



## Review

# The European Society for Vascular Surgery Guidelines for Carotid Intervention: An Updated Independent Assessment and Literature Review

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### WHAT THIS PAPER ADDS

- In 2009, the ESVS published clinical practice guidelines for the invasive treatment of carotid disease. Two years later, 14 societies published guidelines that are in sharp contrast with the ESVS guidelines. The aim of this review was to assess the validity of the ESVS guidelines on carotid stenting based on the evidence available today. Moreover, a meta-analysis of all randomised controlled trials (RCTs) comparing carotid artery stenting (CAS) with carotid endarterectomy (CEA) was performed separately for symptomatic and asymptomatic patients. Such a meta-analysis is presented in the literature for the first time. In summary, this review and meta-analysis
1. Confirms that CEA is preferable, in terms of stroke prevention, to CAS for the majority of symptomatic patients with carotid stenosis;
  2. Questions the role of CAS in asymptomatic patients;
  3. Provides an abbreviated review of the evidence about CAS; and
  4. Prompts for an update of the ESVS guidelines.

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### ABSTRACT

**Background and purpose:** Many medical societies now recommend carotid stenting as an alternative to endarterectomy which raises the question of whether the ESVS guidelines are still valid. This review addresses the validity of the ESVS guidelines that refer to carotid stenting based on the evidence available today.

**Methods:** We conducted a review and meta-analysis based on the original ESVS guidelines paper and articles published over the past 2 years.

**Results:** For symptomatic patients, surgery remains the best option, since stenting is associated with a 61% relative risk increase of periprocedural stroke or death compared to endarterectomy. However, centres of excellence in carotid stenting may achieve comparable results. In asymptomatic patients, there is still no good evidence for any intervention because the stroke risk from an asymptomatic stenosis is very low, especially with the best modern medical treatment. CREST and CAVATAS have verified that mid-term stroke prevention after successful stenting is similar to endarterectomy. EVA-3S, SPACE, ICSS and CREST have provided additional evidence regarding the role of age in choosing therapeutic modality. The role of the cerebral protection devices is challenged by the imaging findings of small randomised trials but supported by large systematic reviews.

**Conclusions:** The ESVS guidelines that refer to carotid stenting not only remain valid but also have been further strengthened by the latest available clinical data. An update of these guidelines including all of the recent evidence is needed to provide an objective and up-to-date interpretation of the data.

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In April 2009, the European Society for Vascular Surgery published clinical practice guidelines for the invasive treatment of carotid disease.<sup>1</sup> The document was based on the evidence available at that time. Two years thereafter, very little progress has been

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made in our knowledge on carotid endarterectomy (CEA). On the contrary, carotid artery stenting (CAS) represents a field of intense clinical research, with several ongoing (ACT I, ACST-2 and SPACE-2) or already published (ICSS, CREST, CAVATAS long-term) multi-centre, randomised clinical trials. Accumulated knowledge over these 2 years raises the question of whether the ESVS guidelines that refer to carotid stenting are still valid. The question was strengthened by the publication of the 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease recommending CAS as an alternative to endarterectomy for symptomatic patients with carotid stenosis >50% as well as for highly selected asymptomatic patients with carotid stenosis >60%.<sup>2</sup> The National Institute for Health and Clinical Excellence has also concluded that current evidence on the safety and efficacy of carotid artery stent placement for symptomatic extracranial carotid stenosis is adequate to support the use of this procedure.<sup>3</sup> More recently, however, the Society for Vascular Surgery opined that CEA is preferred to CAS in the majority of patients with carotid stenosis who are candidates for intervention.<sup>4</sup>

This review as well as meta-analysis addresses the validity of the ESVS guidelines that refer to carotid stenting based on the evidence available today.

**Methods**

A Medline search was performed using the term ‘carotid stenting’, limited to articles published after July 2008, since the ESVS guidelines paper was submitted on 11th August 2008. The last search was performed on the 10th September 2011 and identified 35 reports from randomised controlled trials (RCTs) and 23 meta-analyses. Ten reports from RCTs were selected based on their relevance to the ESVS guidelines<sup>5–14</sup> and nine meta-analyses, including the five meta-analyses that were performed after the publication of ICSS and CREST<sup>15–19</sup> and four meta-analyses addressing issues relevant to the ESVS guidelines.<sup>20–23</sup> RCTs and meta-analyses published before June 2008 were obtained from the ESVS guidelines paper.<sup>1</sup> Two reviewers, working independently, extracted descriptive, methodological and outcome data from the selected articles.

