

Comparison of Recent Practice Guidelines for the Management of Patients With Asymptomatic Carotid Stenosis

Citation for published version (APA):

Paraskevas, K. I., Mikhailidis, D. P., Antignani, P. L., Ascher, E., Baradaran, H., Bokkers, R. P. H., Cambria, R. P., Comerota, A. J., Dardik, A., Davies, A. H., Eckstein, H. H., Faggioli, G., Fernandes, J. F. E., Fraedrich, G., Geroulakos, G., Gloviczki, P., Golledge, J., Gupta, A., Jezovnik, M. K., ... Chaturvedi, S. (2022). Comparison of Recent Practice Guidelines for the Management of Patients With Asymptomatic Carotid Stenosis. *Angiology*, 73(10), 903-910. Article 00033197221081914. <https://doi.org/10.1177/00033197221081914>

Document status and date:

Published: 01/11/2022

DOI:

[10.1177/00033197221081914](https://doi.org/10.1177/00033197221081914)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license


Take down policy







If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Comparison of Recent Practice Guidelines for the Management of Patients With Asymptomatic Carotid Stenosis

Angiology
2022, Vol. 73(10) 903–910
© The Author(s) 2022
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/00033197221081914
journals.sagepub.com/home/ang


Kosmas I. Paraskevas, MD¹ , Dimitri P. Mikhailidis, MD, FFPM, FRCP, FRCPATH², Pier Luigi Antignani, MD, PhD, FIUA³, Enrico Ascher, MD, FACS⁴, Hedyeh Baradaran, MD⁵, Reinoud P.H. Bokkers, MD, PhD, EBIR⁶, Richard P. Cambria, MD, FACS⁷, Anthony J. Comerota, MD, FACS⁸, Alan Dardik, MD, PhD, FACS, DFSVS, FAHA⁹, Alun H. Davies, MA, DM, FRCS¹⁰, Hans-Henning Eckstein, MD, PhD, FEBVS¹¹, Gianluca Faggioli, MD, PhD¹², Jose Fernandes e Fernandes, MD, PhD, FACS, FRCS Eng, FESC, FEBVS¹³, Gustav Fraedrich, MD¹⁴, George Geroulakos, MD, PhD, FRCS¹⁵, Peter Gloviczki, MD¹⁶, Jonathan Golledge, MB, BChir, MA, MChir, FRCS, FRACS¹⁷, Ajay Gupta, MD, MS¹⁸, Mateja K. Jezovnik, MD, PhD¹⁹ , Stavros K. Kakkos, MD, DM, MSc, PhD, RVT²⁰, Niki Katsiki, MSc, PhD, MD²¹ , Michael Knoflach, MD, PhD²², M. Eline Kooi, PhD^{23,24}, Gaetano Lanza, MD, PhD²⁵, George S. Lavenson Jr., MD, FACS, RVT²⁶, Christos D. Liapis, MD, FRCS, FACS²⁷, Ian M. Loftus, BSc, MBChB, MD, FRCS²⁸, Armando Mansilha, MD, PhD, FIUA, FEBVS^{29,30}, Antoine Millon, MD, PhD³¹, Andrew N. Nicolaides, MS, FRCS, PhD (Hons)³², Rodolfo Pini, MD, PhD¹² , Pavel Poredos, MD, PhD³³ , Robert M. Proczka, MD, PhD³⁴, Jean-Baptiste Ricco, MD, PhD, FEBVS³⁵, Thomas S. Riles, MD, FACS³⁶, Peter Arthur Ringleb, MD³⁷, Tatjana Rundek, MD, PhD³⁸, Luca Saba, MD³⁹, Felix Schlachetzki, MD⁴⁰, Mauro Silvestrini, MD⁴¹, Francesco Spinelli, MD⁴², Francesco Stilo, MD, PhD⁴², Sherif Sultan, MD, FACS, FRCS, PhD⁴³, Jasjit S. Suri, PhD, MBA, FIEEE, FAIMBE, FAIUM, FSVM, FAPVS⁴⁴, Alexei V. Svetlikov, MD, PhD⁴⁵ , Clark J. Zeebregts, MD, PhD⁴⁶, and Seemant Chaturvedi, MD⁴⁷

Abstract

Despite the publication of several national/international guidelines, the optimal management of patients with asymptomatic carotid stenosis (AsxCS) remains controversial. This article compares 3 recently released guidelines (the 2020 German–Austrian, the 2021 European Stroke Organization [ESO], and the 2021 Society for Vascular Surgery [SVS] guidelines) vs the 2017 European Society for Vascular Surgery (ESVS) guidelines regarding the optimal management of AsxCS patients. The 2017 ESVS guidelines defined specific imaging/clinical parameters that may identify patient subgroups at high future stroke risk and recommended that carotid endarterectomy (CEA) should or carotid artery stenting (CAS) may be considered for these individuals. The 2020 German–Austrian guidelines provided similar recommendations with the 2017 ESVS Guidelines. The 2021 ESO Guidelines also recommended CEA for AsxCS patients at high risk for stroke on best medical treatment (BMT), but recommended against routine use of CAS in these patients. Finally, the SVS guidelines provided a strong recommendation for CEA+BMT vs BMT alone for low-surgical risk patients with >70% AsxCS. Thus, the ESVS, German–Austrian, and ESO guidelines concurred that all AsxCS patients should receive risk factor modification and BMT, but CEA should or CAS may also be considered for certain AsxCS patient subgroups at high risk for future ipsilateral ischemic stroke.

