Stroke
Journal of the American Heart Association

A Clinical Rule (Sex, Contralateral Occlusion, Age, and Restenosis) to Select Patients for Stenting Versus Carotid Endarterectomy: Systematic Review of Observational Studies With Validation in Randomized Trials

Emmanuel Touzé, Ludovic Trinquart, Rui Felgueiras, Kittipan Rerkasem, Leo H. Bonati, Gayané Meliksetyan, Peter A. Ringleb, Jean-Louis Mas, Martin M. Brown and Peter M. Rothwell
in collaboration with the Carotid Stenting Trialists Collaboration

Stroke. 2013;44:3394-3400; originally published online October 17, 2013;
doi: 10.1161/STROKEAHA.113.002756
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0039-2499. Online ISSN: 1524-4628

A Clinical Rule (Sex, Contralateral Occlusion, Age, and Restenosis) to Select Patients for Stenting Versus Carotid Endarterectomy

Systematic Review of Observational Studies With Validation in Randomized Trials

Emmanuel Touzé, MD, PhD*; Ludovic Trinquart, PhD*; Rui Felgueiras, MD; Kittipan Rerkasem, MD, PhD; Leo H. Bonati, MD, PhD; Gayané Meliksetyan, MD; Peter A. Ringleb, MD, PhD; Jean-Louis Mas, MD; Martin M. Brown, MD, FRCP; Peter M. Rothwell, MD, PhD, FRCP, FMedSci; in collaboration with the Carotid Stenting Trialists' Collaboration

Background and Purpose—Compared with carotid endarterectomy (CEA), carotid angioplasty and stenting (CAS) is associated with a higher risk of procedural stroke or death especially in patients with symptomatic stenosis. However, after the perioperative period, risk is similar with both treatments, suggesting that CAS could be an acceptable option in selected patients.

Methods—We performed systematic reviews of observational studies of procedural risks of CEA or CAS and extracted data on 9 predefined risk factors (age, contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex, hypertension, peripheral artery disease, and type and side of stenosis). We calculated pooled relative risks of procedural stroke or death. Factors with differential effects on risk of CAS versus CEA were identified by interaction tests and used to derive a rule. The rule was tested using individual patient data from randomized trials of CAS versus CEA from the Carotid Stenting Trialists' Collaboration (CSTC).

Results—We identified 170 studies. The effects of sex, contralateral occlusion, age, and restenosis (SCAR) on the procedural risk of stroke or death differed. Patients with contralateral occlusion or restenosis and women <75 years were at relatively low risk for CAS (SCAR negative), with all others being high risk (SCAR positive). Among the 3049 patients in the CSTC validation, 694 (23%) patients were SCAR negative. The pooled RR of procedural stroke and death with CAS versus CEA was 0.93 (0.49–1.77; P=0.83) in SCAR-negative and 2.41 (1.68–3.45; P<0.0001) in SCAR-positive patients (P [interaction]=0.05).

Conclusions—The SCAR rule is potentially useful to identify patients in whom CAS has a similar risk of perioperative stroke or death to CEA. **(*Stroke*. 2013;44:3394-3400.)**

Key Words: atherosclerosis ■ carotid endarterectomy ■ carotid stenosis ■ carotid stenting ■ meta-analysis ■ prevention ■ systematic review

Carotid artery stenting (CAS) is being evaluated as a potential alternative to carotid endarterectomy (CEA) in patients with severe carotid artery stenosis. However, to date, randomized clinical trials have shown that, on average, CAS is associated with a higher procedural risk of stroke than CEA in patients with symptomatic stenosis,[1,2] and that there are only limited data in patients with asymptomatic stenosis.[2] Nevertheless, because the risk of stroke after the perioperative

Received July 9, 2013; accepted September 4, 2013.

From the Université Paris Descartes, Sorbonne Paris Cité, INSERM UMR S894, Service de Neurologie, Hôpital Sainte-Anne, Paris, France (E.T., G.M., J.-L.M.); Université de Caen Basse Normandie, INSERM UMR-S U919, Service de Neurologie, CHU Côte de Nacre, Caen, France (E.T.); French Cochrane Centre, Université Paris Descartes, Sorbonne Paris Cité, INSERM U738, Assistance Publique-Hôpitaux de Paris, Hôpital Hôtel-Dieu, Centre d'Epidémiologie Clinique, Paris, France (L.T.); Neurology Department, Hospital Santo António, Centro Hospitalar do Porto, Largo Professor Abel Salazar, Porto, Portugal (R.F.); Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (K.R.); Department of Neurology and Stroke Unit, University Hospital Basel, Switzerland (L.H.B.); Department of Brain Repair and Rehabilitation, UCL Institute of Neurology, Queen Square, London, UK (L.H.B., M.M.B.); Department of Neurology, University Hospital Heidelberg, Im Neuenheimer Feld 400, Heidelberg, Germany (P.A.R.); and Stroke Prevention Research Unit, Nuffield Department of Clinical Neuroscience, University of Oxford, Oxford, UK (P.M.R.).

Guest Editor for this article was Miguel Perez-Pinzon, PhD.

*Drs Touzé and Trinquart contributed equally.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.113.002756/-/DC1.

Correspondence to Emmanuel Touzé, MD, PhD, Université de Caen Basse Normandie, INSERM UMR-S U919, Service de Neurologie, CHU Côte de Nacre, Caen, France. E-mail touze-e@chu-caen.fr

***Stroke* is available at http://stroke.ahajournals.org** **DOI: 10.1161/STROKEAHA.113.002756**

period seems to be similar for CAS and CEA,[3,4] it has been suggested that CAS may be an acceptable option in selected patients who have a low procedural risk of stroke or death, as indicated in European and American guidelines.[5,6] However, there is no indication as to how patients with a low procedural risk can be identified. The combined analysis of the large European trials and North American trials of CEA versus CAS has shown that CAS was potentially as safe as CEA in younger patients,[2,7] but there remains uncertainty whether age should be used alone as a selection criteria to identify potential candidates for CAS. Other clinical factors are likely to influence the relative procedural risks of the 2 techniques,[8–12] some of which were not addressed in analysis of the randomized trials, and other important groups, such as patients with restenosis, were either excluded from the trials or not reported separately.[13] Moreover, the trials lack the statistical power to detect clinically important interactions between patient characteristics and treatment effect.[7]

In contrast, numerous case series of patients undergoing CEA or CAS are available, and collectively provide data on the risk factors for procedural stroke and death for one or other procedure in several hundred thousand patients.[8–12] We have shown previously that meta-analysis of risk associations from such studies provides reliable and highly consistent data on the clinical characteristics associated with procedural risk of CEA and CAS independently.[7–18] To guide clinical decision making, we now aimed to use this approach to identify those predictors of procedural risk that differ significantly between CEA and CAS and might therefore be useful in determining which procedure is most appropriate in individual patients. We aimed to thereby derive a simple clinical risk rule to target CAS versus CEA and to validate the rule and determine its likely clinical use by using individual patient data from the randomized trials that directly compared CEA and CAS included in The Carotid Stenting Trialists' Collaboration (CSTC) Database.[7]

Methods

Systematic Review of Observational Data

We updated our previous systematic reviews using the same selection criteria and search strategy as previously published,[8–12,14] and following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting.[15]

Selection Criteria

Eligible studies were those which enrolled patients with symptomatic or asymptomatic stenosis located in the region of the carotid bifurcation, treated by CAS or CEA, and in which the numbers of stroke or death could be extracted for any subgroup among a predefined list of 9 risk factors: age (≥75–80 versus <75–80 years, ie, corresponding to the most common cutoffs used to separate elderly from nonelderly patients), contralateral carotid occlusion (severe stenosis was not considered), coronary artery disease, diabetes mellitus, sex (men versus women), hypertension, peripheral artery disease, type of stenosis (restenosis after CEA versus primary atherosclerotic disease), and side of stenosis (right versus left). These factors were identified as potentially relevant from previous systematic reviews or individual studies.[8–12] Studies were considered irrespective of setting and language. Observational studies were defined as cohorts or case series, including administrative databases, of patients undergoing CAS or CEA. We excluded studies that enrolled only specific populations (eg, postradiation stenosis, restenosis after CEA, and patients treated in an emergency context) and case reports.

Search Strategy

The search strategy was based primarily on an electronic search of 3 databases (Medical Literature Analysis and Retrieval System Online, Excerpta Medica, and the Cochrane Central Register of Controlled Trials databases) until July 1, 2011 (Table I in the online-only Data Supplement). We hand-searched the references of all included articles and any relevant reviews. We also searched books of abstracts from recent conferences that were available online (Table II in the online-only Data Supplement), the US Clinical Trial Register (http://www.clinicaltrials.gov), the US Food and Drug Administration (http://www.fda.gov), and the European Medicines Agency (http://www.emea.europa.eu) databases.

Study Selection and Data Collection

Assessment of eligibility of studies was performed by 2 independent reviewers for CAS and CEA separately, from the titles and abstracts as previously reported.[8–12] Final selection was made after reviewing full-text articles. Reviewers extracted information from the reports using a standardized data chart. For each report, a second reviewer ascertained the accuracy of data extracted by the first reviewer. Any disagreement was resolved by discussion.