Random-effects meta-analysis was used to assess odds ratios and the I<sup>2</sup> statistic was used to assess heterogeneity of treatment effect among trials.<sup>24</sup> Average weighted incidence of events is presented for both treatments. The pooled effect estimates were

calculated as the back-transformation of the weighted mean of the transformed proportions, using DerSimonian–Laird weights. The number needed to treat (NNT) was calculated as 1/(CEA group event rate – CAS group event rate). In case of a negative group event rate difference (CEA – CAS), we present number needed to harm (NNH). Statistical analysis was performed with the use of the Comprehensive Meta Analysis software, version 2.2.057 (Biostat Inc., Englewood, NJ, USA).

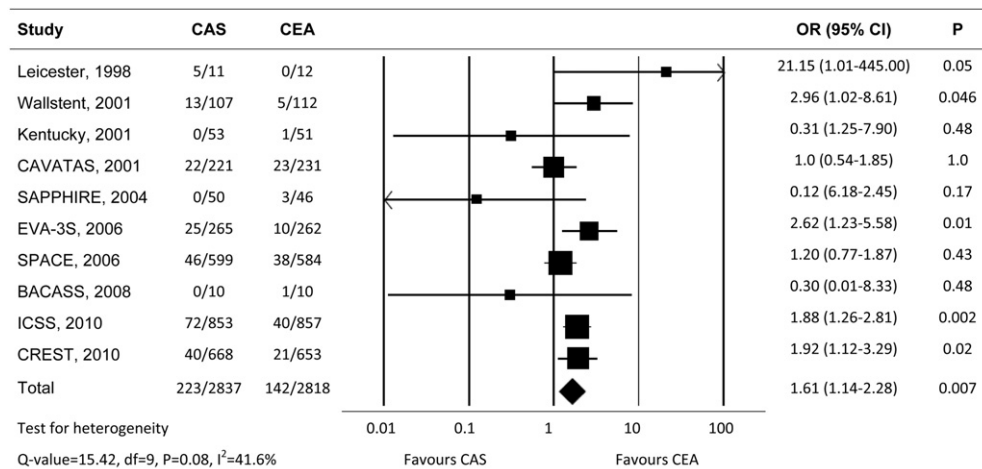
**Results**

*Invasive treatment recommendation 2. CAS in symptomatic patients*

- The available level I evidence suggests that for symptomatic patients, surgery is currently the best option [A].

The recommendation was based on a meta-analysis by The Cochrane Collaboration of eight randomised trials comparing CEA with CAS (CAVATAS, Kentucky, Leicester, Wallstent, SAPPHIRE, EVA-3S, SPACE and BACASS) showing that surgery is associated with lower stroke and death rate within 30 days of treatment (odds ratio (OR): 1.39, 95% confidence interval (CI): 1.05–1.84, *P* = 0.02).<sup>25</sup> The results of two more trials were published thereafter, both of which lending further support to the ESVS recommendation. The ICSS trial showed that the risk of any stroke or death within 120 days of randomisation was higher in the stenting group than in the endarterectomy group (8.5% vs. 4.7%, hazard ratio (HR) 1.86, 1.26–2.74).<sup>26</sup> Similarly, in the subgroup analysis of the symptomatic patients in the CREST trial, the periprocedural stroke or death rate was 6.0% in the stenting group versus 3.2% in the endarterectomy group (HR 1.89, 1.11–3.21, *P* = 0.02).<sup>6</sup> A trend towards a higher rate of myocardial infarction (MI) in the group of symptomatic patients undergoing CEA did not reach statistical significance (1% in the CAS group vs. 2.3% in the CEA group, HR 0.4, 0.18–1.11, *P* = 0.08).