Keywords

asymptomatic carotid stenosis, best medical treatment, stroke, carotid endarterectomy, carotid artery stenting, guidelines

Introduction

Despite the release of >20 national and international guidelines over the last 25 years,^{1,2} the optimal management of patients with asymptomatic carotid stenosis (AsxCS) remains uncertain and controversial. Based on the results of past randomized controlled trials (RCTs), early guidelines provided a strong recommendation for carotid endarterectomy (CEA) over best medical treatment (BMT) alone for patients with ≥ 60 –70% AsxCS provided perioperative stroke/death rates are <3%.^{1,2} However, subsequent improvements in BMT have caused a shift towards a more conservative and selective approach for AsxCS patients.^{1,2}

An earlier systematic review of 28 AsxCS guidelines demonstrated that 24/28 (86%) guidelines endorsed CEA for 50% to 99% average-surgical risk AsxCS patients, recommending either that CEA should or may be provided. Of the 27 guidelines that provided recommendations for carotid artery stenting (CAS) for AsxCS patients, 17/27 (63%) endorsed CAS by recommending that CAS should

(2 guidelines) or may be provided (15 guidelines).² In 8 other guidelines (30%), CAS was explicitly not recommended for average surgical risk AsxCS patients, advising that it should not be performed routinely.² Only one guideline endorsed BMT alone for AsxCS patients by advising that BMT alone may be provided.²

The definition of BMT has improved considerably since the landmark RCTs.³ In addition to recommending a healthy and balanced Mediterranean diet, lifestyle changes (e.g., regular moderate exercise and weight loss) are now strongly recommended for all AsxCS patients.³ Advanced smoking cessation techniques are available, including nicotine replacement therapy (e.g., nicotine gums/patches) and pharmacological agents (such as varenicline or bupropion).³ High-intensity statin treatment together with addition of ezetimibe, fibrate or a pro-protein convertase subtilisin/kexin type 9 (PCSK-9) inhibitor are essential to reduce low density lipoprotein cholesterol (LDL-C) levels to <70 mg/dl.³ A recent guideline from the European Society of Cardiology recommends an LDL-C target of <55 mg/dl for diabetics and other high-risk patients.⁴

¹Department of Vascular Surgery, Central Clinic of Athens, Athens, Greece

²Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London, UK

³Vascular Centre, Nuova Villa Claudia, Rome, Italy

⁴Division of Vascular Surgery, Vascular Institute of New York, Brooklyn, NY, USA

⁵Department of Radiology, University of Utah, Salt Lake City, UT, USA

⁶Department of Radiology, Medical Imaging Center, University Medical Center Groningen, Groningen, The Netherlands

⁷Division of Vascular and Endovascular Surgery, St Elizabeth's Medical Center, Boston, MA, USA

⁸Inova Heart and Vascular Institute, Inova Alexandria Hospital, Alexandria, VA, USA

⁹Division of Vascular and Endovascular Surgery, Yale University School of Medicine, New Haven, CT, USA

¹⁰Section of Vascular Surgery, Imperial College and Imperial Healthcare NHS Trust, London, UK

¹¹Department for Vascular and Endovascular Surgery, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany

¹²Vascular Surgery, University of Bologna "Alma Mater Studiorum", Policlinico S. Orsola Malpighi, Bologna, Italy

¹³Department of Vascular Surgery, University of Lisbon, Lisbon Academic Medical Center, Lisbon, Portugal

¹⁴Department of Vascular Surgery, Medical University of Innsbruck, Innsbruck, Austria

¹⁵Department of Vascular Surgery, "Attikon" University Hospital, National and Kapodistrian University of Athens, Athens, Greece

¹⁶Division of Vascular and Endovascular Surgery, Mayo Clinic, Rochester, MN, USA

¹⁷Queensland Research Centre for Peripheral Vascular Disease, James Cook University and Townsville University Hospital, Townsville, Queensland, Australia

¹⁸Department of Radiology, Weill Cornell Medicine, New York, NY, USA

¹⁹Department of Advanced Cardiopulmonary Therapies and Transplantation, The University of Texas Health Science Centre at Houston, Houston, TX, U.S.A.

²⁰Department of Vascular Surgery, University of Patras Medical School, Patras, Greece

²¹First Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece

²²Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria

²³CARIM School for Cardiovascular Disease, Maastricht University, Maastricht, The Netherlands

²⁴Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

²⁵Vascular Surgery Department, IRCSS MultiMedica Hospital, Castellanza, Italy

²⁶Department of Surgery, Uniformed Services University, Bethesda, MD, USA

²⁷Athens Vascular Research Center, Athens, Greece

²⁸St George's Vascular Institute, St George's University London, London, UK

²⁹Faculty of Medicine of the University of Porto, Porto, Portugal

³⁰Department of Angiology and Vascular Surgery, Hospital de S. Joao, Porto, Portugal

³¹Department of Vascular and Endovascular Surgery, Louis Pradel Hospital, Hospices Civils de Lyon, France

³²Department of Surgery, University of Nicosia Medical School, Nicosia, Cyprus

³³Department of Vascular Disease, University Medical Centre Ljubljana, Slovenia

³⁴1st Department of Vascular Surgery, Medicover Hospital, Warsaw, Poland

³⁵Department of Clinical Research, University of Poitiers, CHU de Poitiers, Poitiers, France

³⁶Department of Surgery, Division of Vascular Surgery, New York University Langone Medical Centre, New York, NY, USA

