxCS from 95 centers in 24 countries to CEA under general (n=1,753) or local (n=1,773) anesthesia.[67] The primary outcome (30-day stroke, MI or death) occurred in 84 (4.8%) patients assigned to surgery under general and 80 (4.5%) to those assigned to surgery under local anesthesia.[67] Three events per 1,000 patients treated were prevented with local anesthesia (95% CI: –11 to 17; risk ratio: 0.94; 95% CI: 0.70-1.27). Furthermore, the 2 groups did not differ significantly with respect to the quality of life, length of hospital stay or the primary outcome in the prespecified subgroups of age, contralateral carotid occlusion, and baseline surgical risk.[67]

A recent systematic review and meta-analysis including 31 studies with 152,376 patients demonstrated that local compared with general anesthesia was associated with a shorter surgical time (weighted mean difference: –9.15 min; 95% CI: –15.55 to –2.75; p=0.005) and a 24% reduction in stroke rates (OR: 0.76; 95% CI: 0.62-0.92; p=0.006), a 41% reduction in cardiac complications (OR: 0.59; 95% CI: 0.47-0.73; p<0.00001) and a 28% reduction in in-hospital mortality (OR: 0.72; 95% CI: 0.59-0.90; p=0.003).[68] Nevertheless, a Cochrane Database Systematic Review including 16 RCTs (4,839

patients) failed to show a difference in 30-day stroke (3.2 *vs.* 3.5%, respectively; OR: 0.91; 95% CI: 0.66-1.26; p=0.58) or stroke and death rates (3.5 *vs.* 4.1%, respectively; OR: 0.85; 95% CI: 0.62-1.16; p=0.31) between patients undergoing CEA under local *vs.* general anesthesia.[69]

As the preference of the type of anesthesia used varies with each individual surgeon, a consensus was not possible on this topic (**Table 9**).

10. Is 80-99% AsxCS associated with a higher risk of future ipsilateral ischemic stroke compared with 60-79% AsxCS?

According to the 2023 ESVS carotid guidelines, CEA should be considered for average surgical risk patients with 60-99% AsxCS in the presence of ≥1 imaging or clinical characteristics that may be associated with an increased risk of late stroke, provided 30-day stroke/death rates are ≤3% and the patient has at least a 5-year life expectancy (Class IIa; Level of Evidence: B).[3] For such AsxCS patients, CAS may be an alternative to CEA (Class IIb; Level of Evidence: B). One of the imaging parameters associated with an increased risk of late ipsilateral stroke is stenosis progression.[3] In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study, 1121 patients with 50-99% AsxCS were followed-up for a mean of 4 years.[70] Regression occurred in 43 individuals (3.8%), no change in 856 study participants (76.4%) and progression in 222 patients (19.8%). For the entire cohort, the 8-year cumulative ipsilateral cerebral ischemic stroke rate was 0% in patients with regression, 9% if the stenosis was unchanged, and 16% if there was progression (average annual stroke rates of 0%, 1.1%, and 2.0%, respectively; log-rank, p=0.05; RR in patients with progression: 1.92; 95% CI: 1.14-3.25).[70]

A systematic review and meta-analysis of all published studies reporting ipsilateral stroke risk in patients with AsxCS identified 56 studies including 13,717 patients; 23 of them (n=8,419 patients) provided data on ipsilateral stroke risk fully stratified by degree of AsxCS.[71] Stroke risk was linearly associated with the degree of ipsilateral stenosis (p<0.0001).[71] Patients with 70-99% AsxCS had a >2-fold higher stroke risk compared with those individuals with 50-69% AsxCS (386 of 3,778 *vs.* 181 of 3,806 patients; OR: 2.1; 95% CI: 1.7-2.5; p<0.0001).[71] Furthermore, patients with 80-99% AsxCS had a 2.5-fold higher stroke risk compared with individuals with 50-79% AsxCS (77 of 727 *vs.*167 of 3,272 patients; OR: 2.5; 95% CI: 1.8-3.5; p<0.0001). It was concluded that "***contrary to the assumptions of current guidelines and the findings of subgroup analyses of previous randomised controlled trials, the stroke risk reported in cohort studies was highly dependent on the degree of asymptomatic carotid stenosis, suggesting that the benefit of endarterectomy might be underestimated in patients with severe stenosis. Conversely, the 5-year stroke risk was low for patients with moderate stenosis on contemporary medical treatment, calling into question any benefit from revascularization"***.[71]

Most of the Delphi participants voted that 80-99% AsxCS is definitely (47/61; 77.1%) or is probably (7/61; 11.4%) associated with a higher stroke risk compared with 60-79% AsxCS (**Table 10**).

11. Should other factors than the grade of stenosis and symptomatology be included in the indications for intervention (e.g., plaque features of vulnerability, presence of intraplaque hemorrhage, etc.)?