The 3 large European randomized trials of CEA versus CAS in patients with symptomatic carotid stenosis (Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis [EVA-3S]; Stent-Protected Angioplasty versus Carotid Endarterectomy [SPACE]; International Carotid Stenting Study [ICSS]), which formed the CSTC,[7] were used for the validation analyses, and the data from these trials were therefore not included in the systematic review of risk associations.

Analysis

The primary outcome was the procedural risk of stroke or death (most commonly defined as the risk during the 30 days after the procedure). Secondary outcomes were stroke and any death separately. Nonfatal myocardial infarction was not included. For each of the 9 potential risk factors and separately for studies of CAS and of CEA, we calculated the relative risks (RR) of a procedural event in patients versus those without the risk factor. Because of differences between studies in which risk factor data were reported, the numbers of studies (and patients) included in each meta-analysis differed. In each meta-analysis, studies with no events occurring in all groups (ie, patients with and without the risk factor) did not contribute to the calculation of the pooled RR. However, when zero cell count was observed in 1 group only, we used a continuity correction, by adding a factor proportional to the reciprocal of the size of the contrasting study group to all cells.[16] Homogeneity of RRs across studies in each meta-analysis was assessed using the I^2 statistic. I^2>30% represents moderate heterogeneity, I^2>50% substantial heterogeneity, and I^2>70% considerable heterogeneity. We report pooled RRs computed through DerSimonian–Laird random effects meta-analyses, although analyses using fixed-effect meta-analysis models according to the Mantel–Haenszel method showed consistent results. For each risk factor, we assessed whether the effect on the procedural risk of event differed between CAS and CEA by performing an interaction test using random effects meta-regressions. As is recommended for such analyses, we considered a probability value of ≤0.10 as evidence of statistically significant interaction.[17]

Derivation of the Rule

From the set of risk factors with differing effects between CAS and CEA (ie, with statistically significant interactions), we took the magnitude and direction of interactions into account to determine the rule. If a large qualitative interaction was found (ie, when RRs were clearly in opposite directions or when the difference from unity was ≥0.50 for the factor with the greater effect and ≤0.10 for the factor with the effect close to the unity), such a risk factor was considered sufficient by itself to identify low-risk patients. Otherwise, factors associated with a high risk after CAS scored +1 and those with a low risk scored −1. Patients with a total score <0 were categorized into low risk. In a secondary analysis, an alternative rule was also derived, in which all

factors were considered equivalent (high risk of CAS scores +1 and low risk for CAS scores −1), and patients were categorized according to the total score.

Validation of the Rule

After having derived the rule, P.M. Rothwell, E. Touzé, and L. Trinquart made a formal request to the CSTC to obtain a data set from EVA-3S, SPACE, and ICSS randomized trials to validate the rule.[7] At no time, did these researchers have access to the data set before they derived the rule. A per-protocol individual data set including the 30-day outcomes (stroke or death, stroke, death) occurrence and the risk factors selected for the clinical rule only were obtained. Definitions of outcomes and risk factors were already standardized across the 3 trials.[7] Patients were categorized into low or high risk according to the rule. We used a 2-stage meta-analytic approach.[18] First, in each low-risk and high-risk category and for CAS and CEA separately, we calculated combined absolute risks of procedural stroke or death. We used a DerSimonian–Laird random effects model to combine absolute risks across trials through the Freeman–Tukey variance stabilizing transformation.[19] Second, in each low-risk and high-risk category, we computed combined RR of stroke or death in patients treated with CAS compared with patients treated with CEA. We tested for interaction of treatment effect between low- and high-risk patients using meta-regression. Given the a priori prediction that the RR of stroke or death occurring in patients treated with CAS compared with patients treated with CEA would be higher in CAS-higher-risk than in CAS-lower-risk patients, we calculated a 1-sided probability value by using a Monte Carlo permutation test.[20]

Results

A total of 170 studies (227 articles, >70 000 patients) provided data for ≥1 of 9 potential risk factors: 115 studies (149 articles) relating to CEA and 68 studies (83 articles) relating to CAS, some being related to both CEA and CAS. The characteristics of these studies and the list of references are shown in Table I in the online-only Data Supplement.

The results of the meta-analyses of the RRs of stroke or death in relation to the 9 potential risk factors in CAS and CEA studies are shown in Figure 1. There was no or little heterogeneity between studies in RRs for age, contralateral occlusion, diabetes mellitus, sex, hypertension, and restenosis among either CAS or CEA studies. The effects of age, sex, contralateral occlusion, and restenosis on the procedural risk of stroke or death differed statistically significantly between CAS and CEA (interaction test probability value of <0.10). There was more heterogeneity in RR between CEA studies concerning coronary artery disease, stenosis side, and peripheral artery disease, but the effects of these variables on the procedural risk of stroke or death did not differ statistically significantly between CAS and CEA.

Age was associated with higher risks of procedural stroke or death for both CAS and CEA but the increase in risk was greater after CAS. Contralateral occlusion and female sex were associated with a higher risk of procedural stroke or death after CEA but had no significant influence on the risk after CAS. Compared with patients with primary atherosclerotic disease, those with restenosis after CEA had a higher risk of procedural stroke or death when treated by CEA but a lower risk when treated by CAS. Analyses based on stroke only yielded qualitatively similar results (Figure I in the online-only Data Supplement).

Therefore, the resulting rule was based on the presence or absence of the 4 following factors: sex, contralateral occlusion, age and restenosis (SCAR rule). Given the large qualitative

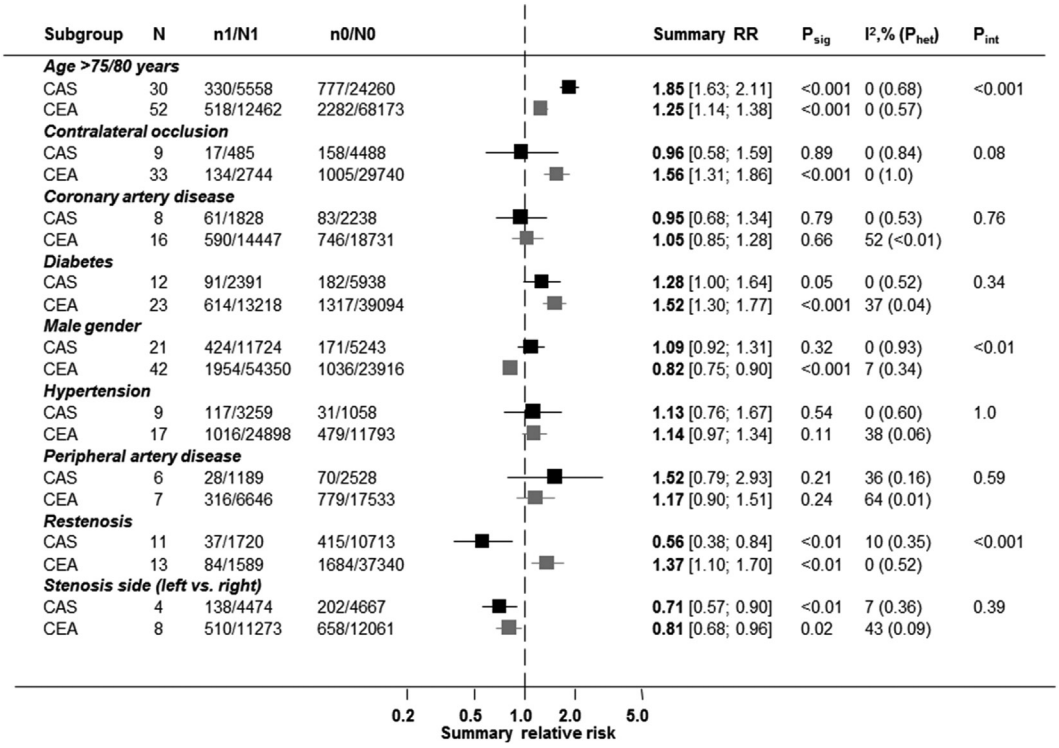


Figure 1. Meta-analyses of the relative risk of stroke or death after carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA) according to the 9 potential risk factors. N indicates number of studies; n1, number of events in patients with clinical factor; N1, number of patients with clinical factor; n0, number of events in patients without clinical factor; N0, number of patients without clinical factor; P_{het}, Cochran homogeneity test probability value; P_{int}, *P* interaction; P_{sig}, *P* significance; and RR, relative risk.

effect of contralateral occlusion and restenosis, we first considered that these risk factors were by themselves sufficient to identify patients in whom CAS would be relatively lower risk (SCAR negative) and comparable with CEA. Otherwise, given the smaller qualitative interaction for sex and the small quantitative interaction for age, only women <75 years would also be expected to be relatively at low risk for CAS (also SCAR negative), all other patients being categorized as higher risk (SCAR positive) for CAS and therefore as candidates for CEA preferentially. In a secondary analysis, we considered all factors equivalent, that is, that all patients with ≥2 factors (age <75 years, women, contralateral occlusion, or restenosis) would be SCAR negative and all others SCAR positive. The only difference between the 2 options being that men >75 years with contralateral carotid occlusion or restenosis are SCAR positive in the second option (Table II in the online-only Data Supplement).

