

# Management of Patients with Asymptomatic Carotid Stenosis May Need to Be Individualized: A Multidisciplinary Call for Action

Kosmas I. Paraskevas,<sup>a</sup> Dimitri P. Mikhailidis,<sup>b</sup> Hadiyah Baradaran,<sup>c</sup> Alun H. Davies,<sup>d</sup> Hans-Henning Eckstein,<sup>e</sup> Gianluca Faggioli,<sup>f</sup> Jose Fernandes e Fernandes,<sup>g</sup> Ajay Gupta,<sup>h</sup> Mateja K. Jezovnik,<sup>i</sup> Stavros K. Kakkos,<sup>j</sup> Niki Katsiki,<sup>k</sup> M. Eline Kooi,<sup>l,m</sup> Gaetano Lanza,<sup>n</sup> Christos D. Liapis,<sup>o</sup> Ian M. Loftus,<sup>p</sup> Antoine Millon,<sup>q</sup> Andrew N. Nicolaides,<sup>r</sup> Pavel Poredos,<sup>s</sup> Rodolfo Pini,<sup>f</sup> Jean-Baptiste Ricco,<sup>t</sup> Tatjana Rundek,<sup>u</sup> Luca Saba,<sup>v</sup> Francesco Spinelli,<sup>w</sup> Francesco Stilo,<sup>w</sup> Sherif Sultan,<sup>x</sup> Clark J. Zeebregts,<sup>y</sup> Seemant Chaturvedi<sup>z</sup>

<sup>a</sup>Department of Vascular Surgery, Central Clinic of Athens, Athens, Greece

<sup>b</sup>Department of Clinical Biochemistry, Royal Free Hospital Campus, University College London Medical School, University College London (UCL), London, UK

<sup>c</sup>Department of Radiology, University of Utah, Salt Lake City, UT, USA

<sup>d</sup>Section of Vascular Surgery, Imperial College & Imperial Healthcare NHS Trust, London, UK

<sup>e</sup>Department of Vascular and Endovascular Surgery, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

<sup>f</sup>Vascular Surgery, University of Bologna "Alma Mater Studiorum", Policlinico S. Orsola Malpighi, Bologna, Italy

<sup>g</sup>Department of Vascular Surgery, University of Lisbon, Lisbon Academic Medical Center, Lisbon, Portugal

<sup>h</sup>Department of Radiology, Weill Cornell Medicine, New York, NY, USA

<sup>i</sup>Department of Advanced Cardiopulmonary Therapies and Transplantation, The University of Texas Health Science Centre at Houston, Houston, TX, USA

<sup>j</sup>Department of Vascular Surgery, University of Patras Medical School, Patras, Greece

<sup>k</sup>First Department of Internal Medicine, AHEPA University Hospital, Thessaloniki, Greece

<sup>l</sup>CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, The Netherlands

<sup>m</sup>Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

<sup>n</sup>Vascular Surgery Department, IRCSS MultiMedica Hospital, Castellanza, Italy

<sup>o</sup>Athens Vascular Research Center, Athens, Greece

<sup>p</sup>St. George's Vascular Institute, St. George's University London, London, UK

<sup>q</sup>Department of Vascular and Endovascular Surgery, Louis Pradel Hospital, Hospices Civils de Lyon, France

<sup>r</sup>Department of Surgery, University of Nicosia Medical School, Nicosia, Cyprus

<sup>s</sup>Department of Vascular Disease, University Medical Centre Ljubljana, Slovenia

<sup>t</sup>Department of Clinical Research, University of Poitiers, CHU de Poitiers, Poitiers, France

<sup>u</sup>Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL, USA

<sup>v</sup>Department of Radiology, Azienda Ospedaliera Universitaria Di Cagliari, Cagliari, Italy

<sup>w</sup>Vascular Surgery Division, Campus Bio-Medico University of Rome, Rome, Italy

<sup>x</sup>Western Vascular Institute, Department of Vascular and Endovascular Surgery, University Hospital Galway, National University of Ireland, Galway, Ireland

<sup>y</sup>Division of Vascular Surgery, Department of Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

<sup>z</sup>Department of Neurology & Stroke Program, University of Maryland School of Medicine, Baltimore, MD, USA

The optimal management of patients with asymptomatic carotid stenosis (ACS) is the subject of extensive debate. According to the 2017 European Society for Vascular Surgery guidelines, carotid endarterectomy should (Class IIa; Level of Evidence: B) or carotid artery stenting may be considered (Class IIb; Level of Evidence: B) in the presence of one or more clinical/imaging characteristics that may be associated with an increased risk of late ipsilateral stroke (e.g., silent embolic infarcts on brain computed tomography/magnetic resonance imaging, progression in the severity of ACS, a

**Correspondence:** Kosmas I.

Paraskevas

Department of Vascular Surgery,

Central Clinic of Athens, 24

Alexander Papagou Street, N. Iraklio

14122, Athens, Greece

Tel: +30-698-3133883

Fax: +30-210-3215792

history of contralateral transient ischemic attack/stroke, microemboli detection on transcranial Doppler, etc.), provided documented perioperative stroke/death rates are <3% and the patient's life expectancy is >5 years. Besides these clinical/imaging characteristics, there are additional individual, ethnic/racial or social factors that should probably be evaluated in the decision process regarding the optimal management of these patients, such as individual patient needs/patient choice, patient compliance with best medical treatment, patient sex, culture, race/ethnicity, age and comorbidities, as well as improvements in imaging/operative techniques/outcomes. The present multispecialty position paper will present the rationale why the management of patients with ACS may need to be individualized.