³⁷Department of Neurology, University Hospital Heidelberg, Germany

³⁸Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA

³⁹Department of Radiology, Azienda Ospedaliera Universitaria Di Cagliari, Cagliari, Italy

⁴⁰Department of Neurology, University of Regensburg, Regensburg, Germany

⁴¹Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Ancona, Italy

⁴²Vascular Surgery Division, Campus Bio-Medico University of Rome, Rome, Italy

⁴³Western Vascular Institute, Department of Vascular and Endovascular Surgery, University Hospital Galway, National University of Ireland, Galway, Ireland

⁴⁴Stroke Diagnosis and Monitoring Division, AtheroPointTM, Roseville, USA

⁴⁵Division of Vascular and Endovascular Surgery, North-Western Scientific Clinical Center of Federal Medical Biological Agency of Russia, St Petersburg, Russia

⁴⁶Division of Vascular Surgery, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

⁴⁷Department of Neurology & Stroke Program, University of Maryland School of Medicine, Baltimore, MD, USA

Corresponding Author:

Kosmas I. Paraskevas, Department of Vascular Surgery, Central Clinic of Athens, 24, Alexander Papagou street, Neo Irakleio I 4122, Athens, Greece. Email: paraskevask@hotmail.com

A 2020 article compared the 2011 Society for Vascular Surgery (SVS)⁵ vs the 2017 European Society for Vascular Surgery (ESVS)⁶ guidelines for the management of AsxCS patients in an attempt to identify which AsxCS patient subgroups should be considered for a prophylactic CEA/CAS.⁷ In addition to receiving risk factor modification, lifestyle measures and BMT for all AsxCS patients, a prophylactic carotid intervention should be considered for young AsxCS patients in centers with documented low perioperative death/stroke rates provided they have ≥ 1 clinical/imaging features associated with an increased risk for late stroke.⁷

A multidisciplinary consensus statement recognized that not all AsxCS patients carry the same stroke risk⁸; it was thus supported that the therapeutic approach for AsxCS patients may need to be individualized and counterbalanced against the general condition of each patient, their personal preferences and the potential long-term benefits.⁸

Recently, three new guidelines for the management of AsxCS patients have been released, namely, the 2020 German–Austrian,⁹ the 2021 European Stroke Organization (ESO),¹⁰ and the 2021 SVS Guidelines.¹¹ The aim of this multidisciplinary document is to compare the recommendations for the optimal management of AsxCS patients between the most recent international guidelines^{6,9–11} (Table 1).

The 2017 ESVS Guidelines

The 2017 ESVS Guidelines were prepared by a multidisciplinary Writing Group including vascular surgeons, stroke physicians, vascular neurologists, and vascular specialists.⁶ The European Society of Cardiology (ESC) system was used for grading levels of evidence and class of recommendation. Each recommendation was reviewed and discussed by all members. If there was no unanimous agreement, the wording, grade and level of evidence of the recommendation was reached via a majority vote.⁶

The 2017 ESVS Guidelines Working Group recognized the improvements in BMT and acknowledged the fact that for CEA/CAS to be beneficial for AsxCS individuals, the predicted patient survival should exceed 5 years and 30-day stroke/death rates should be $< 3\%$.⁶ The ESVS Guidelines Working Group underlined the need to develop clinical and imaging parameters to identify a smaller cohort of AsxCS patients at higher stroke risk on BMT alone in whom CEA/CAS might be targeted. They provided a weak recommendation for CEA to be considered in the presence of ≥ 1 imaging characteristics that may be associated with an increased risk of late ipsilateral stroke (e.g., silent infarction on CT/MRI, stenosis progression, a large plaque area, large juxtaluminous black area on computerized plaque analysis, plaque echolucency, intraplaque hemorrhage on MRI, impaired cerebrovascular reserve, spontaneous embolization on transcranial Doppler monitoring, and others), provided the patient's life expectancy exceeds 5 years and perioperative stroke/death rates are $< 3\%$ (Class IIa; Level of Evidence: B).⁶ The ESVS Guidelines also gave a

weaker recommendation for CAS as an alternative to CEA in average surgical risk patients with 60–99% AsxCS in the presence of ≥ 1 imaging characteristics that may be associated with an increased risk for late ipsilateral stroke, provided the documented perioperative stroke/death rates are $< 3\%$ and the patient's life expectancy exceeds 5 years.⁶ The 2017 ESVS Guidelines were the first to define imaging and clinical parameters able to separate patient subgroups at higher and lower future stroke risk and to suggest that a prophylactic intervention should be considered for high-risk patient subgroups.

Irrespective of the decision to offer an intervention, the ESVS Guidelines recommended a healthy diet, smoking cessation and physical activity (Class I; Level of Evidence: B), 75–325 mg aspirin (Class I; Level of Evidence: A) and statin treatment (Class I; Level of Evidence: A) for all AsxCS patients.⁶ They recommended that LDL-C levels should be lowered to < 70 mg/dl (< 1.8 mmol/l) or decreased by $\geq 50\%$ if the initial LDL-C level is between 70 and 135 mg/dl (1.8–3.5 mmol/l) either by 40–80 mg atorvastatin or 20–40 mg rosuvastatin. These recommendations were based on the 2017 ESC Guidelines,¹² which were released in collaboration with the ESVS. Finally, they recommended anti-hypertensive treatment to maintain long-term blood pressure $< 140/90$ mmHg (Class I; Level of Evidence: A) and strict blood glucose control in diabetic patients (Class I; Level of Evidence: C).⁶