If the results of ICSS and CREST are added in the meta-analysis (Fig. 1), the OR in favour of CEA will be increased from 1.39 to 1.61 (95% CI: 1.14–2.28) and the statistical significance from 0.02 to 0.007, meaning that, in symptomatic patients, CAS is associated with a 61% relative risk (RR) increase of periprocedural stroke or death compared to CEA. The average weighted risk of stroke or death in symptomatic patients submitted to CAS is 7.4%, whereas in patients submitted to CEA it is 5.2%. Consequently, the NNH is 47, meaning that every 47 patients submitted to CAS instead of CEA one extra stroke or death will occur.



**Figure 1.** Forest plot of stroke or death within 30 days of procedure (except for ICSS where events occurring within 120 days of randomization are reported) in symptomatic patients submitted to CAS or CEA.

Three out of the 10 RCTs included in the meta-analysis may be deemed less relevant to current clinical practice: the CAVATAS trial,<sup>26</sup> in which only 26% of patients received stents, the Leicester trial,<sup>27</sup> in which non-dedicated stents were used without routine predilation and the Wallstent trial,<sup>28</sup> the full details of which have never been published and was performed when no dedicated material was available for carotid stenting. The results, however, of the meta-analysis remain virtually the same, even when these three RCTs are excluded (OR: 1.62, 95% CI: 1.14–2.31,  $P = 0.008$ ).

Given the results of these meta-analyses, which are similar to the results of the five most recent meta-analyses in the literature,<sup>15–19</sup> it seems strange that the recommendations of different societies about the treatment of symptomatic carotid stenoses by CEA or CAS are rather contradictory. The controversy is based on the different importance given to MI as an outcome measure. The ESVS<sup>1</sup> and the SVS<sup>4</sup> guidelines are apparently based on the premise that stroke prevention is the key determinant of practice and, in this context, they recommend CEA rather than CAS for the majority of symptomatic patients. On the other hand, the American Heart Association/American Stroke Association (AHA/ASA)<sup>29</sup> and the 14 societies<sup>2</sup> guidelines are based on the premise that MI is considered to be the equivalent of stroke and death in the primary end point and, thus, their indications for CAS are more liberal.

Although in no way can an MI be disregarded as an outcome, there are two points of concern raised by its inclusion in the primary endpoint, as in the CREST trial. The first point is that an asymptomatic MI cannot be considered as an equivalent to death or stroke and be given the same importance by being included in the same, composite end point. The results of the CREST trial are actually in support of this notion, showing that even minor strokes had a significant, adverse effect on physical health at 1 year, according to the SF-36 physical component scale, whereas the effect of periprocedural MI was not statistically significant.<sup>6</sup> On the other hand, a post hoc analysis from the CREST showed that both MI and biomarker elevation only were independently associated with increased future mortality.<sup>7</sup> This finding, however, does not justify the inclusion of asymptomatic MIs in a composite end point that already includes mortality.

The second point of criticism is that, if asymptomatic MIs are to be included in the primary end point, then asymptomatic cerebral infarctions should be included as well. In a substudy of the ICSS, 50% of the patients in the stenting group and 17% of the patients in the endarterectomy group had at least one new lesion detected on post-treatment magnetic resonance imaging (MRI) scans done a median of 1 day after treatment (adjusted OR 5.21, 95% CI 2.78–9.79;  $P < 0.0001$ ).<sup>8</sup> However, differences between CAS and CEA in effect on cognition were not found to be statistically significant in the two participating centres that performed neuropsychological examinations before and 6 months after revascularisation.<sup>9</sup> Thus, asymptomatic brain lesions detected by MRI after a carotid intervention cannot be included in the same, composite end point with other complications causing disability or death.

- Mid-term stroke prevention after successful CAS is similar to CEA [A].

The recommendation was based on the mid-term outcomes of EVA-3S and SPACE.<sup>10,11</sup> The more recently published long-term results of CAVATAS<sup>12</sup> and the mid-term results of CREST<sup>6</sup> are in accordance with these data. The long-term results of the CAVATAS trial showed that the 8-year incidence of ipsilateral non-perioperative stroke was 11.3% in the CAS group versus 8.6% in the CEA group (HR 1.22, 95% CI 0.59–2.54).<sup>12</sup> Likewise, the CREST trial showed that, after the periprocedural period, the 4-year incidence of ipsilateral stroke was similarly low with CAS and with CEA

(2.0% and 2.4%, respectively;  $P = 0.85$ ).<sup>6</sup> Because the life expectancy of the patients included in CREST was 15 years after the procedure, outcomes are being assessed out to 10 years and are awaited.