E-mail: [paraskevask@hotmail.com](mailto:paraskevask@hotmail.com)  
<https://orcid.org/0000-0001-6865-2919>

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## Introduction

The optimal management of patients with asymptomatic carotid stenosis (ACS) is a controversial and much debated issue. According to the 2020 Heart Disease and Stroke Statistics, each year around 800,000 Americans experience a new or recurrent stroke.<sup>1</sup> Of these, about 600,000 are first strokes, while the rest are recurrent episodes.<sup>1</sup> Projections show that by 2030, an additional 3.4 million United States adults will have suffered a stroke, representing a 20.5% increase in the prevalence from 2012.<sup>1</sup>

The global prevalence of ischemic stroke in 2017 was 82.4 million; that is, a 16.1% increase from 2007 to 2017 and a 10.1% increase from 1990 to 2017.<sup>1</sup> Furthermore, a total of 2.7 million individuals died globally of ischemic stroke in 2017.<sup>1</sup> In Europe, there are approximately 1.4 million strokes/year causing about 1.1 million deaths annually.<sup>2</sup> Around 10% to 15% of those strokes occur as a result of thromboembolism from a previously asymptomatic significant carotid stenosis.<sup>2,3</sup>

Medical treatment has improved considerably in the last 10 to 15 years.<sup>4</sup> It was thus supported that the annual risk of stroke while on current best medical treatment (BMT) alone may be declining compared with the randomized controlled trials (RCTs) performed 20 to 30 years ago.<sup>2</sup> Consequently, it was proposed that there is a need to develop clinical/imaging algorithms for identifying a smaller, but higher-risk for stroke cohort in whom carotid endarterectomy (CEA)/carotid artery stenting (CAS) might be targeted.<sup>2,5</sup> The 2017 European Society for Vascular Surgery (ESVS) guidelines for the management of patients with carotid artery stenosis recommended that in "average surgical risk" patients with a 60% to 99% ACS, CEA should (Class IIa; Level of Evidence: B) or CAS may be considered (Class IIb; Level of Evidence: B) in the presence of one or more clinical/imaging characteristics that may be associated with an increased risk

of late ipsilateral stroke, provided documented perioperative stroke/death rates are <3% and patient life expectancy is >5 years.<sup>2</sup> These clinical/imaging characteristics included silent embolic infarcts on brain computed tomography (CT)/magnetic resonance imaging (MRI), progression in the severity of ACS, a history of contralateral transient ischemic attack/stroke, microemboli detection on transcranial Doppler, the presence of intraplaque hemorrhage or plaque ulceration on MRI, reduced cerebrovascular reserve, a large plaque area (>40 mm<sup>2</sup>) on ultrasound longitudinal images and plaque echolucency as shown by a low gray scale median (<30) and presence of a large (>8 mm<sup>2</sup>) juxtaluminal hypoechoic area after image normalization of Duplex ultrasound images.<sup>2,5-7</sup>

Besides these clinical/imaging characteristics, there are additional individual, ethnic/racial, cultural or social factors that should probably be evaluated in the decision process regarding the optimal management of these patients. The current position statement considers the evidence why the optimal management of patients with ACS may occasionally need to be individualized.

## Individual characteristics to consider

Some factors/characteristics that may prompt physicians to consider individualization of the management of ACS in specific patients include.

### Individual patient needs/patient choice

Not all patients have the same lifestyle and social/cultural background. Some patients are more active, others live more sedentary lives. The management of patients with different lifestyles should be tailored to their individual needs. In addition, patients have different characters and attitudes towards their disease; individual perception and emotional attitude are im-

portant parameters.<sup>8</sup> For some patients it may be quite stressful knowing that they have a high-grade ACS, which may lead to a stroke. In contrast, others may not wish to undergo a surgical procedure.<sup>8</sup> Such individual factors, surroundings and attitudes should be taken into account when discussing the management of ACS with each patient. Patients have the right to choose if they want to undergo a procedure and accept the perioperative risk associated with CEA/CAS, or instead be managed by BMT alone.

Traditional models where all treatment decisions are made by the health professionals are no longer desired by patients and their families.<sup>9</sup> Patients want to be active participants in decision-making regarding their health and treatment choices.<sup>9</sup> A survey from the UK a few years ago regarding the management of a unilateral 70% ACS revealed that 48% of the study participants would opt for BMT alone whereas 52% preferred an intervention (30% CEA; 22% CAS).<sup>10</sup> The most common reasons for choosing BMT over an intervention were avoidance of surgery and the risk of periprocedural stroke/death.