Among the 4 components of the SCAR rule, effects of sex, contralateral occlusion, and age could be validated with the individual data from the CSTC, but patients with restenosis were excluded from the trials. Data on contralateral carotid occlusion were missing in 275 patients (262 from SPACE and 13 from ICSS). Exclusion of these patients left 3049 patients for the analyses. Using our primary definition of the SCAR rule, 694 (22·8%) patients were classified as SCAR negative: 135 patients had contralateral carotid occlusion, and the other 559 patients were women <75 years. Among these SCAR-negative patients, the absolute risks of any stroke or death were similar between CAS and CEA (absolute risks 5.6%, 95% confidence interval [3.0–9.0] versus 5.6% [3.4–8.4]). However, among SCAR-positive patients, the absolute risk of CAS was more than twice that of CEA (8.4%, 6.9–10.1 versus 3.5%, 2.6–4.6; Figure II in the online-only Data Supplement).

Figure 2 shows the RRs of any procedural stroke or death occurring in patients treated by CAS compared with patients treated by CEA. Among SCAR-negative patients, the pooled RR was 0.93 (95% confidence interval [0.49–1.76], I^2=0%; *P* (sig)=0.83) whereas, among SCAR-positive patients, it was 2.44 (1.71–3.48, I^2=0%; *P* (sig)<0.0001). The interaction was statistically significant (*P*=0.05). Analyses based on the procedural risk of stroke (RR=0.93; 0.48–1.80 in SCAR-negative patients versus 2.45; 1.70–3.64 in SCAR-positive patients; *P* for interaction=0.05; Figure III in the online-only Data Supplement) and death (RR=0.83; 0.15–4.52 in SCAR-negative patients versus 2.57; 1.00–6.62 in SCAR-positive patients; *P*=0.20) led to similar results. In the sensitivity analysis considering all 4 risk factors as equivalent, the results were similar (Figure IV in the online-only Data Supplement).

In the absence of contralateral occlusion and restenosis, only women <75 years are identified as low risk for CAS by the SCAR rule, consistent with the finding that men aged <75 years without contralateral carotid occlusion remained at higher risk of procedural stroke or death when treated by CAS versus CEA (RR=1.94; 95% confidence interval [1.22–3.07]).

Finally, considering that CSTC and CREST have both shown that CAS is not inferior to CEA in patients <70 years (rather than the 75-year cut point derived from our systematic review), we performed a sensitivity analysis including only patients who were SCAR positive and aged <70 years from the CSTC data set (data obtained secondarily from the CSTC). In this subset of patients, the trend toward a higher procedural risk of stroke or death with CAS compared with CEA remained (RR=1.77; 95% confidence interval [0.98–3.21]).

Discussion

We have derived and partially validated a simple rule to categorize patients with severe symptomatic carotid stenosis according to their RR of periprocedural stroke or death with CAS versus CEA and to thereby identify a subset of patients in whom CAS may be noninferior to CEA. We used the strongest evidence available from large systematic reviews to identify the relevant risk factors and then validated the resulting

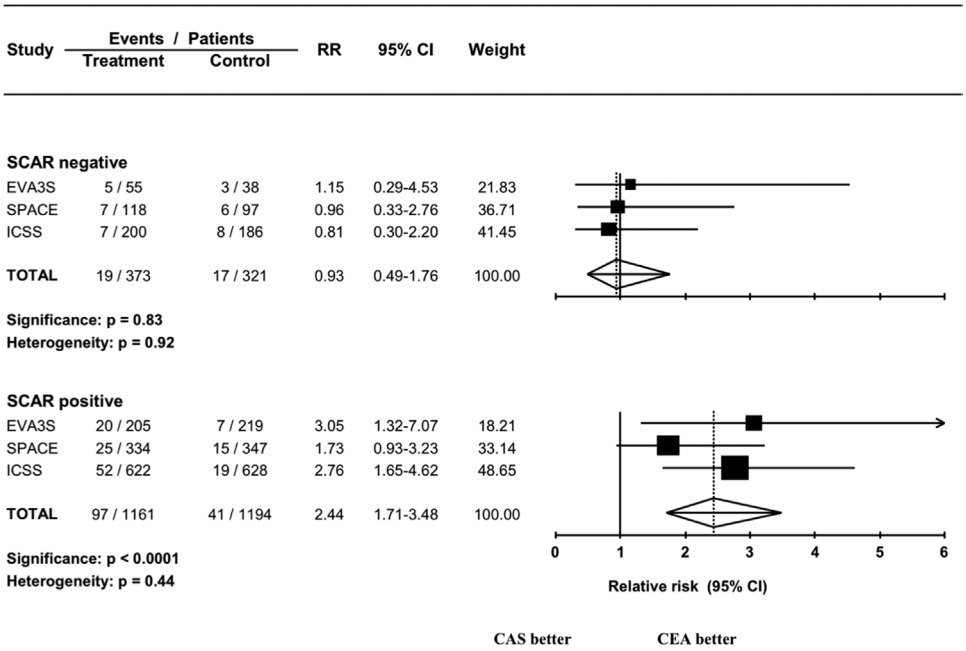


Figure 2. Application of the sex, contralateral occlusion, age, and restenosis (SCAR) rule to the pooled data on procedural risk of stroke and death from the 3 large randomized trials of carotid endarterectomy (CEA) versus carotid angioplasty and stenting (CAS) in the Carotid Stenting Trialists' Collaboration (CSTC).[1] CI indicates confidence interval; EVA3S, Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis; ICSS, International Carotid Stenting Study; RR, relative risk; and SPACE, Stent-Protected Angioplasty versus Carotid Endarterectomy.

rule in the largest available data set of randomized trial data comparing CAS with CEA. In this validation analysis, the results were highly consistent across trials. In the pooled data set of the 3 major European trials, the SCAR-negative patients accounted for about one fourth of the population, although patients with restenosis after previous CEA were excluded from the trials. Thus, in clinical practice, the rule would allow clinicians to identify those patients who might be able to undergo CAS without a higher procedural risk of stroke and death than with CEA (ie, patients with restenosis or contralateral occlusion and women aged <75 years).

In most trials and registries of patients with carotid stenosis, women account for about one third of the population recruited. Randomized trials of CEA for both symptomatic and asymptomatic carotid stenosis and systematic reviews of observational data have demonstrated that benefit is decreased in women, partly because of a high operative risk, which is independent of age.[8,21,22] By contrast, whether there are also sex differences in risk of CAS has remained uncertain.[11,23,24] By pooling all available data, we have confirmed that women are at higher risk of procedural stroke or death after CEA and shown that there is no evidence of an increased risk of periprocedural stroke or death after CAS, the risk being slightly higher in men. This sex difference between CEA and CAS mainly results from a higher risk of periprocedural complications after CEA in women, which has been attributed to sex differences in carotid size and in the nature of the atheromatous plaque.[25,26]

Less than 10% of patients with severe carotid artery stenosis have contralateral carotid occlusion. Most studies that analyzed the impact of contralateral carotid occlusion on procedural risks after CEA had limited statistical power, with inconsistent findings.[27] Although it has been suggested that routine use of shunts during CEA may reduce the risk of complications in this situation,[28] there is no strong evidence to support this view.[29] On the basis that the duration of carotid occlusion is shorter during CAS than during CEA, some authors have suggested that endovascular therapy might be preferable in patients with contralateral occlusion, but there was little evidence.[30–32] Our systematic review showing that patients with severe carotid stenosis and contralateral carotid occlusion are at high risk of periprocedural complications after CEA, but not after CAS, and the validation on RCTs provide useful new evidence and have practical implications.

Although previous meta-analyses of RCTs and registries have consistently shown that age has only a small impact on the risk of complications after CEA,[8] elderly patients have been considered at high surgical risk and therefore to be potentially good candidates for CAS by several authors.[13,33–35] However, as shown in our previous systematic reviews,[7–11] and more recently in RCTs,[2,7] increasing age has more impact on the procedural risk of CAS than CEA. This is also in agreement with studies showing that elderly patients are more likely to have tortuous and severely calcified vessels, resulting in an increased risk of embolization during wire manipulation and catheter exchanges at some stage in CAS.[12,36,37]

Restenosis occurs in ≥10% of patients treated by CEA,[38] and is generally attributed to neointimal hyperplasia during the early postoperative period or recurrent atherosclerosis thereafter. Although most carotid restenoses are asymptomatic, reoperation has been considered necessary in ≤8% of patients.[39] Surgical treatment for recurrent carotid stenosis is more technically difficult than primary procedures, notably because dissection of the neck tissues and the artery is more challenging. Several authors and guidelines have suggested that CAS may be the preferred treatment for post-CEA restenosis.[40,41] Using all available data, we have shown that in comparison with primary stenosis, restenosis is associated with a higher risk of stroke or death after CEA, but with a lower risk after CAS. We could not validate the finding in RCT data, but an RCT comparing CEA with CAS specifically in patients with carotid restenosis is unlikely to be performed in the future.