- CAS should be offered to symptomatic patients, if they are at high risk for CEA, in high-volume centres with documented low periprocedural stroke and death rates or inside an RCT [C].

The recommendation was based on experts' opinion, with the term 'high risk for CEA' referring mainly to adverse vascular and local anatomic features, such as contralateral laryngeal nerve palsy, previous radical neck dissection, cervical irradiation, prior CEA (restenosis), high bifurcation or intracranial extension of a carotid lesion.

The term 'high-volume centres with low-procedural stroke and death rates' had not been sufficiently documented in the original paper, but now there are sufficient data, though not level A, to support it. In a review of 18 599 CAS procedures, the stroke rate after CAS was found to be significantly different between low- and high-volume hospitals (2.35% vs. 1.78%, respectively;  $P = 0.02$ ), as well as between low- and high-volume practitioners (2.19% vs. 1.51%,  $P = 0.02$ ). The characterisation 'high-volume' was arbitrarily granted to hospitals performing >30 CAS/year and practitioners performing >15 CAS/year.<sup>30</sup> Similarly, a systematic review of the literature showed that, in active CAS units, it may take almost 2 years before the stroke/death rates fall below an arbitrary 5% threshold.<sup>31</sup>

#### *Invasive treatment recommendation 3. CAS in asymptomatic patients*

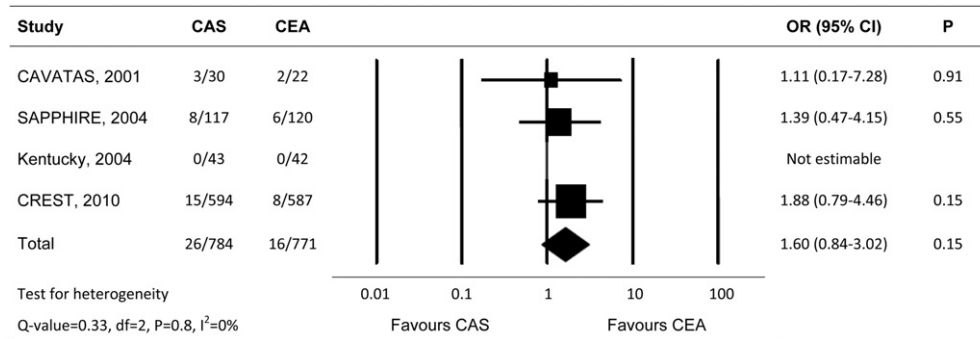
- It is advisable to offer CAS in asymptomatic patients only in high-volume centres with documented low periprocedural stroke and death rates or within well-conducted clinical trials [C].

The recommendation was based on the fact that data on asymptomatic patients were very weak, coming only from one small randomised trial, comprising only 85 patients,<sup>32</sup> and a subgroup analysis of the SAPHIRE trial, which was not pre-specified.<sup>33</sup> Both studies showed that CAS and CEA are equally effective in preventing stroke and death in asymptomatic patients.

Another subgroup analysis from the more recently published CREST trial showed similar findings. The rate of periprocedural stroke or death in asymptomatic patients included in CREST was 2.5% in CAS versus 1.4% in CEA (OR 1.88, 0.79–4.42,  $P = 0.15$ ).<sup>6,13</sup> No statistically significant difference was also found in the rate of MI (1.2% vs. 2.2%, OR 0.55, 0.22–1.38,  $P = 0.2$ ), in the rate of any periprocedural stroke (2.5% vs. 1.4%, OR 1.88, 0.79–4.42,  $P = 0.15$ ) or in the rate of the composite primary end point (any periprocedural stroke, MI or death: 3.5% vs. 3.6%, OR 1.02, 0.55–1.86,  $P = 0.96$ ).<sup>6,13</sup>

A meta-analysis of the subgroup data from all trials that have included asymptomatic patients (Fig. 2) shows that there is no statistically significant difference in the stroke or death rate between CAS (pooled incidence 4.1%) and CEA (pooled incidence 3.0%) in asymptomatic patients (OR 1.60, 0.84–3.02,  $P = 0.15$ ). However, the number of patients included in the meta-analysis is small to detect a difference between 4.1% and 3.0%. It is also very interesting that the OR in our meta-analysis was virtually the same in symptomatic (1.61) and asymptomatic (1.60) patients submitted to CAS or CEA. Further data from randomised trials on the outcomes of CAS versus CEA in asymptomatic patients will not be available for several years until the ongoing ACT-1 and ACST-2 trials are completed.