A subgroup analysis by gender demonstrated that 43% of men and 60% of women opted for BMT.<sup>10</sup> Another 35% of men and 20% of women selected CEA, while CAS was preferred by 22% of men and 20% of women.<sup>10</sup> A subgroup analysis by age revealed that BMT was preferred by 39% of patients aged <70 years versus 55% for those ≥70 years, whereas CEA by 35% (<70 years) versus 27% (≥70 years) and CAS by 26% (<70 years) versus 18% (≥70 years), respectively. Patients with a first-degree relative who had suffered a stroke were equally likely to choose an intervention compared with individuals who did not have a similar history (52% vs. 53%, respectively).<sup>10</sup> Furthermore, a larger proportion of patients who had suffered a contralateral event chose BMT compared with those who had never had a stroke or transient ischemic attack (64% vs. 47%). Active smokers expressed a modest preference for CEA (8/21, 38%) over BMT (7/21, 33%) or CAS (6/21, 29%), while ex- and non-smokers preferred BMT (42/81, 52%) over CEA (23/81, 28%) or CAS (16/81, 20%).<sup>10</sup> Overall, the group most likely to opt for an open/endovascular intervention was male smokers under 70 years of age.<sup>10</sup>

Avoidance of surgery and the associated periprocedural risk may be valid reasons to choose BMT over CEA/CAS.<sup>10</sup> On the other hand, the lower stroke/death rates associated with CEA compared with CAS may play a pivotal role for some patients when selecting an intervention. By contrast, others opt for the less invasive CAS over CEA, placing more emphasis on the scar size, a previous positive experience with arterial stenting elsewhere (e.g., in the lower limb arteries) and the lower cranial nerve injury rates.<sup>10</sup> Thus, individual ACS patients may opt for

different treatment options using a variety of criteria.

### Individual patient culture/ethnicity/race

The decision to undergo CEA may vary by ethnicity/race. Black patients may have higher aversion scores to CEA compared with white individuals.<sup>11</sup> One of the reasons that might influence this decision to avoid CEA may be the fact that CEA does not relieve pain or prolong life, but is performed to reduce the risk of future stroke.<sup>11</sup> According to the authors,<sup>11</sup> the "risk of future stroke" may be a difficult concept to explain to some individuals.

A large study (n=890,680 patients undergoing CEA/CAS; 92.1% for ACS) identified ethnic/racial and financial disparities in the decision to be offered CEA for ACS.<sup>12</sup> Compared with white ACS patients, black (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.69 to 0.75;  $P<0.0001$ ), Hispanic (OR, 0.79; 95% CI, 0.76 to 0.82;  $P<0.0001$ ), and Asian patients (OR, 0.81; 95% CI, 0.76 to 0.82;  $P<0.0001$ ) were less likely to be offered a carotid revascularization procedure for ACS.<sup>12</sup> When adjusted for age (<65 years vs. ≥65 years), black (OR, 0.73; 95% CI, 0.69 to 0.78;  $P<0.0001$ ), and Hispanic ACS patients (OR, 0.79; 95% CI, 0.74 to 0.85;  $P<0.0001$ ) were less likely to be offered a revascularization procedure compared with white ACS patients <65 years, whereas Asian patients did not differ significantly (OR, 0.91; 95% CI, 0.78 to 1.06;  $P>0.05$ ). In contrast, for those ≥65 years, black (OR, 0.74; 95% CI, 0.71 to 0.78;  $P<0.0001$ ), Hispanic (OR, 0.79; 95% CI, 0.76 to 0.83;  $P<0.0001$ ), and Asian patients (OR, 0.77; 95% CI, 0.70 to 0.84;  $P<0.0001$ ) were all less likely to be offered a carotid revascularization procedure for ACS compared with white individuals. Finally, Medicaid (OR, 0.60; 95% CI, 0.58 to 0.64;  $P<0.0001$ ), private insurance (OR, 0.78; 95% CI, 0.77 to 0.79;  $P<0.0001$ ), and self-pay patients (OR, 0.37; 95% CI, 0.28 to 0.46;  $P<0.0001$ ) were less likely to be offered CEA for ACS compared with Medicare individuals.<sup>12</sup>

Minority patients and individuals of lower socioeconomic status have generally less access to medical care for the treatment of vascular risk factors. An analysis of data from the National Health and Nutrition Examination Surveys demonstrated that Hispanic and black patients were significantly less likely to have adequate control of hypertension and hypercholesterolemia compared with white patients.<sup>13</sup> Another study demonstrated that black patients were less likely to be aware of and controlled/treated for dyslipidemia compared with white patients.<sup>14</sup> Finally, a report from the Center for Disease Control and Prevention showed that black patients not only had higher rates of hypertension compared with white patients, but they were also less likely to have blood pressure control.<sup>15</sup>