The 2020 German–Austrian Guidelines

The 2020 multidisciplinary German–Austrian guidelines⁹ updated the 2013 guidelines.¹³ Overall, 21 medical societies and organizations were involved in this revision (e.g., the German Vascular Society, the German Stroke Society, the German Society of Neurology, the German Society of Angiology/Vascular Medicine, and the Austrian Union of Vascular Medicine).⁹ Each society/organization was entitled to cast 1 vote on every decision. All recommendations were agreed at a consensus conference or by means of a structured Delphi consensus.⁹ A systematic literature search was carried out focusing on guidelines published from 2014 onwards, systematic reviews/meta-analyses published from 2011 onwards, RCTs, cohort and case-control studies (if the latter were relevant to decision-making or if no systematic reviews/guidelines were available for a particular topic).⁹

The recommendations supporting an action were classified as: (i) “strongly recommended,” (ii) “recommended/should be considered,” (iii) “open recommendation/may be considered,” and, (iv) “expert consensus.” The recommendations against the use of an intervention were classified either as “not recommended” or as “definitely not recommended.”⁹

Regarding the conservative approach of AsxCS patients, the German–Austrian guidelines provided a strong recommendation for risk factor modification and lifestyle measures (including smoking cessation, adoption of exercise, and

Table 1. Recommendations of recent guidelines for the management of patients with asymptomatic carotid stenosis.

Guideline	Recommendations	Class/Strength of recommendation (level of Evidence)
2017 ESVS ⁶	● A healthy diet, smoking cessation, and physical activity are recommended for all AsxCS patients	Class I (B)
	● Low-dose aspirin (75–325 mg) is recommended for AsxCS patients for prevention of late cardiovascular events	Class I (A)
	● Clopidogrel 75 mg/day should be considered in AsxCS patients if aspirin tolerant	Class IIa (C)
	● Statins are recommended for AsxCS patients for long-term prevention of stroke, MI and cardiovascular events	Class I (A)
	● Antihypertensive treatment is recommended for hypertensive AsxCS patients to maintain BP < 140/90 mmHg	Class I (A)
	● In diabetic patients with AsxCS, strict glycemic control is recommended	Class I (C)
	● In “average surgical risk” patients with a 60–99% AsxCS, CEA should be considered in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and the patient’s life expectancy exceeds 5 years	Class IIa (B)
	● In “average surgical risk” patients with a 60–99% AsxCS in the presence of one or more imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, CAS may be an alternative to CEA, provided documented perioperative stroke/death rates are <3% and the patient’s life expectancy exceeds 5 years	Class IIb (B)
2020 German–Austrian ⁹	● All AsxCS patients should be advised to quit smoking, exercise regularly, and have a balanced diet	Strongly recommended (2a)
	● All patients with ≥50% AsxCS should receive aspirin 100 mg/day, provided the bleeding risk is low	Strongly recommended (2a)
	● All patients with ≥50% AsxCS should take a statin for long-term prevention of cardiovascular events	Expert consensus
	● CEA should be considered for patients with 60–99% AsxCS provided there is no increased surgical risk and ≥1 clinical/imaging findings are available that are associated with an increased risk of future carotid-related stroke	Recommended (I)
	● CAS may be considered for patients with 60–99% AsxCS provided there is no increased procedural risk and ≥1 clinical/imaging findings are available that are associated with an increased risk of future carotid-related stroke	Open recommendation (2a)
	● The periprocedural stroke/death rate should be as low as possible for CEA/CAS of AsxCS. The in-hospital stroke/death rate should be monitored by expert neurologists and should not exceed 2%	Strongly recommended (2a)
2021 ESO ¹⁰	● CEA is recommended in patients with ≥60% AsxCS considered to be at increased risk of stroke on BMT alone	Strong (moderate)
	● The committee recommended against CAS as a routine alternative to BMT alone for AsxCS patients	Weak (very low)
	● In AsxCS patients in whom revascularization is considered to be appropriate, CEA is recommended over CAS as the treatment of choice	Weak (moderate)
2021 SVS ¹¹	● In low-surgical risk patients with ≥70% AsxCS, CEA plus BMT is recommended over BMT alone for the long-term prevention of stroke and death provided the patient has a 3–5 years of life-expectancy and perioperative stroke/death rates are ≤3%	Grade I (B)
	● There are insufficient data to recommend transfemoral CAS as primary therapy for patients with ≥70% AsxCS	Expert consensus
	● High-intensity statin treatment is recommended for AsxCS patients ≤75 years and moderate-intensity statin treatment for individuals >75 years or patients who do not tolerate the high-intensity statin treatment	Expert consensus
	● Antiplatelet treatment, smoking cessation, antihypertensive treatment aiming at maintain the blood pressure below 130/80 mmHg and tight glucose control in diabetic patients aiming at maintaining the hemoglobin A _{1c} <7% are recommended for all AsxCS patients	Expert consensus

ESVS, European Society for Vascular Surgery; AsxCS, asymptomatic carotid stenosis; MI, myocardial infarction; BP, blood pressure; BMT, best medical treatment; CEA, carotid endarterectomy; CAS, carotid artery stenting; ESO, European Stroke Organization; SVS, Society for Vascular Surgery.

balanced wholefood nutrition).⁹ All AsxCS patients should receive aspirin 100 mg/day and statins for long-term prevention of cardiovascular events. Similar with the 2017 ESVS Guidelines,⁶ they recommended that LDL-C levels should be lowered to <70 mg/dl (<1.8 mmol/l) or decreased by $\geq 50\%$ if the initial LDL-C level is between 70 and 135 mg/dl (1.8–3.5 mmol/l). For “high-risk” atherosclerosis patients, they recommended lowering LDL-C levels <50 mg/dl. Finally, they recommended that conditions like diabetes mellitus and hypertension should be treated according to current guidelines.⁹