Our analysis has several potential limitations. First, because, the European RCTs did not include asymptomatic stenosis, further studies are required to validate the rule in this situation. However, there is no evidence from the literature suggesting a potential interaction between the clinical indication and any of the components of the SCAR rule concerning the periprocedural risk of stroke or death after CEA or CAS, and the components of the rule were identified from studies that included both symptomatic and asymptomatic patients. Second, a recent analysis of data from the CREST trials suggested that women have a higher risk of periprocedural stroke or death after CAS (5.5% versus 3.7%).[24] However, the treatment-by-sex interaction was not significant, and the results are not consistent with other trial data or case series, and no results were reported for women <75 years.[23] Moreover, these CREST data were included in our meta-analyses, with little effects on the overall estimates. Third, the cutoff we used for age may be questionable. Indeed, the pooled analysis of the European trials and CREST have detected an interaction between age and treatment effect, with a crossover at an age of ≈70 years; CAS being better at younger ages, and CEA better at older ages.[2,7] However, in most observational studies, the cutoffs used to categorize patients were either 75 or 80 years, and SCAR-positive patients <70 years were still at higher risk for procedural stroke or death after CAS compared with CEA in the CSTC data set. Fourth, we were unable to study some potential risk factors attributable to limited availability of published data from observational studies or lack of collection of data in the randomized trials. For instance, technical and anatomic factors, especially extreme angulation of the carotid artery or calcifications, can have an impact on the risks of CAS,[12] but there are few similar data published for CEA. We have also not been able to analyze patients according to both protection device systems and the risk factors simultaneously. However, there is no known interaction between the use of protection device systems and risk factors we examined. Leukoariaosis has been shown to be a risk factor for CEA in NASCET,[42] and also for CAS in ICSS,[43] but has not been widely studied. Similarly, the RR of periprocedural stroke or death in relation to the timing of the procedure might differ between CAS and CEA,[9,44] but definitions of early and late intervention differ widely in observational studies. Fifth, although the pooled absolute risks of periprocedural stroke or death in SCAR-negative patients were identical between CAS and CEA in the validation population, our approach cannot formally demonstrate noninferiority. Finally, although the rule can already be considered useful for clinical practice, further

refinement will be required in the future, notably to identify the best option between the 2 potential rules we tested.

Appendix

CSTC Collaborators: The CSTC Steering Committee comprises A. Algra (independent chair); EVA-3S A. Branchereau, G. Chatellier, J.-L. Mas; SPACE G. Fraedrich, P.A. Ringleb, H. Zeumer; ICSS L.H. Bonati, M.M. Brown, W.P. Mali; J. Dobson (meta-analysis statistician). Steering committees of trials included in CSTC: EVA-3S J.-L. Mas (chair), G. Chatellier (cochair), J.-P. Becquemin, J.-F. Bonneville, A. Branchereau, D. Crochet, J.C. Gaux, V. Larrue, D. Leys, J. Watelet; SPACE W. Hacke (chair), M. Hennerici, J.R. Allenberg, P.C. Maurer, H.-H. Eckstein, H. Zeumer, O. Jansen; ICSS A. Algra, J. Bamford (chair), J. Beard, M. Bland, A.W. Bradbury, M.M. Brown (chief investigator), A. Clifton, P. Gaines, W. Hacke, A. Halliday, I. Malik, J.-L. Mas, A.J. McGuire, P. Sidhu, G. Venables.

Contributors: The study was conceived by P.M. Rothwell, and the protocol was drafted by E. Touzé and L. Trinquart. E. Touzé, L. Trinquart, R. Felgueiras, K. Rerkasem, and G. Meliksetyan were responsible for data collection. E. Touzé, L. Trinquart, and P.M. Rothwell were responsible for data analysis, data interpretation, and preparation of the report. L.H. Bonati, J.-L. Mas, P.A. Ringleb, and M.M. Brown provided data from the CSTC. All authors contributed to data interpretation, critical revision of the report, and approved the final version.

Role of the Funding Sources: This study was not funded. The sponsors of the contributing trials (EVA-3S, SPACE, ICSS) had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the discussion to submit for publication.

Sources of Funding

Dr Rothwell holds a National Institute of Health Research (NIHR) Senior Investigator Award and a Wellcome Trust Senior Investigator Award and is funded by the NIHR Biomedical Research Center, Oxford. ICSS was funded by grants from the Medical Research Council (MRC), The Stroke Association, Sanofi Synthelabo, and the European Commission. The funding from the MRC was managed by NIHR on behalf of the MRC-NIHR partnership. Dr Rerkasem has been funded by The Thailand Research Fund (RSA5580008) and Faculty of Medicine, Chiang Mai University. Dr Brown's Chair in Stroke Medicine at University College London is supported by the Reta Lila Weston Trust for Medical Research. Part of this work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centers funding scheme. Dr Bonati was supported by grants from the Swiss National Science Foundation (PBBSB-116873), the University of Basel, Switzerland, and The Stroke Association. EVA-3S was funded by the French Ministry of Health (Program Hospitalier de Recherche Clinique, Assitance Publique des Hôpitaux de Paris [AOM 97066]).

Disclosures

None.

References

1. Bonati LH, Lyrer P, Ederle J, Featherstone R, Brown MM. Percutaneous transluminal balloon angioplasty and stenting for carotid artery stenosis. *Cochrane Database Syst Rev*. 2012;9:CD000515.
2. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, et al; CREST Investigators. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.
3. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, et al; EVA-3S investigators. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol*. 2008;7:885–892.
4. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol*. 2008;7:893–902.
5. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, et al; American College of Cardiology Foundation; American Stroke Association; American Association of Neurological Surgeons; American College of Radiology; American Society of Neuroradiology; Congress of Neurological Surgeons; Society of Atherosclerosis Imaging and Prevention; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society of NeuroInterventional Surgery; Society for Vascular Medicine; Society for Vascular Surgery. 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: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. *Circulation*. 2011;124:489–532.
6. Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clement D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). *Eur Heart J*. 2011;32:2851–2906.
7. Bonati LH, Dobson J, Algra A, Branchereau A, Chatellier G, Fraedrich G, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. *Lancet*. 2010;376:1062–1073.
8. Bond R, Rerkasem K, Cuffe R, Rothwell PM. A systematic review of the associations between age and sex and the operative risks of carotid endarterectomy. *Cerebrovasc Dis*. 2005;20:69–77.
9. Bond R, Rerkasem K, Rothwell PM. Systematic review of the risks of carotid endarterectomy in relation to the clinical indication for and timing of surgery. *Stroke*. 2003;34:2290–2301.
10. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke*. 2009;40:e564–e572.
11. Touzé E, Trinquart L, Chatellier G, Mas JL. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke*. 2009;40:e683–e693.
12. Naggara O, Touzé E, Beyssen B, Trinquart L, Chatellier G, Meder JF, et al; EVA-3S Investigators. Anatomical and technical factors associated with stroke or death during carotid angioplasty and stenting: results from the endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial and systematic review. *Stroke*. 2011;42:380–388.
13. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med*. 2004;351:1493–1501.
14. Rerkasem K, Rothwell PM. Temporal trends in the risks of stroke and death due to endarterectomy for symptomatic carotid stenosis: an updated systematic review. *Eur J Vasc Endovasc Surg*. 2009;37:504–511.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264–269.
16. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. *Stat Med*. 2004;23:1351–1375.
17. Fleiss JL. Analysis of data from multiclinic trials. *Control Clin Trials*. 1986;7:267–275.
18. Koopman L, van der Heijden GJ, Hoes AW, Grobbee DE, Rovers MM. Empirical comparison of subgroup effects in conventional and individual patient data meta-analyses. *Int J Technol Assess Health Care*. 2008;24:358–361.
19. Freeman M, Tukey J. Transformations related to the angular and the square root. *Ann Math Stat*. 1950;21:607–611.

20. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med*. 2004;23:1663–1682.
21. Rothwell PM. ACST: which subgroups will benefit most from carotid endarterectomy? *Lancet*. 2004;364:1122–1123.
22. Rothwell PM, Eliasziw M, Gutnikov SA, Warlow CP, Barnett HJ; Carotid Endarterectomy Trialists Collaboration. Endarterectomy for symptomatic carotid stenosis in relation to clinical subgroups and timing of surgery. *Lancet*. 2004;363:915–924.
23. Brown MM, Raine R. Should sex influence the choice between carotid stenting and carotid endarterectomy? *Lancet Neurol*. 2011;10:494–497.
24. Howard VJ, Lutsep HL, Mackey A, Demaerschalk BM, Sam AD II, Gonzales NR, et al; CREST investigators. Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST). *Lancet Neurol*. 2011;10:530–537.
25. Lee JW, Pomposelli F, Park KW. Association of sex with perioperative mortality and morbidity after carotid endarterectomy for asymptomatic carotid stenosis. *J Cardiothorac Vasc Anesth*. 2003;17:10–16.
26. Rockman CB, Castillo J, Adelman MA, Jacobowitz GR, Gagne PJ, Lamparello PJ, et al. Carotid endarterectomy in female patients: are the concerns of the Asymptomatic Carotid Atherosclerosis Study valid? *J Vasc Surg*. 2001;33:236–240.
27. Goodney PP, Wallaert JB, Scali ST, Stone DH, Patel V, Shaw P, et al. Impact of practice patterns in shunt use during carotid endarterectomy with contralateral carotid occlusion. *J Vasc Surg*. 2012;55:61–71.
28. Aburahma AF, Mousa AY, Stone PA. Shunting during carotid endarterectomy. *J Vasc Surg*. 2011;54:1502–1510.
29. Bond R, Rerkasem K, Counsell C, Salinas R, Naylor R, Warlow CP, et al. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev*. 2002;2002:CD000190.
30. Touzé E, Calvet D, Chatellier G, Mas JL. Carotid stenting. *Curr Opin Neurol*. 2008;21:56–63.
31. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al; CAPTURE Trial Collaborators. The CAPTURE registry: predictors of outcomes in carotid artery stenting with embolic protection for high surgical risk patients in the early post-approval setting. *Catheter Cardiovasc Interv*. 2007;70:1025–1033.
32. Gray WA, Chaturvedi S, Verta P; Investigators and the Executive Committees. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ Cardiovasc Interv*. 2009;2:159–166.
33. Safian RD, Bresnahan JF, Jaff MR, Foster M, Bacharach JM, Maini B, et al; CREATE Pivotal Trial Investigators. Protected carotid stenting in high-risk patients with severe carotid artery stenosis. *J Am Coll Cardiol*. 2006;47:2384–2389.
34. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, et al. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv*. 2007;69:341–348.
35. Katzen BT, Criado FJ, Ramee SR, Massop DW, Hopkins LN, Donohoe D, et al; CASES-PMS Investigators. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. *Catheter Cardiovasc Interv*. 2007;70:316–323.
36. Bazan HA, Pradhan S, Mojibian H, Kyriakides T, Dardik A. Increased aortic arch calcification in patients older than 75 years: implications for carotid artery stenting in elderly patients. *J Vasc Surg*. 2007;46:841–845.
37. Lam RC, Lin SC, DeRubertis B, Hynecek R, Kent KC, Faries PL. The impact of increasing age on anatomic factors affecting carotid angioplasty and stenting. *J Vasc Surg*. 2007;45:875–880.
38. Frericks H, Kievit J, van Baalen JM, van Bockel JH. Carotid recurrent stenosis and risk of ipsilateral stroke: a systematic review of the literature. *Stroke*. 1998;29:244–250.
39. AbuRahma AF, Jennings TG, Wulu JT, Tarakji L, Robinson PA. Redo carotid endarterectomy versus primary carotid endarterectomy. *Stroke*. 2001;32:2787–2792.
40. Lal BK, Hobson RW II. Management of carotid restenosis. *J Cardiovasc Surg (Torino)*. 2006;47:153–160.
41. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease. *J Vasc Surg*. 2011;54:e1–31.
42. Streifler JY, Eliasziw M, Benavente OR, Alamowitch S, Fox AJ, Hachinski VC, et al; North American Symptomatic Carotid Endarterectomy Trial Group. Prognostic importance of leukoaraiosis in patients with symptomatic internal carotid artery stenosis. *Stroke*. 2002;33:1651–1655.
43. Ederle J, Davagnanam I, van der Worp HB, Venables GS, Lyrer PA, Featherstone RL, et al; ICSS investigators. Effect of white-matter lesions on the risk of periprocedural stroke after carotid artery stenting versus endarterectomy in the International Carotid Stenting Study (ICSS): a prespecified analysis of data from a randomised trial. *Lancet Neurol*. 2013;12:866–872.
44. Collaboration CST. The risk of carotid artery stenting compared with carotid endarterectomy is greatest in patients treated within 7 days of symptoms. *J Vasc Surg*. 2013;57:619–626.

Supplemental Material

A clinical rule (SCAR) to select patients for stenting versus carotid endarterectomy: a systematic review of observational studies with validation in randomised trials

Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed.

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Age (years)	**CAS**	30	Age (years)	71.1	63.0	74.0
			Male (%)	69.7	59.0	86.0
			Symptomatic (%)	40.8	14.0	100.0
			Study size (N patients)	410	15	5341
			Single-center studies (N)	14		
			Consecutive enrollment (N)	16		
			Prospective studies (N)	15		
	CEA	52	Age (years)	69.3	57.0	84.0
			Male (%) (%)	74.0	52.0	95.0
			Symptomatic (%)	55.8	0.0	100.0
			Study size (N patients)	523	79	13622
			Single-center studies (N)	34		
			Consecutive enrollment (N)	31		
			Prospective studies (N)	17		
Contralateral occlusion	**CAS**	9	Age (years)	71.3	69.0	73.0
			Male (%)	68.7	62.0	84.0
			Symptomatic (%)	32.0	26.0	61.0
			Study size (N patients)	471	58	2001
			Single-center studies (N)	6		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	5		
	CEA	33	Age (years)	68.3	57.0	75.0
			Male (%)	67.8	58.0	93.0
			Symptomatic (%)	53.8	0.0	100.0
			Study size (N patients)	526	83	6038
			Single-center studies (N)	24		
			Consecutive enrollment (N)	19		
			Prospective studies (N)	11		
Coronary artery disease	**CAS**	8	Age (years)	70.8	61.0	72.0
			Male (%)	70.3	65.0	74.0
			Symptomatic (%)	39.7	24.0	100.0
			Study size (N patients)	353	26	1380
			Single-center studies (N)	7		
			Consecutive enrollment (N)	5		
			Prospective studies (N)	2		
	CEA	16	Age (years)	68.5	57.0	75.0
			Male (%)	66.1	58.0	76.0
			Symptomatic (%)	51.8	21.0	100.0
			Study size (N patients)	600	83	6038
			Single-center studies (N)	8		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	4		

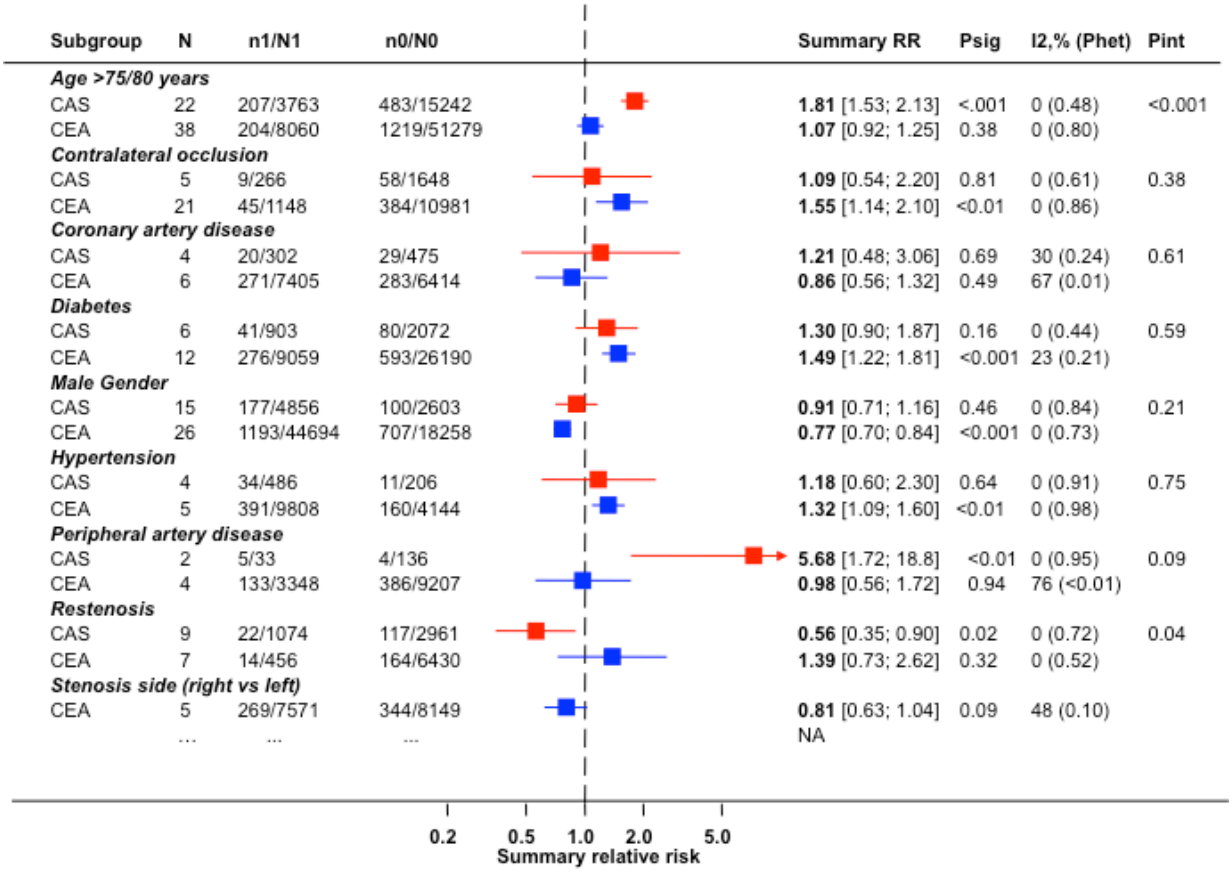
Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed (continued).