Besides the factors associated with a patient's likelihood to be offered CEA or his/her decision to undergo CEA (which

may vary according to ethnic criteria/beliefs), another parameter which may affect individual decision-making is that CEA outcomes may vary by ethnicity/race. In the New York Carotid Artery Surgery Study (n=9,308 CEA procedures), individuals of Hispanic-Latino ethnicity undergoing CEA had considerably higher death and stroke rates compared with non-Hispanic black or non-Hispanic white patients (9.50% vs. 6.93% vs. 3.80%, respectively;  $P<0.0001$ ).<sup>16</sup> Possible explanations for these disparities in outcomes according to patient ethnicity include increased comorbidities preoperatively, poor patient selection, confounding by socioeconomic status and other non-medical factors including increased proportion of non-white patients offered CEA at low-volume institutions by less experienced surgeons.<sup>16-20</sup> Chaturvedi et al.<sup>20</sup> demonstrated that black ACS patients receiving CEA in two urban hospitals tended to have higher stroke or myocardial infarction (MI) rates compared with white individuals (15.4% vs. 5.6%,  $P=0.065$ ). In black patients who received surgery in the hospital with the lowest CEA volume, stroke or MI rates were significantly higher (20.5%,  $P<0.05$ ) compared with white patients.<sup>20</sup> The reasons for these unfavorable outcomes after CEA in black ACS patients included a higher prevalence of vascular risk factors (e.g., hypertension, diabetes, and smoking) and more women treated with CEA.<sup>20</sup> Consequently, the association between individual ethnic parameters with CEA outcomes may affect the type of treatment selected by patients or offered by physicians.

### Patient age/comorbidities

As active and well-informed participants by health professionals, patients can make their own decision about whether to undergo a prophylactic CEA. Age and comorbidities may play a key role in their decision-making (Table 1).<sup>16,21-27</sup> According to national statistics, the 5-year mortality of individuals aged 80 to 85 years is nearly 30.0% and it is higher in males than in females (40.6% vs. 23.4%, respectively;  $P<0.0001$ ).<sup>21</sup> Due to the high non-stroke-related mortality in this age group (e.g., due to cancer, respiratory causes, etc.), the net benefit of a prophylactic CEA in such elderly patients is debatable.<sup>21,28</sup> Furthermore, octogenarians and nonagenarians have been excluded from past RCTs; consequently, the number needed to treat to prevent one stroke in elderly ACS patients is unknown.<sup>28,29</sup> The need to be cautious when offering a carotid intervention to elderly patients was underlined by some authors.<sup>22,23</sup> Appropriate and rigorous patient selection for a carotid intervention is mandatory, especially in such a fragile population.<sup>24</sup>

Patients with multiple comorbidities have a high risk not only of surgical/periprocedural complications, but also of future stroke. A large study collected data from the National Surgi-

cal Quality Improvement Program (NSQIP) about preoperative risk factors for all patients undergoing CEA from 2005 to 2011 (n=44,832; 27,136 ACS patients).<sup>30</sup> A frailty Risk Analysis Index (RAI) score was developed using various comorbidities (e.g., malignant disease, congestive heart failure, shortness of breath at rest, renal insufficiency, etc.) and social parameters (e.g., functional status, type of residency [home, assisted living, nursing home], etc.).<sup>30</sup> A linear correlation was demonstrated in ACS patients undergoing CEA between increasing frailty RAI score with perioperative risk of stroke. Perioperative stroke/death rates increased with increasing frailty RAI score, at some point reaching and exceeding the perioperative stroke/death threshold of 3%.<sup>30</sup>

In another more recent (2005 to 2012) analysis of the NSQIP data, frailty was strongly associated with morbidity and mortality among patients undergoing CEA, but not CAS.<sup>31</sup> Among 37,875 patients undergoing a carotid intervention, frailty was an independent predictor of complications (23.5% vs. 7.2%, respectively;  $P<0.001$ ), mortality (5.2% vs. 1.1%, respectively;  $P=0.02$ ), failure to rescue (12.1% vs. 4.7%, respectively;  $P=0.02$ ), and 30-day readmissions (14.9% vs. 3.7%, respectively;  $P=0.03$ ) compared with non-frail patients. Consequently, the potential benefits of offering an intervention (CEA/CAS) plus BMT versus BMT alone in elderly ACS patients must be counterbalanced against the potential risks associated with each option.