Similar with the 2017 ESVS guidelines,⁶ the 2020 German–Austrian guidelines recommended that CEA should be considered and CAS may be considered for average surgical/average-procedural risk patients provided these patients had ≥ 1 clinical/imaging findings that are associated with an increased risk of future carotid-related stroke.⁹ However, the 2020 German–Austrian guidelines were the first to recommend lowering the threshold for perioperative/periprocedural stroke risk from <3% to <2%.⁹

The 2021 ESO Guidelines

A multidisciplinary Module Working Group consisting of 12 experts in vascular neurology, vascular surgery, and neuroradiology prepared the 2021 ESO guidelines.¹⁰ The guidelines were developed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology.¹⁰ A series of Population, Intervention, Comparator, Outcome (PICO) questions were developed; 4 for the comparison of CEA vs best medical therapy (BMT) alone, 4 for the comparison of CAS vs BMT alone, and 11 PICO questions for the comparison of CAS vs CEA in separate trials in AsxCS individuals and in patients with symptomatic carotid stenosis.¹⁰

Regarding the conservative treatment of AsxCS patients, the 2021 ESO Guidelines¹⁰ endorsed the 2017 ESC/2017 ESVS Guidelines and recommended that LDL-C levels should be lowered to <70 mg/dl (<1.8 mmol/l) or decreased by $\geq 50\%$ if the initial LDL-C level is between 70 and 135 mg/dl (1.8–3.5 mmol/l).¹² Regarding the invasive management of AsxCS patients, all 12 experts agreed that in selected patients with $\geq 60\%$ AsxCS and an expected survival of ≥ 5 years, who are considered to be at an increased risk of stroke on BMT alone, CEA was suggested after careful consideration of the risks and benefits at a multidisciplinary meeting.¹⁰ Importantly, this recommendation was independent of sex and stenosis severity. Furthermore, the committee recommended against CAS as a routine alternative to BMT alone for AsxCS patients.¹⁰ Similar with the 2020 German–Austrian guidelines,⁹ all 12 experts agreed that the independently assessed risk of in-hospital stroke or death following CEA or CAS for AsxCS should be as low as possible and ideally <2%.¹⁰

Similar with the 2017 ESVS Guidelines,⁶ the 2021 ESO guidelines recognized that BMT has evolved considerably since the landmark RCTs were carried out (e.g., wider

use of statins and adoption of lifestyle measures) and therefore downgraded the overall level of evidence of their recommendations.¹⁰

The 2021 SVS Guidelines

The SVS selected a writing group consisting of vascular surgeons with an interest in the management of patients with carotid artery stenosis.¹¹ The most important and/or controversial issues and questions were identified and addressed in the revised Clinical Practice Guidelines.¹¹ Each topic area was discussed and summary recommendations reflecting the unanimous opinion of the Writing Group were reached by consensus.¹¹

The 2021 SVS Guidelines Writing Group used the GRADE approach to rate the certainty of evidence and grade the strength of recommendations.¹¹ Recommendations were categorized as “strong” (GRADE 1) or “weak (conditional)” (GRADE 2) on the basis of the certainty of evidence, the balance between desirable and undesirable effects, the patients’ characteristics and preferences, as well as other factors.¹¹

The SVS Guidelines Committee recognized the fact that the question of whether modern BMT (including statins) is equivalent or superior to CEA or CAS has not yet been addressed in well-designed, appropriately funded, prospective, multicentre RCTs.¹¹ Nevertheless, it was accepted that patients undergoing CEA on lipid-lowering medications had a lower stroke incidence compared with those not on lipid-lowering drugs. Statins were therefore strongly recommended for AsxCS patients whether managed conservatively or scheduled for a carotid intervention. Furthermore, a strong recommendation was provided for CEA plus BMT over BMT alone for patients at low-surgical risk with $\geq 70\%$ AsxCS documented by validated duplex ultrasound or CT angiography for long-term prevention of stroke and death provided the patient has a 3- to 5-years life expectancy and perioperative stroke/death rates are $\leq 3\%$ (Grade I; Level of Evidence: B).¹¹ Finally, the 2021 SVS Guidelines concluded that there is insufficient data to recommend transfemoral CAS as primary therapy for patients with $\geq 70\%$ AsxCS.¹¹

The 2021 SVS¹¹ Guidelines were largely similar with the 2017 ESVS Guidelines,⁶ with 2 notable exceptions.¹⁴ The first was the recommendation regarding staged/synchronous CEA/CAS in patients with a unilateral 70–99% ACS scheduled for coronary artery bypass grafting (CABG) procedures and the second was the recommendation for CEA in ACS patients (routine¹¹ vs selective⁶ recommendation).¹⁴

Regarding the conservative treatment of AsxCS patients, the SVS released a separate implementation document.¹⁵ They recommended high-intensity statin treatment (atorvastatin 40–80 mg/day or rosuvastatin 20–40 mg/day) for AsxCS patients ≤ 75 years and moderate-intensity statin treatment (atorvastatin 10–20 mg/day or simvastatin 20–40 mg/day or rosuvastatin 5–10 mg/day or fluvastatin XL 80 mg/day or lovastatin 40 mg/day or pitavastatin 2–4 mg/day or pravastatin