On the other hand, there is growing evidence that rates of ipsilateral and any-territory stroke with medical intervention alone



**Figure 2.** Forest plot of stroke or death within 30 days of procedure in asymptomatic patients submitted to CAS or CEA.

have fallen significantly since the mid-1980s, with recent estimates overlapping those of patients who underwent CEA in randomised trials<sup>20,34</sup> or contemporary series.<sup>35</sup> The average annual risk of ipsilateral stroke in asymptomatic patients with >50% stenosis was >3% in 1985, but has fallen to approximately 0.5% in 2008.<sup>20</sup> The most recent, prospective, population-based study, recruiting patients from 2002 to 2009 who were given intensive contemporary medical treatment, showed that the average annual event rates on medical treatment were 0.34% for any ipsilateral ischaemic stroke, 0% for disabling ipsilateral stroke and 1.78% for ipsilateral transient ischaemic attack (TIA).<sup>36</sup> Given this new evidence, current vascular disease medical intervention alone may now be best for stroke prevention associated with asymptomatic severe carotid stenosis. Until the results of the SPACE-2 study, which is a three-armed comparison among up-to-date best medical treatment, CAS and CEA in patients with asymptomatic CAD, are available, the role of CAS in asymptomatic patients will be questionable. TACIT and CREST-2 trials are designed similar to SPACE-2 but have yet to open or be funded.

Similar to the previously mentioned findings on the importance of the 'high volume' operator and centre on the outcome of stenting for symptomatic carotid stenosis, the value of the learning curve and the operator's experience has also been proven for the asymptomatic patients. In a recently published analysis of the CAPTURE-2 study, in 3388 asymptomatic non-octogenarian subjects, an inverse relationship between event rates and hospital patient volume, as well as between event rates and individual operator volume, was observed; a threshold of 72 cases was found to be necessary for consistently achieving a death and stroke rate of <3% in this later-phase single-arm study.<sup>37</sup>

#### *Invasive treatment recommendation 4. Treatment options influenced by medical co-morbidities*

- For asymptomatic patients at 'extremely' high risk (several medical co-morbidities at the same time), best medical treatment might be the best option instead of invasive intervention [C].
- CAS should not be offered to asymptomatic 'high-risk' patients if the peri-interventional complication rate is >3% [C].

There is still no indication from the literature that a 'high risk' for surgery patient is also at 'high risk' for stroke if medically treated. Therefore, a peri-interventional stroke or death risk of >3% in 'high-risk for surgery' patients with asymptomatic carotid stenosis cannot be accepted.

- CAS is associated to higher risk of embolisation in octogenarians [B]. CEA is performed in octogenarians without increased risk of embolisation and with an acceptable rate of neurological and cardiac complications [C].

The recommendation was based on several papers demonstrating that octogenarians undergoing CAS are at a higher risk than non-octogenarians for periprocedural complications, including neurological events and death.<sup>38,39</sup> The finding that the risk of CAS is higher in older patients has been verified by several studies published over the past 2 years, although the exact cut-off point of age after which CAS is worse than CEA is still to be defined. In the CREST trial an interaction between age and treatment efficacy was detected, with a crossover at an age of approximately 70 years; CAS tended to show greater efficacy at younger ages, and CEA at older ages.<sup>6</sup>

In accordance with these findings, a recently published pooled analysis of EVA-3S, SPACE and ICSS showed that, in patients <70 years old, the 120-day stroke or death risk was 5.8% in CAS and 5.7% in CEA (RR 1.00, 0.68–1.47), whereas in patients 70 years or older, there was an estimated twofold increase in risk with CAS over CEA (12.0% vs. 5.9%, RR 2.04, 1.48–2.82, interaction  $P = 0.0053$ ).<sup>21</sup>