The value of informed consent is crucial. Patients should not be provided data from obsolete trials such as the Asymptomatic Carotid Atherosclerosis Study (ACAS),<sup>32</sup> but instead should be counseled with the best possible information on outcomes with current BMT and surgical results. The results of an objective assessment of comorbidities by the treating physician (including patient frailty and life-expectancy) should be presented to the patient.<sup>9</sup> They need to understand the uncertainty, risks and benefits of the management of ACS.<sup>9</sup> Younger ACS patients with a longer life expectancy may prefer to have a prophylactic CEA, while older ACS patients may choose to avoid CEA/CAS.<sup>10</sup>

In an analysis of the Statutory German Quality Assurance Database on all CEAs performed between 2009 and 2014 (n=142,074; 85,738 for ACS), there was a strong association between in-hospital stroke/death rates with age.<sup>25</sup> Age was associated with a higher risk of any in-hospital stroke/death (relative risk [RR] per 10-year increase, 1.19; 95% CI, 1.14 to 1.24;  $P<0.01$ ) and a higher risk of death alone (RR, 1.68; 95% CI, 1.54 to 1.84;  $P<0.01$ ) in CEA patients. Age was also associated with a higher risk of stroke alone (RR, 1.05; 95% CI, 1.00 to 1.11;  $P<0.05$ ), but this relationship was weaker.<sup>25</sup>

A study presenting the outcomes after 22,516 CAS procedures (10,677 on symptomatic [47.4%] and 11,839 on ACS patients [52.6%]) revealed an interesting finding.<sup>33</sup> ACS patients

**Table 1.** Studies reporting outcomes of carotid revascularization procedures in elderly ACS patients

Study	Study aim/study design	Results
Studies comparing different age groups		
Halm et al. <sup>16</sup> (2009)	Analysis of the results of 9,308 CEAs by age (<70 years: 2,152 CEAs; 70–79 years: 4,958 CEAs; ≥80 years: 2,198 CEAs)	Ipsilateral stroke/death rates (≥80 vs. 70–79 years): 4.82% vs. 3.73%; <i>P</i> <0.02
Rajamani et al. <sup>22</sup> (2013)	Comparison of outcomes stratified by age (<75 vs. 75 to <80 vs. 80 to <85 vs. >85 years) among symptomatic (n=1,376) and asymptomatic (n=2,773) patients undergoing CEA	Overall mortality for patients <75 vs. >85 years: 0.1% vs. 1.7%; <i>P</i> =0.002 In-hospital death/stroke/MI for patients <75 vs. >85 years: 2.2% vs. 5.6%; <i>P</i> =0.003
Schmid et al. <sup>25</sup> (2017)	Analysis of 142,074 CEAs (85,738 for ACS; 56,336 for symptomatic carotid stenosis) from the Statutory German Quality Assurance Database between 2009–2014	Crude risk of any in-hospital stroke/death for ACS patients aged <65, 65–69, 70–74, 75–79, and ≥80 years: 1.0% vs. 1.3% vs. 1.3% vs. 1.5% vs. 1.9%, respectively ( <i>P</i> <0.001 for trend)
Studies reporting outcomes in the elderly		
Rinckenbach et al. <sup>27</sup> (2007)	Evaluation of outcomes after CEA in 57 ACS patients ≥80 years old	Perioperative ipsilateral stroke/death rate: 8.8% Kaplan-Meier 5-year survival: 52%
De Rango et al. <sup>21</sup> (2012)	Assessment of the clinical relevance of carotid revascularization procedures in patients ≥80 years old (n=348 procedures in 323 patients; 179 ACS patients)	All-cause 5-year mortality: 65.4% All-cause 5-year mortality in ACS patients: 67.8%
Salomon du Mont et al. <sup>24</sup> (2014)	Overview of the results of 132 CEAs in 118 patients ≥80 years (50 CEAs on symptomatic; 82 CEAs on ACS patients)	Ipsilateral stroke/death rate for ACS patients: 4.88%
Wach et al. <sup>23</sup> (2015)	Evaluation of CAS safety and efficacy in patients aged ≥90 years (n=21 CAS procedures in 20 patients; 11 symptomatic; 9 ACS patients [10 CAS procedures])	Perioperative stroke rate for ACS patients: 10% 50% of ACS patients were alive at 47 months
Hobbs et al. <sup>26</sup> (2020)	Analysis of CEA outcomes offered to 33 ACS patients ≥90 years	30-day mortality rate: 6.1% Median survival: 29.4 months

ACS, asymptomatic carotid stenosis; CEA, carotid endarterectomy; MI, myocardial infarction; CAS, carotid artery stenting.

offered CAS had periprocedural death, stroke and MI rates of 1.0% (95% CI, 0.9 to 1.2), 2.3% (95% CI, 2.1 to 2.6), and 2.2% (95% CI, 2.0 to 2.5), respectively. Nevertheless, mortality rates during a mean follow-up time of 2 years for ACS patients were as high as 27.7% (95% CI, 26.4 to 28.9). For ACS patients aged ≥80 years in particular (n=7,255 patients), a staggering mean 2-year mortality of 41.5% (95% CI, 39.7 to 43.3) was reported.<sup>33</sup> Therefore, almost half of those ACS patients aged ≥80 years did not live long enough to obtain benefit from CEA in terms of stroke prevention.<sup>33</sup> Similar results were reported in a more recent single-center study discussing the outcomes of CEA in ACS nonagenarians.<sup>26</sup> Based on the reported median postoperative survival of 29 months in their group of ACS nonagenarians, the authors advised that the enthusiasm for offering CEA to elderly ACS individuals should be tempered by the low survival rates.<sup>26</sup> This finding raises some serious concerns about the appropriateness of offering carotid revascularization procedures to very elderly ACS patients.