40–80 mg/day or fluvastatin 40 mg twice daily) for individuals >75 years or patients who do not tolerate the high-intensity statin treatment.¹⁵ In addition, they recommended antiplatelet treatment, smoking cessation, antihypertensive treatment aiming at maintain the blood pressure below 130/80 mmHg and tight glucose control in diabetic patients aiming at maintaining the hemoglobin A_{1c} <7%.¹⁵

Discussion

The role of BMT in the management of AsxCS patients is undisputable. Nevertheless, there is a clear need for individual stroke risk stratification and appropriate patient selection for whom a prophylactic carotid intervention should or may be considered.^{6,8-11} Individual patient needs and characteristics, including plaque morphology assessment, identifying established markers of plaque vulnerability or transcranial Doppler detection of microemboli, should be taken into account by physicians. A recent meta-analysis demonstrated that the presence of MRI-detected intraplaque hemorrhage is associated with an increased risk of stroke even in patients with <50% AsxCS.¹⁶ The risks and benefits of an intervention compared with BMT alone should be communicated to the patient.⁸

Patient compliance with intensive BMT in real-world settings is an under-recognized and under-appreciated issue. A large percentage of patients cannot quit smoking.^{17,18} Drug discontinuation due to side-effects or intolerance is also quite common with some drugs (e.g., statins).^{19,20} Up to nearly 30% of patients may also be resistant to clopidogrel or aspirin.²¹ Drug resistance/discontinuation rates among AsxCS patients are important limitations in real-world contemporary BMT practices that have a negative effect on effective stroke prevention strategies.

Centralization of CEA/CAS procedures is probably necessary to optimize outcomes. A prospective, multicenter (n = 36) study from China, the Revascularization of Extracranial Carotid Artery Stenosis (RECAST) trial, demonstrated that AsxCS patients offered CEA in low-volume centers received suboptimal medical therapy preoperatively compared with high-volume centers, including aspirin (73.0 vs 88.7%, respectively; P <.001) and statins (25.6 vs 34.9%, respectively; P =.008).²² A similar analysis from the United States using the Vascular Quality Initiative database and including patients undergoing CEA (n = 71 283) and CAS (n = 12 053) between 2012 and 2017 demonstrated that around 10–12% of patients did not receive an antiplatelet agent preoperatively, whereas approximately 20% did not receive a statin.²³

The recently published Asymptomatic Carotid Surgery Trial (ACST)-2 reported outcomes in 3625 patients randomly allocated between January 15, 2008 and December 31, 2020 to CAS (n = 1811) or CEA (n = 1814).²⁴ A disabling stroke or death occurred in about 1% of the procedures (15 patients allocated to CAS and 18 to CEA), while another 2% of the patients suffered a non-disabling periprocedural stroke (48 CAS and 29 CEA patients).²⁴ Kaplan-Meier estimates of

5-year outcomes were 2.5% in each group for fatal or disabling stroke. ACST-2 demonstrated that stroke or death is similarly uncommon after both CAS and CEA, while the long-term effects of the two carotid revascularization procedures on fatal or disabling stroke are comparable.²⁴

It is important to note that the data and the available evidence for CAS refer only to transfemoral CAS. Transcarotid artery revascularization (TCAR) is a novel approach which is quickly gaining support.²⁵⁻²⁷ Current evidence suggests that TCAR is associated with similar stroke/death rates with CEA and with better outcomes compared with transfemoral CAS.²⁵⁻²⁷ However, TCAR is not yet widely available. Furthermore, so far there is no available data for TCAR from RCTs. Recent pooled data indicate that in asymptomatic patients the results for TCAR are better than in symptomatic patients.²⁸ The emerging role and the possible potential of TCAR for the treatment of carotid patients was recognized in the most recent guidelines, the 2021 ESO¹⁰ and 2021 SVS¹¹ guidelines. However, both guidelines admitted that it is premature to make any solid recommendations at this stage.

A possible limitation of all current guidelines is the lack of a proper and uniform definition of terms like “low-surgical” or “average-surgical” risk. Another limitation in the future stroke risk stratification proposed is that not all centers employ multimodality imaging techniques including transcranial Doppler detection of microemboli, carotid plaque characteristics on MRI, and impaired cerebrovascular reserve. Furthermore, most of these markers are not fully validated for accurate independent stroke risk prediction. Often patients are followed-up in the same institute with the same protocols and often by the same technologist. Carotid ultrasound is easier and less financial demanding than many of the complex imaging techniques.

Progression of carotid stenosis on Duplex ultrasound is one of the suggested imaging characteristics in the 2017 ESVS⁶ and the 2020 German–Austrian⁹ guidelines to consider a prophylactic carotid intervention in AsxCS patients. In support of this recommendation, a recent systematic review and meta-analysis (n = 23 studies; 8419 patients) demonstrated that the risk of ipsilateral stroke increases significantly with the degree of stenosis in patients with ACS.²⁹ More specifically, this meta-analysis revealed a linear association of stroke risk with degree of stenosis (P <.0001), with a >2-fold higher risk for patients with 70–99% vs 50–69% stenosis (odds ratio [OR]: 2.1; 95% confidence interval [CI]: 1.7–2.5; P <.0001) and a 2.5-fold risk for patients with 80–99% vs 50–79% stenosis (OR: 2.5; 95% CI: 1.8–3.5; P <.0001).²⁹ This meta-analysis²⁹ was discussed in detail in the 2021 SVS guidelines^{11,15} and is a reason for the change in their recommendations on when to consider intervention.