In the last few years, it has become apparent that the degree of carotid stenosis alone is not an adequate marker of increased stroke risk, able to indicate when a prophylactic carotid intervention is required.[3] Other clinical and radiologic markers have emerged as more accurate predictors of future stroke risk.[3,72-76] Examples include impaired cerebrovascular reserve, microembolic signals detected with transcranial Doppler, carotid plaque echolucency, intraplaque hemorrhage on MRI, large juxtaluminal echolucent (black) areas on computerized ultrasound plaque analysis, silent ipsilateral infarction on brain CT scans, etc.[72-76] The presence of one or more such markers of increased future stroke risk may identify high-risk AsxCS individuals who will benefit from a prophylactic carotid intervention.[3,72-76]

The 2023 ESVS Carotid Guidelines recommended that for average surgical risk patients with a 60-99% AsxCS, CEA should be considered in the presence of one or more imaging or clinical characteristics that may be associated with an increased risk of late stroke, provided 30-day stroke/death rates are ≥3% and patient life expectancy exceeds 5 years (Class IIa, Level of Evidence: B). In these patients CAS may be an alternative to CEA (Class IIb; Level of Evidence: B).[3] The vast majority of the participants in this Delphi Consensus concurred that other factors than the grade of AsxCS and symptomatology should definitely (56 of 61; 91.9%) or should probably/possibly (4 of 61; 6.6%) be included in determining the indications for intervention in an AsxCS patient (**Table 11**).

12. Should shunting be used routinely, selectively, or never?

The routine *vs.* selective *vs.* non-use of shunts during CEA has been the subject of debate for >3 decades. In addition to numerous studies addressing this issue, this topic has been the subject of Cochrane Database Systematic Reviews since 2000 and has been updated 4 times.[77-81] The first Cochrane Database Systematic Review in 2000 concluded that the data at the time were too limited to either support or refute the use of routine or selective shunting in CEA.[77] It was also suggested that large-scale RCTs of routine *vs.* selective shunting were required.[77] Finally, it was concluded that no method of monitoring in selective shunting has been shown to produce better outcomes. The same conclusions have been reached in all subsequent Cochrane Database Systematic Reviews since then, including the last one published in 2022.[78-81]

Vascular surgeons tend to be routine, selective, or never shunters, based on their training. While there are several methods to monitor brain perfusion during carotid clamping (e.g., electroencephalography, stump pressure, backflow, transcranial Doppler monitoring, transcranial cerebral oximetry and near-infrared spectroscopy), the only reliable method is the patient's neurological status with CEA under locoregional anesthesia. Both the 2022 SVS[2] and 2023 ESVS[3] Guidelines recommended that for patients undergoing CEA, decisions regarding shunting (routine, selective, never) should be considered at the discretion of the operating surgeon.

Based on their personal preference rather than the presence of objective data, most of the Delphi Consensus participants (47 of 61; 77.1%) recommended that a shunt be selectively used (**Table 12**). Nevertheless, it should be noted that this recommendation does not rely on Level I Evidence, but rather on individual preferences.

13. What is the best material to use for patch closure: autologous vein, polyester (Dacron) or biological (Xeno) graft?

The optimal material to use for patch closure in CEA procedures is another controversial topic that has been the subject of debate for several decades. To define the best patch material, several studies and RCTs have compared different types of patches, namely autologous vein *vs.* synthetic (PTFE or Dacron) *vs.* biological (e.g., bovine pericardium).[82-87]

A 2021 Cochrane Database Systematic Review included 14 trials involving a total of 2,278 CEAs with patch closure operations: 7 trials compared vein closure with PTFE closure, 5 compared Dacron grafts with other synthetic materials and 2 compared bovine pericardium with other synthetic materials.[88] Overall, this systematic review concluded that the number of outcome events is too small to allow any meaningful conclusions to be drawn. There appears to be little (if any) difference in terms of perioperative or long-term ipsilateral stroke rates between the different patch materials.[88] There is some evidence that PTFE patches may be superior to Dacron grafts in terms of perioperative stroke/TIA rates and both early and late arterial restenosis and occlusion.[88] Pseudoaneurysm formation may be more common after the use of a vein patch than after the use of a synthetic patch.[88] Finally, the bovine pericardial patch may reduce the risk of perioperative fatal stroke, death and infection compared with other synthetic patches.[88]

Both the 2023 ESVS[3] and the 2022 SVS[2] guidelines recommended that for patients undergoing CEA, the choice of patch closure material should be considered at the discretion of the operating surgeon. This is also reflected in the responses of the Delphi

Consensus participants, where each vascular surgeon essentially provided his/her personal preference(s) (**Table 13**).