### Patient sex

A previous analysis of combined results from ACAS<sup>11</sup> and the Asymptomatic Carotid Surgery Trial (ACST)<sup>29</sup> revealed that asymptomatic men had a 51% RR reduction with CEA, whereas

there was no clear benefit in women.<sup>34</sup> Women with ACS tend to be older and their perioperative outcomes are worse.<sup>34</sup> Elderly ACS women in particular have high mortality rates due to ischemic stroke (up to 40.0% at 5 years), which prevents a net benefit from carotid revascularization.<sup>21</sup>

Consequently, not only are older women at higher perioperative stroke/death risk after CEA, but they are also more likely to experience more severe strokes and higher stroke disability. According to the 2020 United States Heart Disease and Stroke Statistics, each year approximately 55,000 more females than males suffer a stroke.<sup>1</sup> Sex-specific stroke rates in some areas have declined significantly since 1993 for males, but not for females.<sup>35</sup> This trend was seen for all-strokes and ischemic strokes, but not for hemorrhagic strokes.<sup>35</sup>

In addition, studies evaluating carotid plaques in women who have undergone CEA demonstrated more smooth muscle cells and a smaller degree of macrophage infiltration, suggesting a more stable phenotype.<sup>36</sup> Clinicians also need to consider competing risks of stroke. Elderly women, in particular, are more likely to have an ischemic stroke due to atrial fibrillation rather than ACS.<sup>37</sup>

An *in vivo* 3.0-T MRI study of carotid plaque features attempted to explain the sex differences indicative of higher-risk

plaques in males.<sup>38</sup> A total of 131 ACS individuals (67 males, 64 females) were imaged with a 3.0-T whole-body scanner. By univariate linear regression analysis, male patients had a higher prevalence of thin/ruptured fibrous cap (48% vs. 17%, for males vs. females, respectively; OR, 4.41; 95% CI, 1.97 to 9.87;  $P<0.01$ ), lipid-rich necrotic core (73% vs. 50%, respectively; OR, 2.72; 95% CI, 1.31 to 5.65;  $P=0.01$ ) and a higher incidence of intra-plaque hemorrhage (33% vs. 17%, respectively; OR, 2.36; 95% CI, 1.03 to 5.38;  $P=0.04$ ) compared with females.<sup>38</sup> In multivariate logistic regression analysis after adjusting for body mass index, hyperlipidemia, statin use, and angiographic stenosis on MRI, the adjusted OR remained virtually unchanged for the prevalence of thin/ruptured fibrous cap (adjusted OR, 4.41; 95% CI, 1.97 to 9.87;  $P<0.01$ ) and the presence of a lipid-rich necrotic core (adjusted OR, 3.66; 95% CI, 1.67 to 8.00;  $P=0.01$ ). However, the prevalence of intraplaque hemorrhage was no longer significantly different (adjusted OR, 2.15; 95% CI, 0.93 to 4.98;  $P=0.07$ ).<sup>38</sup> These results support a sex-specific approach for the invasive management of ACS.

An expert committee undersigning a multidisciplinary consensus document recognized that the landmark RCTs have not been powered to assess outcomes specifically for women, because females were largely under-represented in all RCTs.<sup>39</sup> A *post hoc* subgroup analysis of ACAS showed that the sex differences in CEA outcomes were mainly related to the higher operative stroke/death risk observed in women compared with men (3.6% vs. 1.7%, respectively), resulting in an inferior RR reduction in the overall benefit gained from CEA over time in females vs males compared with BMT alone (5-year relative RR, 17% vs. 66%, for females vs. males, respectively).<sup>32</sup> However, ACAS was performed between 1987 and 1993 and the trial did not have a pre-specified sex subgroup analysis, as was the case with ACST I.<sup>29</sup> In ACST I,<sup>29</sup> the 5-year benefit gained from CEA in women was half of that achieved in men (absolute RR, 4.08% vs. 8.21%, respectively). At 10 years, a benefit gained from CEA was only seen in women <75 years of age, but it was still inferior to that provided by CEA in asymptomatic men of similar age.<sup>40</sup> A meta-analysis of ACAS<sup>32</sup> and ACST I<sup>29</sup> data showed a significant benefit with surgery compared with BMT for ACS men (OR, 0.49; 95% CI, 0.36 to 0.66), but not for women (OR, 0.96; 95% CI, 0.63 to 1.45; pooled interaction  $P=0.01$ ).<sup>41</sup> A possible reason for the inferior results of CEA/CAS in women compared with men may be the fact that females with ACS often receive suboptimal medical care.<sup>42</sup>