Finally, the CAS and CEA techniques (e.g., eversion vs patch CEA or transfemoral CAS vs TCAR) differ with respect to outcomes. The differences in outcomes between the various techniques (as well as from one center to another) may justify a different approach for individual patients. A practice

Table 2. Summary of recommendations of recent guidelines.

Guideline	BMT	CEA	CAS
2017 ESVS ⁶	For all AsxCS patients	Recommended for AsxCS patients at high stroke risk	Weak recommendation for selected AsxCS patients
2020 German–Austrian ⁹	For all AsxCS patients	Recommended for AsxCS patients at high stroke risk	Weak recommendation for selected AsxCS patients
2021 ESO ¹⁰	For all AsxCS patients	Recommended for AsxCS patients at high stroke risk	Recommended against CAS routinely
2021 SVS ¹¹	For all AsxCS patients	Recommended over BMT for AsxCS patients	No recommendation

ESVS, European Society for Vascular Surgery; ESO, European Stroke Organization; SVS, Society for Vascular Surgery; BMT, best medical treatment; CEA, carotid endarterectomy; CAS, carotid artery stenting; AsxCS, asymptomatic carotid stenosis.

recommendation without taking into account individual physician's and center's expertise, as well as individual patient preferences and needs, may not be generalizable. In addition, the recent guidelines have not made any recommendation based on patient age or sex. A prior guideline from a Neurology panel recommended CEA only for asymptomatic patients between 40 and 75 years.³⁰

Conclusions

All 4 recent guidelines^{6,9-11} have made considerable improvements in their recommendations for patients with severe AsxCS (Table 2). It is clear that all AsxCS patients do not have the same stroke risk. Therefore, a “one-size-fits-all” approach is neither justified nor appropriate. Although implementation of risk factor modification and BMT is essential for all AsxCS patients to reduce not only future stroke risk but also cardiac and all-cause mortality,³¹ certain AsxCS patient subgroups at high future stroke risk need to be considered for a prophylactic carotid intervention. Each patient should be considered individually and the appropriate therapeutic approach should be tailored accordingly. Besides the general recommendations of guidelines, patient preference and local surgical/institutional expertise are additional factors that play an important role in the management of AsxCS patients. Several criteria that determine the therapeutic approach of individual AsxCS patients should be strongly considered (e.g., morphological characteristics of the lesion, general health status of the patient, patient preference, and needs and expectations). A multidisciplinary approach and a direct involvement of AsxCS patients in decision-making are essential to ensure the delivery of optimal management to individuals with AsxCS. Institutional multidisciplinary team meetings may consider individual factors for increased spontaneous or procedural risk, intensifying BMT and using surrogate supplementary imaging features for increased stroke risk in AsxCS patients.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: All authors are members of the Faculty Advocating Collaborative and Thoughtful Carotid Artery Treatments (FACTCATS; available at www.FACTCATS.org) with the shared goal of

optimizing stroke prevention. The views of particular FACTCATS do not necessarily reflect the views of other FACTCATS. Dr. Gupta reports non-financial support from GE Healthcare and Siemens Medical Solutions U.S.A., Inc. Dr. Mikhailidis has given talks, acted as a consultant or attended conferences sponsored by Amgen and Novo Nordisk. Dr. Katsiki has given talks, attended conferences and participated in trials sponsored by Angelini, Astra Zeneca, Bausch Health, Boehringer Ingelheim, Elpen, Mylan, Novo Nordisk, Sanofi, and Servier. Dr. Chaturvedi is on the executive committee of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) 2 and the Asymptomatic Carotid Trial (ACT) I. The other authors have no conflicts of interest.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Kosmas I. Paraskevas  <https://orcid.org/0000-0001-6865-2919>

Mateja K. Jezovnik  <https://orcid.org/0000-0002-5317-0148>

Niki Katsiki  <https://orcid.org/0000-0003-0894-2644>

Rodolfo Pini  <https://orcid.org/0000-0001-6459-1135>

Pavel Poredos  <https://orcid.org/0000-0002-9913-1419>

Alexei V. Svetlikov  <https://orcid.org/0000-0001-8652-8778>

References

1. Paraskevas KI, Mikhailidis DP, Antignani PL, et al. Optimal management of asymptomatic carotid stenosis in 2021: the jury is still out. An international, multispecialty, expert review and position statement. *J Stroke Cerebrovasc Dis* 2022; 31: 106182. DOI: [10.1016/j.jstroke.cerebrovasdis.2021.106182](https://doi.org/10.1016/j.jstroke.cerebrovasdis.2021.106182). Online ahead of print
2. Abbott AL, Paraskevas KI, Kakkos SK, et al. Systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis. *Stroke* 2015; 46: 3288–3301.
3. Paraskevas KI, Mikhailidis DP, Veith FJ, et al. Definition of best medical treatment in asymptomatic and symptomatic carotid artery stenosis. *Angiology* 2016; 67: 411–419.
4. Visseren FLJ, Mach F, Smulders YM et al. and ESC Scientific Document Group, 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021; 42: 3227–3337.