Similar results were reported by the CAPTURE 2 trial which, as of January 2009, had enrolled 5297 patients, 1166 of whom were octogenarians.<sup>40</sup> The death/stroke rate for the overall cohort was 3.3%; stroke rate was 2.7% (0.8% major, 1.9% minor). Death/stroke rates were significantly higher for octogenarians than non-octogenarians (4.5% vs. 3.0%) as were stroke rates (3.8% vs. 2.4%). An earlier meta-analysis of procedural stroke and death among octogenarians undergoing CAS (826 patients) or CEA (7017 patients) had shown that octogenarians undergoing CAS had a significantly higher absolute risk of stroke than those undergoing CEA (7% vs. 1.9%,  $P < 0.01$ ), with no significant difference in mortality (2% vs. 1.1%,  $P = 0.25$ ) and a trend towards a lower rate of MI (0.9% vs. 2.2%,  $P = 0.08$ ).<sup>23</sup>

Further studies are needed to show whether the suggested, by the pooled analysis of EVA-3S, SPACE and ICSS, equivalence between CEA and CAS in patients <70 years old will become a level A recommendation. The main caveat is that the potentially higher rate of recurrent stenosis after stenting compared to endarterectomy may lead to an unfavourable long-term outcome in young patients with a long life expectancy. So far, we have subgroup analyses regarding the perioperative outcome of CAS versus CEA in young patients, but we still do not have any analysis regarding the mid- or long-term outcome in this particular group of patients.

#### *Invasive treatment recommendation 13. Improving the CAS outcome*

- Cerebral protection devices are probably beneficial [C].

The recommendation was based on a systematic review of all studies reporting on the incidence of CAS complications that were published between 1990 and 2002,<sup>41</sup> as well as on a subsequent report by the Global Carotid Artery Stent Registry documenting a 5.3–5.5% rate of stroke and death in cases performed without protection, compared with 1.8–2.2% in cases performed with cerebral protection.<sup>42</sup>

A randomised study of CAS with or without a distal cerebral protection filter, published before the ESVS guidelines, had shown that, contrary to the initial expectations, new MRI lesions developed in 72% of the cerebral protection group compared with 44% in the no cerebral protection group ( $P = 0.09$ ).<sup>43</sup> Most of these lesions were silent, with the stroke rate being equal in the two groups (11%). The major limitation of this study was the small number of cases included (36 stenting procedures in 35 patients), which was due to the reluctance of the patients to participate in a study with no cerebral protection group.

Interestingly, the findings of this study were recently duplicated by another randomised trial, which showed that filter-protected CAS is associated with an increase in new lesions on diffusion-weighted magnetic resonance imaging (29% vs. 18%) and significantly higher rates of total and particulate microembolisation on transcranial Doppler (426.5 and 251.3 vs. 165.2 and 92, respectively) than unprotected CAS.<sup>14</sup> This study was also very small (30 patients) and the differences in MRI lesions did not reach statistical significance. Larger studies are clearly warranted, though recruiting for such studies is expected to be very difficult, due to the already established, widespread belief that, as the ESVS recommendation states, “cerebral protection devices are probably of benefit”.

This belief is also reinforced by the findings of the most recent systematic review comparing stroke outcomes in protected and unprotected CAS.<sup>22</sup> The review included 134 articles reporting on 12 263 protected CAS patients and 11 198 unprotected CAS patients. Using pooled analysis, the RR for stroke was 0.62 (95% CI 0.54–0.72) in favour of protected CAS. Subgroup analysis revealed a significant benefit for protected CAS in both symptomatic (RR 0.67; 95% CI 0.52–0.86) and asymptomatic (RR 0.61; 95% CI 0.41–0.90) patients ( $P < 0.05$ ).

## Conclusions

At this time, the latest available data have rather strengthened the ESVS guidelines on the management of carotid artery disease. CEA remains the gold standard, whereas CAS retains its role in symptomatic patients at high risk for CEA, in the hands of experienced interventionalists and in high-volume centres with documented low periprocedural event rates. The role of CAS in asymptomatic patients is questionable. Since these conclusions are in sharp contrast with those of other recently published guidelines, an update of the ESVS guidelines is needed to provide an objective and up-to-date interpretation of the data. Although the recommendations are not expected to drastically change, it is important for the Society to provide new guidelines incorporating the results of the recently published series on the natural history of asymptomatic carotid stenosis and the comparison between CAS and CEA.

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None.

## Conflict of Interest Statement

None.

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