According to the recommendations of the committee participating in the multidisciplinary consensus document, an equipoise between CAS/CEA and modern BMT for ACS is likely, but there is limited evidence to consider BMT alone as the best

choice for the management of women with severe ACS (Grade 2, Level of Evidence: B).<sup>42</sup> A strong recommendation for CEA was provided for women with 60% to 99% ACS for reduction of long-term risk of stroke, provided the patient has a 5- to 10-year life-expectancy and perioperative stroke/death rates are  $\leq 2.0\%$  (Grade 1, Level of Evidence B). Furthermore, CAS for ACS females should mainly be offered within the context of RCTs including a medical arm with/without a CEA arm.<sup>42</sup> It was concluded that the overall benefit of carotid revascularization in stroke prevention for women with ACS is expected to be lower than for ACS men (Grade 2, Level of Evidence: B).<sup>42</sup>

### Patient adherence with BMT

Up to 50% of vascular patients cannot quit smoking.<sup>43,44</sup> Other patients may discontinue taking their drugs (e.g., statins) because of side-effects or intolerance<sup>45,46</sup> and older patients may forget to take their medication. A possible pharmacological resistance to clopidogrel or aspirin should also be taken under consideration.<sup>47</sup> Due to drug resistance/discontinuation or lack of adherence, patients often end up receiving suboptimal BMT and, consequently, inadequate stroke prevention therapy.

As a result of the rigorous surveillance by the investigators in RCTs, patients may be more adherent in RCTs than in clinical practice. Consequently, the results of RCTs may often underestimate or overestimate the benefit of a therapeutic approach.<sup>48</sup> This discrepancy in the results between RCTs and real-life observational studies/registries should be taken into account when dealing with individual patients. Patients with multiple risk factors may have a higher chance of progression of ACS and may therefore need to be considered for more aggressive treatment strategies, including CEA or CAS.

The outcomes of ACS patients managed with BMT alone and not offered CEA/CAS may be worse in everyday clinical practice compared with those reported in RCTs. A study from Boston, USA, addressed the natural history of patients with moderate (50% to 69%) ACS managed with BMT alone and not offered any intervention ( $n=794$  patients; 900 carotid arteries).<sup>49</sup> Plaque progression occurred in 262 arteries. Of these, 36 patients (13.7%) developed ipsilateral neurologic symptoms. Of the entire cohort, 90 patients (11.3%) developed ipsilateral ischemic symptoms despite receiving BMT; 58% of these were strokes. The 5-year freedom from symptoms was  $88.4\% \pm 1.5\%$ , while the 5-year actuarial survival for the entire cohort was  $81.9\% \pm 1.5\%$ , with no advantage seen with BMT.<sup>49</sup>

In the Asymptomatic Carotid Stenosis and Risk of Stroke (ACSRS) study, 1,121 patients with 50% to 99% ACS receiving BMT underwent 6-monthly clinical assessment and carotid duplex ultrasound examinations for up to 8 years (mean fol-

low-up, 4 years).<sup>50</sup> ACS progression occurred in 222 patients (19.8%), while 130 first ipsilateral cerebral or retinal ischemic events (59 strokes) were recorded. For patients with 70% to 99% ACS at baseline, the 8-year cumulative ipsilateral cerebral ischemic event rate was 12% in the absence and 21% in the presence of progression.<sup>50</sup>

A prospective, multicenter (n=36) study from China, the Revascularization of Extracranial Carotid Artery Stenosis (RECAS) trial, demonstrated that ACS patients offered CEA in low-volume centers received suboptimal medical therapy preoperatively compared with high-volume centers, such as aspirin (73.0% vs. 88.7%, respectively;  $P < 0.001$ ) and statins (25.6% vs. 34.9%, respectively;  $P = 0.008$ ).<sup>51</sup> 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 similar results.<sup>42</sup> Around 10% to 12% of patients did not receive an antiplatelet agent preoperatively, whereas approximately 20% did not receive a statin.<sup>42</sup> Finally, in a review of data from 3,382 patients admitted to a tertiary referral center with an ischemic stroke, 219 radiographically confirmed strokes adjudicated as carotid-mediated were studied.<sup>52</sup> On admission, 50% were receiving antiplatelet therapy and 55% were receiving lipid-lowering agents, most commonly statins (53%). A total of 35% individuals were receiving both an antiplatelet and lipid-lowering medication.<sup>52</sup> Nearly half (96/219 patients; 43%) of the (previously asymptomatic)

patients presented with an occluded carotid artery as the culprit of their carotid stroke. Based on these results, the authors concluded that BMT alone is unlikely to provide sufficient stroke prevention for all patients with significant ACS.<sup>52</sup> It was suggested that the stroke risk of individual ACS patients should be stratified and the treatment should be tailored to each patient's needs.<sup>53-55</sup>

### Risk prediction tools/improvements in CEA outcomes for ACS patients

Improvements in MRI/CT imaging techniques and technology nowadays make it possible to identify plaque features associated with increased stroke risk.<sup>56,57</sup> Irregular plaque morphology and/or ulcerated plaque surface are associated with an increased risk for future stroke. Similarly, the detection of intraplaque hemorrhage is an identifying feature of the vulnerable plaque and is strongly associated with cerebrovascular events.<sup>56</sup> Intraplaque hemorrhage may be a stronger predictor of stroke risk than clinical risk factors.<sup>57</sup> Consequently, the use of MRI/CT imaging techniques may help to identify ACS patients at high risk for stroke who would benefit from a prophylactic carotid revascularization procedure.<sup>57</sup>