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Diabetes	**CAS**	12	Age (years)	71.2	67.0	73.0
			Male (%)	69.5	63.0	84.0
			Symptomatic (%)	33.7	22.0	100.0
			Study size (N patients)	584	26	1729
			Single-center studies (N)	8		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	3		
	CEA	23	Age (years)	68.4	57.0	75.0
			Male (%)	77.9	53.0	95.0
			Symptomatic (%)	53.6	0.0	100.0
			Study size (N patients)	678	57	13622
			Single-center studies (N)	12		
			Consecutive enrollment (N)	11		
			Prospective studies (N)	9		
Gender	**CAS**	21	Age (years)	70.1	61.0	73.0
			Male (%)	70.1	47.0	90.0
			Symptomatic (%)	47.3	24.0	100.0
			Study size (N patients)	418	15	5341
			Single-center studies (N)	13		
			Consecutive enrollment (N)	7		
			Prospective studies (N)	10		
	CEA	42	Age (years)	67.9	62.0	75.0
			Male (%)	72.4	43.0	95.0
			Symptomatic (%)	61.7	0.0	100.0
			Study size (N patients)	520	53	13622
			Single-center studies (N)	24		
			Consecutive enrollment (N)	22		
			Prospective studies (N)	13		
Hypertension	**CAS**	9	Age (years)	70.7	61.0	72.0
			Male (%)	71.1	65.0	84.0
			Symptomatic (%)	40.0	24.0	100.0
			Study size (N patients)	333	26	1380
			Single-center studies (N)	8		
			Consecutive enrollment (N)	6		
			Prospective studies (N)	1		
	CEA	17	Age (years)	68.7	62.0	75.0
			Male (%)	66.5	53.0	76.0
			Symptomatic (%)	49.3	0.0	100.0
			Study size (N patients)	752	252	6038
			Single-center studies (N)	6		
			Consecutive enrollment (N)	6		
			Prospective studies (N)	5		

Supplementary table I – Characteristics of studies included in the systematic review and meta-analysis according to the 9 risk factors analysed (continued).

Subgroup	Intervention	N studies (N)	Variable	Mean	Min	Max
Peripheral artery disease	**CAS**	6	Age (years)	71.3	69.0	72.0
			Male (%)	71.2	65.0	77.0
			Symptomatic (%)	27.5	24.0	50.0
			Study size (N patients)	470	26	1380
			Single-center studies (N)	5		
			Consecutive enrollment (N)	4		
			Prospective studies (N)	2		
	CEA	7	Age (years)	68.4	57.0	72.0
			Male (%)	67.5	65.0	74.0
			Symptomatic (%)	56.9	21.0	100.0
			Study size (N patients)	3056	83	6038
			Single-center studies (N)	2		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	3		
Restenosis	**CAS**	11	Age (years)	70.7	61.0	74.0
			Male (%)	69.1	56.0	74.0
			Symptomatic (%)	44.3	17.0	96.0
			Study size (N patients)	418	47	5341
			Single-center studies (N)	6		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	7		
	CEA	13	Age (years)	71.9	68.0	74.0
			Male (%)	59.5	51.0	70.0
			Symptomatic (%)	57.9	37.0	74.0
			Study size (N patients)	1341	352	20940
			Single-center studies (N)	11		
			Consecutive enrollment (N)	12		
			Prospective studies (N)	5		
Stenosis side	**CAS**	4	Age (years)	69.8	67.0	70.0
			Male (%)	70.8	68.0	71.0
			Symptomatic (%)	59.8	55.0	100.0
			Study size (N patients)	562	77	5341
			Single-center studies (N)	2		
			Consecutive enrollment (N)	3		
			Prospective studies (N)	1		
	CEA	8	Age (years)	66.6	57.0	69.0
			Male (%)	66.5	65.0	74.0
			Symptomatic (%)	72.2	60.0	100.0
			Study size (N patients)	1807	83	6038
			Single-center studies (N)	2		
			Consecutive enrollment (N)	4		
			Prospective studies (N)	2		

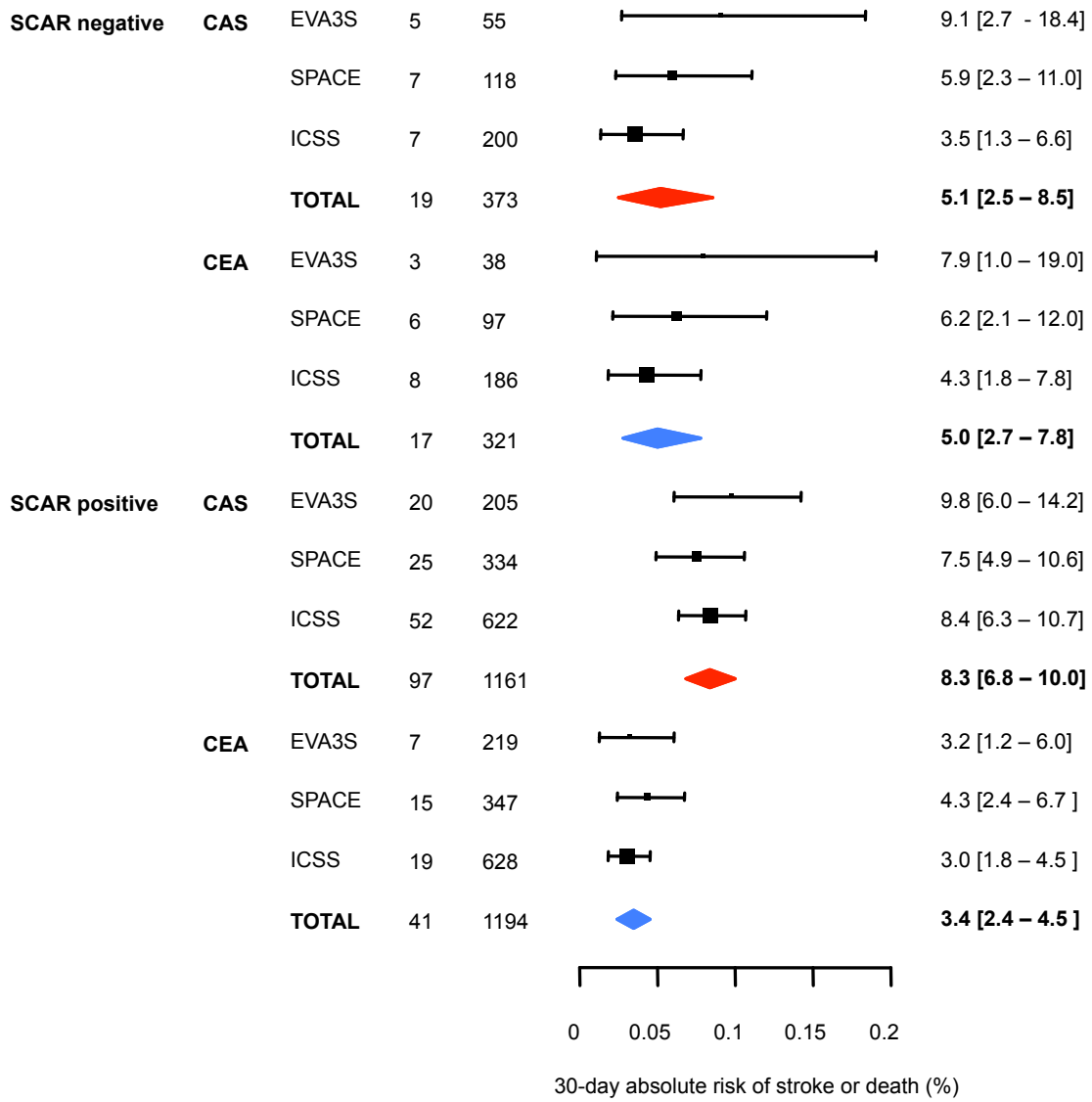
Supplementary figure I – Meta-analyses of the relative risk of stroke after CAS and CEA according to the 9 potential risk factors.



Supplementary table II – Categorization of patients according to the 2 potential definitions of the SCAR rule.

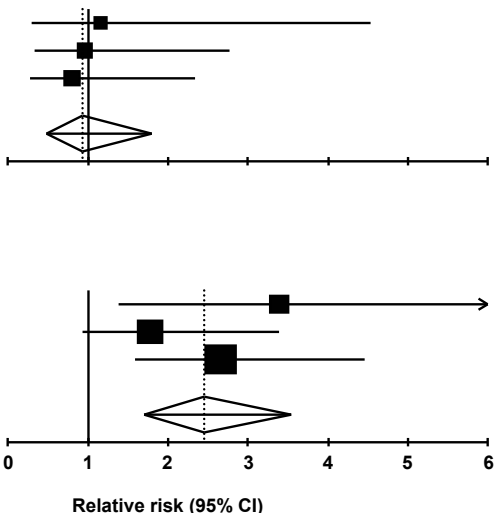
	Contralateral occlusion								No contralateral occlusion							
	Restenosis				No restenosis				Restenosis				No restenosis			
	Women		Men		Women		Men		Women		Men		Women		Men	
Age	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75	<75	>75
SCAR primary option	-	-	-	-	-	-	-	-	-	-	-	-	-	+	+	+
SCAR secondary option	-	-	-	-	-	-	-	+	-	-	-	+	-	+	+	+

Supplementary figure II – Pooled absolute risks of stroke and death according to the SCAR rule in the three large randomised trials of CEA vs. CAS in the CSTC.



Supplementary figure III – Application of the SCAR rule (primary definition) to the pooled data on procedural risk of stroke from the three large randomised trials of CEA vs. CAS in the CSTC.