14. Should protamine be given to counteract heparin effects at the end of the procedure?

A 2016 meta-analysis comparing the outcomes in 3,817 patients undergoing CEA who received protamine reversal *vs.* 6,070 CEA patients who did not receive protamine demonstrated that protamine reversal significantly reduced wound re-exploration for neck hematomas (OR: 0.42; 95% CI: 0.22-0.8; p=0.008), with no evidence that it increased perioperative stroke rates (OR: 0.71; 95% CI: 0.49-1.03; p=0.07).[89] However, the authors reported that taking into account the limitations of the analysis, further studies were needed to increase the level of evidence provided by their meta-analysis.[89]

A multi-center (n=12) report evaluated whether protamine use after CEA increased within the Vascular Study Group of New England (VSGNE) in response to studies indicating that protamine reduces bleeding complications associated with CEA without increasing the risk of stroke.[90] From 2003 to 2007, protamine use remained stable at 43%. Protamine usage increased to 52% in 2008 (p<0.01), coincident with new centers joining the VSGNE, and subsequently increased to 62% in 2010 (p<0.01), shortly after the presentation of the data showing a benefit of protamine use.[90] Reoperation for bleeding was reduced from 1.44 to 0.6% (RR reduction: 57.2%; p<0.001) without increasing perioperative stroke/death rates.[90]

Both the 2022 SVS[2] and the 2023 ESVS[3] guidelines provided a weak recommendation suggesting that protamine reversal of heparin should be considered (Class IIa; Level of

Evidence: B). Most vascular surgeons have a personal preference about routine/selective heparin reversal with protamine *vs.* no reversal. Therefore, a consensus on this topic could not be reached (**Table 14**).

Discussion

The present multi-specialty, expert-based Delphi Consensus document provided answers to certain unresolved questions regarding the management of AsxCS and SxCS patients. At the same time, it revealed topics where the evidence is currently insufficient for definitive conclusions to be drawn and thus identified areas requiring further research.

Most experts agreed that the traditional periprocedural/in-hospital stroke/death thresholds for performing CEA/CAS in SxCS (<6%) and AsxCS (<3%) are now too high and should be reduced. The 2020 German-Austrian,[6] followed by the 2021 ESO[4] Guidelines, proposed new lower perioperative thresholds, namely 4% for SxCS and 2% for AsxCS patients. It could be argued that it may not always be possible to achieve such low stroke/death rates in all patients. Nevertheless, it is worth pursuing the lowest possible stroke/death rates in patients undergoing CEA/CAS/TCAR.

Whether or not new ischemic cerebral lesions after CEA/CAS/TCAR are associated with long-term cognitive impairment is an area that remains uncertain. Although many experts would imagine that such silent lesions may have long-term effects on the cognitive function, there is no definitive evidence currently available. The same applies to the possible association between AsxCS with cognitive dysfunction, as well as to the role of carotid interventions in reversing cognitive impairment. These are “grey” areas that need to be addressed in well-designed studies in the future.

Although completion imaging after CEA may be preferred or routinely performed by some surgeons, there is no definitive evidence that it reduces postoperative stroke rates. Therefore, many participants were reluctant to recommend completion imaging routinely. Uncertainty also exists about the value of DAPT before and during CEA (except for recently symptomatic patients),[3] the clinical significance and the optimal management of restenosis following CEA, as well as the superiority of local/regional over general anesthesia in patients undergoing CEA.

TCAR has emerged as a considerably better revascularization option compared with transfemoral CAS and is quickly gaining ground in the management of patients with AsxCS and SxCS. Advantages of this procedure include that it can be performed safely under local anesthesia and no intensive care unit stay,[91] with stroke/death rates comparable to those of the gold-standard CEA.[92] Disadvantages include the limited availability of the procedure outside the U.S. and its relatively high cost,[93] but hopefully these will improve in the future.

Most experts agreed that 80-99% AsxCS is associated with a higher risk of future ipsilateral ischemic stroke than 60-79% AsxCS, but also that other factors besides the degree of stenosis should be valued when deciding to offer an intervention to an AsxCS patient. There seems to be a gradual change in the way of perceiving increased stroke risk from the classical stratification based on the degree of luminal stenosis. This is certainly an area that requires further investigation. Nevertheless, regardless of the risk of future stroke, patients with severe AsxCS have very high all-cause and cardiac mortality;[94] therefore, aggressive management of vascular risk factors and implementation of best medical treatment is essential in all patients. Finally, the type of patch material selected

and the topic of protamine reversal of the effects of heparin after CEA are issues that are largely based on personal preferences of the individual vascular surgeons.

This study has some limitations. Firstly, the opinion of the study participants does not necessarily reflect the opinion of other experts in the field. Secondly, a different composition in the Delphi Consensus group (e.g., more stroke physicians or more interventional cardiologists) could have produced different results. Thirdly, all experts provided their recommendations based on the available evidence and their personal experience. Their recommendation may differ in the future if new evidence becomes available.

In conclusion, this international, multi-specialty, expert-based Delphi Consensus document attempted to provide answers to several unresolved questions and issues concerning the optimal management of AsxCS and SxCS patients. Although a consensus was possible on some of these topics, the Delphi participants disagreed on other topics, based largely on their personal clinical experience and interpretation of the available evidence. Nevertheless, in the context of the uncertainty regarding several unanswered questions and until the publication of more robust evidence, as well as Society Practice guidelines addressing these topics, this Consensus document should be viewed as an opportunity to aid clinicians in their everyday quest for the optimal management of patients with SxCS and AsxCS.

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