Besides the improvement in annual stroke rates with BMT alone,<sup>4</sup> it should be considered that the periprocedural stroke rates associated with CEA for ACS patients have also improved. There are data from some centers where CEA was performed on

**Table 2.** Predictors/prognostic factors associated with reduced long-term survival in asymptomatic carotid patients undergoing carotid endarterectomy

Study	Age	CAD	COPD	DM	CKD	CCO	Smoking	No statin	Low Hb	Other
Kragsterman et al. <sup>59</sup> (2006)	v	v		v						Previous vascular surgery
Ballotta et al. <sup>60</sup> (2007)		v		v		v				
Alcocer et al. <sup>61</sup> (2013)	v	v	v	v	v					
Conrad et al. <sup>62</sup> (2013)	v	v	v	v				v		Neck irradiation
Wallaert et al. <sup>63</sup> (2013)	v	v	v	v	v	v	v	v		
Gupta et al. <sup>64</sup> (2013)	v	v	v							PAD, dependent functional status
Wallaert et al. <sup>65</sup> (2016)	v	v	v	v	v	v	v	v		
Cooper et al. <sup>66</sup> (2016)	v	v	v				v			
DeMartino et al. <sup>67</sup> (2017)	v	v	v	v		v	v	v	v	Low BMI, prior vascular surgery, ASA IV/V, no aspirin, prior contralateral CEA
Morales-Gisbert et al. <sup>68</sup> (2017)	v	v	v	v						
Carmo et al. <sup>69</sup> (2018)	v	v	v	v	v			v		
Keyhani et al. <sup>70</sup> (2019)	v	v	v	v	v				v	Low BMI, dementia
Dasenbrock et al. <sup>71</sup> (2019)				v	v	v				ASA IV/V

CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; CKD, chronic kidney disease±dialysis; CCO, contralateral carotid occlusion; Hb, hemoglobin; PAD, peripheral arterial disease; BMI, body mass index; ASA, American Society for Anesthesiology; CEA, carotid endarterectomy.

ACS patients with death/stroke rates as low as 0.5%.<sup>58</sup> Therefore, the optimal management of some ACS patients (i.e., BMT alone vs. CEA+BMT) may also be guided by local surgical/medical expertise.

An essential pre-requisite in order to offer a prophylactic carotid intervention to ACS patients is that those individuals should have a reasonable life-expectancy for maximum benefit from the procedure.<sup>2</sup> Carotid guidelines do not recommend offering an intervention to patients not expected to live long enough to benefit from the procedure.<sup>2</sup> Various risk prediction models have been developed in an attempt to identify prognostic factors associated with long-term survival in ACS patients undergoing CEA (Table 2).<sup>59-71</sup> A number of negative prognostic factors have been identified, including old age (12 studies),<sup>59,61-71</sup> cardiac disease (12 studies),<sup>59-70</sup> diabetes mellitus (11 studies),<sup>59-63,65,67-71</sup> chronic obstructive pulmonary disease (10 studies),<sup>61-70</sup> chronic kidney disease with/without dialysis (six studies),<sup>61,63,65,69-71</sup> statin non-use (five studies),<sup>62,63,65,67,69</sup> contralateral carotid occlusion (five studies),<sup>60,63,65,67,70</sup> and smoking (four studies).<sup>63,65-67</sup> The simultaneous presence of several of these conditions/criteria in ACS patients should prompt physicians to consider BMT instead of CEA/CAS for the management of these individuals.

## Conclusions

It has been supported that international guidelines are the "Holy Grail" in Medicine.<sup>72</sup> Such guidelines ensure that the management of patients is uniform and based on Level I Evidence generated by high-quality RCTs. Large, ongoing RCTs, such as the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)-2<sup>73</sup> and ACST-2,<sup>74</sup> will generate high-quality data and evidence for clinical practice and should be vigorously supported with enrollment of all eligible patients. However, due to local social/cultural population differences and resources in different parts of the world, a "one-size-fits-all" guideline policy may not be appropriate for all patients.<sup>72</sup> Besides RCTs, future guidelines should also consider evidence from propensity-matched trials (preferably multi-center), audited registries and multi-registry analyses.<sup>72</sup>

Physicians should always seek to optimize patient adherence to BMT according to current guidelines because all-cause and cardiac mortality in ACS are very high.<sup>75</sup> Nevertheless, some patients may require specific modifications based on individual lifestyle, personal traits, social and cultural characteristics, as well as emerging advances in the field (for example, specific vulnerable carotid plaque features like intraplaque hemorrhage, neovascularization, plaque volume and inflammation that can

be detected with the newer imaging approaches).<sup>53,76</sup> Deciding which is the right treatment for the right patient is crucial. Some patients deserve/require a more aggressive (or a more conservative) approach than others. Consequently, the management of specific ACS patients may need to be individualized, with active patient participation in making health and treatment choices.

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