5. Ricotta JJ, AbuRahma A, Ascher E et al. and Society for Vascular Surgery. Updated society for vascular surgery guidelines for management of extracranial carotid disease. *J Vasc Surg* 2011; 54: e1–e31.
6. Naylor AR, Ricco J-B, de Borst GJ, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the european society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg* 2018; 55: 3–81.
7. Paraskevas KI, Veith FJ, AbuRahma AF, et al. A comparison of the society for vascular surgery and the european society for vascular surgery guidelines to identify which asymptomatic carotid patients should be offered a carotid endarterectomy. *J Vasc Surg* 2020; 72: 2149–2152.
8. Paraskevas KI, Mikhailidis DP, Baradaran H, et al. Management of patients with asymptomatic carotid stenosis may need to be individualized: a multidisciplinary call for action. *J Stroke* 2021; 23: 202–212.
9. Eckstein H-H, Kühnl A, Berkefeld J, et al. Diagnosis, treatment and follow-up in extracranial carotid stenosis. *Dtsch Arztebl Internat* 2020; 117: 801–807.
10. Bonati LH, Kakkos S, Berkefeld J, et al. European stroke organisation guideline on endarterectomy and stenting for carotid artery stenosis. *European Stroke Journal* 2021; 6: I–XLVII. DOI: [10.1177/239698732110122121](https://doi.org/10.1177/239698732110122121).
11. AbuRahma AF, Avgerinos ED, Chang RW, et al. Society for vascular surgery clinical practice guidelines for management of extracranial cerebrovascular disease. *J Vasc Surg* 2022; 75: 4S–22S.
12. Aboyans V, Ricco JB, Bartelink MEL et al. and ESC Scientific Document Group. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the European society for vascular surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European stroke organization (ESO) the task force for the diagnosis and treatment of peripheral arterial diseases of the european society of cardiology (ESC) and of the european society for vascular surgery (ESVS). *Eur Heart J* 2018; 39: 763–816.
13. Eckstein H-H, Kühnl A, Dörfler A, et al. The diagnosis, treatment and follow-up of extracranial carotid stenosis. *Dtsch Arztebl Int* 2013; 110: 468–476.
14. Naylor AR. More unites us than divides us. *J Vasc Surg* 2022; 75: 2S–3S.
15. AbuRahma AF, Avgerinos ED, Chang RW, et al. The society for vascular surgery implementation document for management of extracranial cerebrovascular disease. *J Vasc Surg* 2022; 75: 26S–98S.
16. Schindler A, Schinner R, Altaf N, et al. prediction of stroke risk by detection of hemorrhage in carotid plaques. *JACC Cardio-vasc Imaging* 2020; 13: 395–406.
17. McHugh SM, Eisenberg N, Montbriand J, et al. Smoking cessation rates among patients undergoing vascular surgery in a canadian center. *Ann Vasc Surg* 2017; 45: 138–143.
18. Almaaitah S, Ciemins EL, Joshi V, et al. Variation in patient smoking cessation rates among health-care providers. *Chest* 2020; 158: 2038–2046.
19. Paraskevas KI, Mikhailidis DP and Veith FJ. Optimal statin type and dosage for vascular patients. *J Vasc Surg* 2011; 53: 837–844.
20. Banach M and Mikhailidis DP. Statin Intolerance. *Cardiol Clin* 2018; 36: 225–231.
21. Alakbarzade V, Huang X, Ster IC, et al. High on-clopidogrel platelet reactivity in ischaemic stroke or transient ischaemic attack: systematic review and meta-analysis. *J Stroke Cerebrovasc Dis* 2020; 29: 104877.
22. Yang B, Ma Y, Wang T, et al. Carotid endarterectomy and stenting in a chinese population: safety outcome of the revascularization of extracranial carotid artery stenosis trial. *Transl Stroke Res* 2021; 12: 239–247.
23. Dansey KD, Pothof AB, Zettervall SL, et al. Clinical impact of sex on carotid revascularization. *J Vasc Surg* 2020; 71: 1587–1594.
24. Halliday A, Bulbulia R, Bonati LH et al. and ACST-2 Collaborative Group. Second asymptomatic carotid surgery trial (ACST-2): a randomised comparison of carotid artery stenting versus carotid endarterectomy. *Lancet* 2021; 398: 1065–1073.
25. Naazie IN, Cui CL, Osaghae I, et al. A systematic review and meta-analysis of transcarotid artery revascularization with dynamic flow reversal versus transfemoral carotid artery stenting and carotid endarterectomy. *Ann Vasc Surg* 2020; 69: 426–436.
26. Mehta A, Patel PB, Bajakian D, et al. Transcarotid artery revascularization versus carotid endarterectomy and transfemoral stenting in octogenarians. *J Vasc Surg* 2021; 74: 1602–1608.
27. Malas MB, Elsayed N, Naazie I, et al. Propensity score-matched analysis of 1-year outcomes of transcarotid revascularization with dynamic flow reversal, carotid endarterectomy, and transfemoral carotid artery stenting. *J Vasc Surg* 2022; 75: 213–222.
28. Galyfos GC, Tsoutsas I, Konstantopoulos T, et al. Editor's Choice - early and late outcomes after transcarotid revascularisation for internal carotid artery stenosis: a systematic review and meta-analysis. *Eur J Vasc Endovasc Surg* 2021; 61: 725–738.
29. Howard DPJ, Gaziano L, Rothwell PM. and Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review, and meta-analysis. *Lancet Neurol* 2021; 20(3): 193–202.
30. Chaturvedi S, Bruno A, Feasby T, et al. Carotid endarterectomy—An evidence-based review: report of the therapeutics and technology assessment subcommittee of the american academy of neurology. *Neurology* 2005; 65: 794–801.
31. Giannopoulos A, Kakkos S, Abbott A, et al. Long-term mortality in patients with asymptomatic carotid stenosis: implications for statin therapy. *Eur J Vasc Endovasc Surg* 2015; 50: 573–582.