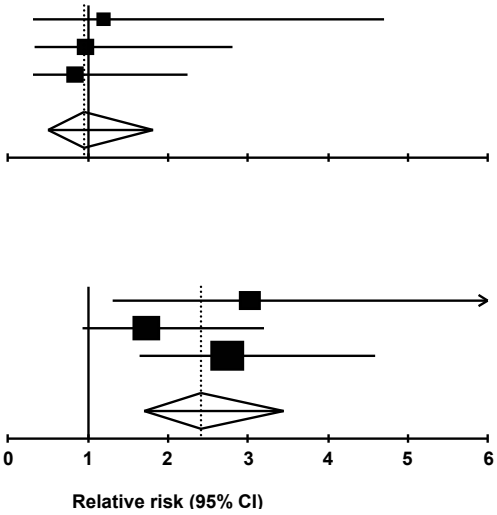
Study	Events / Patients		RR	95% CI
	Treatment	Control		
SCAR negative				
EVA3S	5 / 55	3 / 38	1.15	0.29-4.53
SPACE	7 / 118	6 / 97	0.96	0.33-2.76
ICSS	6 / 200	7 / 186	0.80	0.27-2.33
TOTAL	18 / 373	16 / 321	0.93	0.48-1.80
Significance: p = 0.83				
Heterogeneity: p = 0.92				
SCAR positive				
EVA3S	19 / 205	6 / 219	3.38	1.38-8.30
SPACE	24 / 334	14 / 347	1.78	0.94-3.38
ICSS	50 / 622	19 / 628	2.66	1.59-4.45
TOTAL	93 / 1161	39 / 1194	2.45	1.70-3.54
Significance: p = <0.0001				
Heterogeneity: p = 0.46				



Supplementary figure IV – Application of the SCAR rule (secondary definition, i.e. all factors are considered as equivalent) to the pooled data on procedural risk of stroke and death (A) and stroke (B) from the three large randomised trials of CEA vs. CAS in the CSTC.

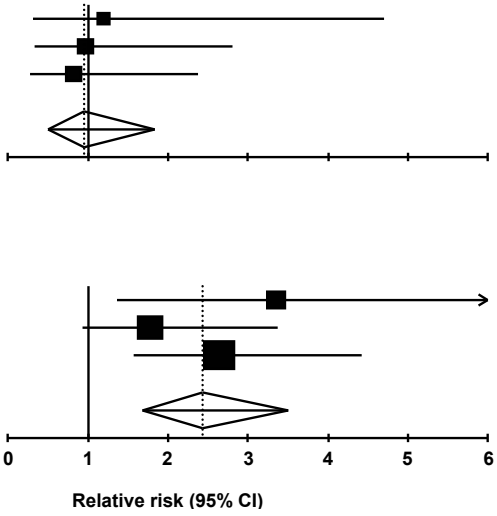
A – Stroke and death

Study	Events / Patients		RR	95% CI
	Treatment	Control		
SCAR negative				
EVA3S	5 / 53	3 / 38	1.19	0.30-4.70
SPACE	7 / 115	6 / 96	0.97	0.34-2.80
ICSS	7 / 189	8 / 180	0.83	0.31-2.25
TOTAL	19 / 357	17 / 314	0.95	0.50-1.80
Significance: p = 0.88				
Heterogeneity: p = 0.92				
SCAR positive				
EVA3S	20 / 207	7 / 219	3.02	1.31-7.00
SPACE	25 / 337	15 / 348	1.72	0.92-3.21
ICSS	52 / 633	19 / 634	2.74	1.64-4.58
TOTAL	97 / 1177	41 / 1201	2.42	1.69-3.45
Significance: p = <0.0001				
Heterogeneity: p = 0.44				



B – Stroke

Study	Events / Patients		RR	95% CI
	Treatment	Control		
SCAR negative				
EVA3S	5 / 53	3 / 38	1.19	0.30-4.70
SPACE	7 / 115	6 / 96	0.97	0.34-2.80
ICSS	6 / 189	7 / 180	0.82	0.28-2.38
TOTAL	18 / 357	16 / 314	0.95	0.49-1.84
Significance: p = 0.89				
Heterogeneity: p = 0.91				
SCAR positive				
EVA3S	19 / 207	6 / 219	3.35	1.36-8.22
SPACE	24 / 337	14 / 348	1.77	0.93-3.36
ICSS	50 / 633	19 / 634	2.64	1.57-4.42
TOTAL	93 / 1177	39 / 1201	2.43	1.69-3.51
Significance: p = <0.0001				
Heterogeneity: p = 0.47				



List of all references included in the systematic review.
Subgroup=Age
CAS
Zarins CK *et al*. J Endovasc Ther 2009;16:397-409.
Takayama K *et al*. Radiat Med 2008;26:348-354.
Stabile E *et al*. J Am Coll Cardiol 2010;55:1661-1667.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Perona F *et al*. Radiology 2009;250:178-183.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
Henry M *et al*. Catheter Cardiovasc Interv 2008;72:309-317.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Chaturvedi S *et al*. Stroke 2010;41:757-764.
Bacharach JM *et al*. Ann Vasc Surg 2010;24:153-159.
Almekhlafi MA *et al*. Can J Neurol Sci 2011;38:446-451.
Katzen B *et al*. Am J Cardiol 2006;98(suppl 1):11M.
Kastrup A *et al*. AJNR Am J Neuroradiol 2008;29:608-612.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Kadkhodayan Y *et al*. Neuroradiology 2007;49:933-938.
Gray WA *et al*. Catheter Cardiovasc Interv 2007;70:1025-1033.
Zahn R *et al*. Eur Heart J 2007;28:370-375.
Teitelbaum GP *et al*. Surgical Neurology 1998;50:300-311.
Shawl F *et al*. J Am Coll Cardiol 2000;35:1721-1728.
Reimers B *et al*. Am J Med 2004;116:217-222.
Roubin GS *et al*. Circulation 2001;103:532-537.
Ahmadi R *et al*. J Endovasc Ther 2002;9:559-565.
Hobson RW *et al*. J Vasc Surg 2004;40:1106-1111.
Setacci C *et al*. J Endovasc Ther 2006;13:302-309.
Safian RD *et al*. J Am Coll Cardiol 2006;47:2384-2389.
Lam RC *et al*. J Vasc Surg 2007;45:875-880.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Zarins CK *et al*. J Endovasc Ther 2009;16:397-409.
Young B *et al*. Stroke 1996;27:2216-2224.
Wong JH *et al*. Stroke 1997;28:891-898.
Van Damme H *et al*. Acta Chir Belg 1996;96:71-77.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Ting ACW *et al*. Cardiovasc Surg 2000;8:441-445.
Taylor DW *et al*. Lancet 1999;353:2179-2184.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Sternbergh WC *et al*. The Ochsner Journal 2003;5:24-30.
Sokol D *et al*. Acta Neurochir (Wien) 2011;153:363-369.
Schultz RD *et al*. Surg Gynecol Obstet 1988;166:245-251.
Schneider JR *et al*. J Vasc Surg 2000;31:927-935.
Salameh JR *et al*. Arch Surg 2002;137:1284-1288.
Rockman CB *et al*. Ann Vasc Surg 2003;17:9-14.
Reed AB *et al*. J Vasc Surg 2003;37:1191-1199.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Pruner G *et al*. Cardiovasc Surg 2003;11:105-112.
Perler BA *et al*. J Am Coll Surg 1996;183:559-564.
Papachristou EA *et al*. Vasc Surg 1994;28:531-537.
Ouriel K *et al*. Surg Gynecol Obstet1986;162:334-336.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Ommer A *et al*. Cardiovasc Surg 2001;9:552-558.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
Navas Vinagre I *et al*. Neurologia 2008;23:408-414.
Miller MT *et al*. J Vasc Surg 2005;41:231-237.

Maxwell JG *et al*. Am Surg 2000;66:773-780.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Love A *et al*. Cardiovasc Surg 2000;8:429-435.
Lau D *et al*. Am J Surg 2005;190:795-799.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363(9420):1491-1502.
Goldman KA *et al*. Vasc Surg 1999;33:451-460.
Fabiani A *et al*. Cardiovasc Surg 2001;9:2-2.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Dorafshar AH *et al*. Ann Vasc Surg 2004;18:729-735.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Debing E *et al*. Surg Neurol 2007;67:467-471.
Coyle KA *et al*. Ann Vasc Surg 1994;8:417-420.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Cartier B *et al*. Ann Vasc Surg 2002;16:751-755.
Brown MM *et al*. Pract Neurol 2008;8:39-45.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. J Vasc Surg 2009;50:518-525.
Aune S *et al*. Int Angiol 2003;22:421-425.
Ascher E *et al*. Ann Vasc Surg 2001;15:275-280.
Alozairi O *et al*. Eur J Vasc Endovasc Surg 2003;26:245-249.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Contralateral occlusion

CAS

Stabile E *et al*. J Am Coll Cardiol 2010;55:1661-1667.
Perona F *et al*. Radiology 2009;250:178-183.
Massop D *et al*. Catheter Cardiovasc Interv 2009;73:129-136.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Silvestro A *et al*. J Cardiovasc Med (Hagerstown) 2008;9:137-141.
Reimers B *et al*. Am J Med 2004;116:217-222.
Sabeti S *et al*. Radiology 2004;230:70-76.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.

CEA

Tu JV *et al*. Stroke 2003;34:2568-2573.
Simo G *et al*. Cardiovasc Surg 2001;9:29-29.
Schneider JR *et al*. J Vasc Surg 2002;35:1114-1122.
Samson RH *et al*. Cardiovasc Surg 1998;6:475-484.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Perler BA *et al*. J Vasc Surg 1992;16:347-352.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
McCarthy WJ *et al*. Am J Surg 1993;166:168-171.
Mattos MA *et al*. Surgery 1992;112:670-679.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Lacroix H *et al*. Cardiovasc Surg 1994;2:26-31.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Karmeli R *et al*. Cardiovasc Surg 2001;9:334-338.
Julia P *et al*. Ann Vasc Surg 1998;12:566-571.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Jansen C *et al*. Ann Vasc Surg 1993;7:95-101.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Furst H *et al*. World J Surg 2001;25:969-974.
Fitzpatrick CM *et al*. Mil Med 2005;170:1069-1074.
ECST. Lancet 1998;351:1379-1387.

Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Domenig C *et al*. Ann Vasc Surg 2003;17:622-628.
Deriu GP *et al*. Ann Vasc Surg 1994;8:337-342.
da Silva AF *et al*. Br J Surg 1996;83:1370-1372.
Cao P *et al*. Eur J Vasc Endovasc Surg 1995;10:16-22.
Bunt TJ *et al*. Am Surg 1985;51:61-69.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Baker WH *et al*. Stroke 2000;31:2330-2334.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.
AbuRahma AF *et al* .Stroke 2000;31:1566-1571.

Coronary artery disease
CAS
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Wong JH *et al*. Stroke 1997;28:891-898.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Magnan PE *et al.* Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*.Neurosurgery 1999;45:786-791.
Kucey DS *et al*.J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Diabetes
CAS
Schluter M *et al*. J Endovasc Ther 2007;14:271-278.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Criado E *et al*. Am J Cardiol 2006;98(suppl 1):243M.
Setacci C *et al*. Am J Cardiol 2006;98(suppl 1):12M.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O. *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Young B *et al*. Stroke 1996;27:2216-2224.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Pistolese GR *et al*. J Vasc Surg 2001;33:148-154.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.

Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Debing E *et al*. Vasc Endovasc Surg 2011;45:28-32.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. Surgery 2001;129:146-152.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.
Aguiar ET *et al*. Sao Paulo Medical Journal 2001;119:206-211.

Gender
CAS
Tietke MW *et al*. Neuroradiology 2010;52:611-618.
Takayama K *et al*. Radiat Med 2008;26:348-354.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Perona F *et al*. Radiology 2009;250:178-183.
Park B *et al*. Vasc Endovasc Surg 2008;42:321-328.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
Howard VJ *et al*. Lancet Neurol 2011;10:530-537.
Howard VJ *et al*. Stroke 2009;40:1140-1147.
Goldstein LJ *et al*. J Vasc Surg 2009;49:315-323.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Kypta A *et al*. Am J Cardiol 2006;98(suppl 1):244M.
Gonzalez-Marcos JR *et al*. Int J Stroke 2006;1(suppl 1):65.
Arjomand H *et al*. J Am Coll Cardiol 2008;52:B78 (abstract)
Iihara K *et al*. J Neurosurg 2006;105:546-554.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Teitelbaum GP *et al*. Surgical Neurology 1998;50:300-311.
Reimers B *et al*. Am J Med 2004;116:217-222.
Biasi GM *et al*. Circulation 2004;110:756-762.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Vigo J *et al*. Bol Asoc Med P R 1992;84:128-131.
JAMA 1995;273:1421-1428.
Taylor DW *et al*. Lancet 1999;353:2179-2184.
Syrek JR *et al*. Surgery 1999;125:96-101.
Stoner MC *et al*. J Vasc Surg 2006;43:285-295.
Sternbach Y *et al*. Surgery 2000;127:272-275.
Sokol D *et al*. Acta Neurochir (Wien) 2011;153:363-369.
Schneider JR *et al*. J Vasc Surg 1997;25:890-896.
Sarac TP *et al*. J Vasc Surg 2002;35:748-753.
Perler BA *et al*. Cardiovasc Surg 1995;3:631-636.
Park B *et al*. Vasc Endovasc Surg 2008;42:321-328.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Naylor AR *et al*. J Vasc Surg 2000;32:750-759.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Lane JS *et al*. J Vasc Surg 2003;37:568-574.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Kapral MK *et al*. Stroke 2003;34:1120-1124.
Kapral MK *et al*. J Women's Health Gender Med 2000;9:987-994.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
James DC *et al*. Am J Surg 2001;182:654-657.

Hugl B *et al*. Ann Vasc Surg 2006;20:602-608.
Howard VJ *et al*. Lancet Neurol 2011;10:530-537.
Hartmann A *et al*. Cerebrovasc Dis 1999;9:152-156.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Halliday A *et al*. Lancet 2004;363:1491-1502.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
ECST. Lancet 1998;351:1379-1387.
Eckstein HH *et al*. J Vasc Surg 2002;36:997-1004.
Dorigo W *et al*. J Vasc Surg 2009;50:1301-1306.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Chang JB *et al*. Vasc Endovasc Surg 2002;36:21-27.
Cebul RD *et al*. JAMA 1998;279(16):1282-1287.
Blohme L *et al*. Eur J Vasc Endovasc Surg 1999;17:213-218.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Ballotta E *et al*. Ann Surg 2000;232:119-125.
Archie JP *et al*. J Vasc Surg 1999;29:654-664.
Akbari CM *et al*. J Vasc Surg 2000;31:1103-1109.
Aguiar ET *et al*. Sao Paulo Medical Journal 2001;119:206-211.

Hypertension
CAS
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Kawabata Y *et al*. J Vasc Interv Radiol 2009;20:9-16.
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Young B *et al*. Stroke 1996;27:2216-2224.
Wong JH *et al*. Stroke 1997;28:891-898.
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Taylor DW *et al* .Lancet 1999;353:2179-2184.
Magnan PE *et al*. Ann Vasc Surg 1993;7:521-529.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Kerdiles Y *et al*. J Cardiovasc Surg (Torino) 1997;38:327-334.
Hannan EL *et al*. Stroke 2001;32:2890-2897.
Halm EA *et al*. Stroke 2009;40:221-229.
Goodney PP *et al*. J Vasc Surg 2008;48:1139-1145.
Furst H *et al*. World J Surg 2001;25:969-974.
Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Cebul RD *et al*. JAMA 1998;279:1282-1287.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.

Peripheral artery disease Intervention
CAS
Karkos CD *et al*. Cardiovasc Intervent Radiol 2010;33:34-40.
De Rango P *et al*. J Vasc Surg 2010;51:337-344.
Cremonesi A *et al*. EuroIntervention 2009;5:589-598.
Lanzer P *et al*. Clin Res Cardiol 2006;95:4-12.
Hofmann R *et al*. Stroke 2006;37:2557-2561.
Aydiner O *et al*. Anadolu Kardiyol Derg 2007;7:152-157.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Halm EA *et al*. Stroke 2009;40:221-229.
ECST. Lancet 1998;351:1379-1387.
Dorigo W *et al*. J Vasc Surg 2011;53:44-52.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

Restenosis
CAS
Vos JA *et al*. J Vasc Surg 2009;50:755-761.
Massop D *et al*. Catheter Cardiovasc Interv 2009;73:129-136.
Cuadra S *et al*. Ann Vasc Surg 2009;23:330-334.
AbuRahma AF *et al*. J Vasc Surg 2009;50:1031-1039.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Biasi GM *et al*. Circulation 2004;110:756-762.
Kasirajan K *et al*. Int J Angiol 2006;15:20-24.
Gupta AK *et al*. Neurol India 2006;54:68-72.
Halabi M *et al*. Catheter Cardiovasc Interv 2006;67:513-518.
Safian RD *et al*. J Am Coll Cardiol 2006;47:2384-2389.
Mehta RH *et al*. Am J Cardiol 2007;99:1288-1293.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Pulli R *et al*. Am J Surg 2005;189:714-719.
Organ N *et al*. Eur J Vasc Endovasc Surg 2008;35:273-279.
Maxwell BG *et al*. Am Surg 2000;66:793-796.
Magnadottir HB *et al*. Neurosurgery 1999;45:786-791.
Kresowik TF *et al*. J Vasc Surg 2004;39:372-380.
Jordan WD *et al*. J Vasc Surg 2002;35:16-21.
Hill BB *et al*. J Vasc Surg 1999;30:26-35.
Hertzer NR *et al*. J Vasc Surg 1997;26:1-10.
Domenig C *et al*. Ann Vasc Surg 2003;17:622-628.
Coyle KA *et al*. Ann Surg 1995;221:517-521.
Cho JS *et al*. J Vasc Surg 2004;39:155-161.
AbuRahma AF *et al*. Vasc Surg 2001;35:167-174.

Stenosis side
CAS
Zahn R *et al*. Catheter Cardiovasc Interv 2009;74:1-8.
Randall MS *et al*. Circ Cardiovasc Interv 2010;3:50-56.
Theiss W *et al*. Stroke 2008;39:2325-2330.
Topakian R *et al*. Eur J Neurol 2007;14:672-678.

CEA
Tu JV *et al*. Stroke 2003;34:2568-2573.
Tretter MJ *et al*. J Vasc Surg 1999;30:618-631.
Kucey DS *et al*. J Vasc Surg 1998;28:1051-1058.
Halm EA *et al*. Stroke 2009;40:221-229.
Girard LP *et al*. Circ Cardiovasc Qual Outcomes 2009;2:642-647.
ECST. Lancet 1998;351:1379-1387.
Barnett HJ *et al*. N Engl J Med 1998;339:1415-1425.
Allcutt DA *et al*. Br J Neurosurg 1991;5:257-264.

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5

PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9 & Suppl
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9, 22, Suppl
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9, 22, Suppl
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9, Suppl
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8