Periprocedural Myocardial Infarction After Carotid Endarterectomy and Stenting: Systematic Review and Meta-Analysis

Marion Boulanger, MD; Lucie Camelière, MD; Rui Felgueiras, MD; Ludovic Berger, PhD; Kittipan Rerkasem, PhD; Peter M. Rothwell, PhD; Emmanuel Touzé, PhD

Background and Purpose—Carotid angioplasty and stenting (CAS) is associated with higher risk of periprocedural stroke and death when compared with carotid endarterectomy (CEA). By contrast, the risk of myocardial infarction (MI) was higher after CEA than after CAS in randomized trials. However, numbers were small, and risk factors are unknown.

Methods—We performed a systematic review and a meta-analysis of studies published from January 1980 to June 2014 and collected unpublished data. We extracted data on 9 predefined risk factors (age, contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex, hypertension, peripheral artery disease, type stenosis, and clinical presentation). We selected studies with data available on MI in at least 1 subgroup, calculated absolute and relative risks, and identified differential effects on risks of MI.

Results—The 30-day absolute risk of MI was 0.87% (95% confidence interval, 0.69–1.07) after CEA and 0.70% (95% confidence interval, 0.54–0.88) after CAS (P=0.38). After CAS, patients with symptomatic stenosis and restenosis were at higher risk of MI, whereas men were at lower risk. After CEA, age, history of coronary artery disease, peripheral artery disease, and restenosis increased the risk of MI. Only the effect of sex differed between CAS and CEA with men being at lower risk of MI than women after CAS, whereas there was no difference between after CEA (P=0.01).

Conclusions—The risk of MI after CEA and CAS did not significantly differ. Risk factors for MI are overall similar in both techniques except that men are at lower risk of MI after CAS but not after CEA. (Stroke. 2015;46:2843-2848. DOI: 10.1161/STROKEAHA.115.010052)

Key Words: atherosclerosis ▪ carotid stenosis ▪ endarterectomy, carotid ▪ myocardial infarction ▪ review, systematic

Carotid artery stenosis accounts for 15% to 20% of patients with ischemic stroke or transient ischemic attack. In clinical trials, carotid endarterectomy (CEA) reduces the absolute risk of ischemic stroke by ≥50% in patients with symptomatic or asymptomatic carotid stenosis when compared with medical treatment.1-3 Carotid angioplasty and stenting (CAS) has been evaluated as an alternative to CEA for several years. In the 3 European trials conducted in patients with symptomatic stenosis, the 30-day risk of stroke or death was higher after CAS than after CEA.4 In Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), a similar higher risk of periprocedural stroke or death was observed in symptomatic and asymptomatic stenosis.5 Outcomes after CEA and CAS on long-term follow-up are similar, but the overall stroke risk with CAS remains increased because of the excess initial periprocedural risk.6-7

An excess risk of periprocedural myocardial infarction (MI) after CEA was observed in all randomized controlled trials (RCTs) (pooled odds ratio, 2.23; 95% confidence interval [CI], 1.37–3.63; 6 studies; 5725 patients; I²=0%; Figure 1 in the online-only Data Supplement). Thus, in CREST, the 4-year composite outcome (stroke, MI, and death) did not differ between CEA and CAS. This excess of MI after CEA is not well understood, and the clinical importance of these coronary events has been questioned, mainly because some asymptomatic events manifest as small elevations of cardiac enzymes were counted as outcomes in CREST.8,9 On the contrary, it has been shown that small elevations of cardiac enzymes after non-cardiac and cardiac procedures are associated with increased future mortality.8,9-17 Thus, although stroke is correlated with functional impairment, MI could be an important cause of periprocedural death. Although this finding is consistent...
across all trials, the total number of events observed in these trials was small (<100) and risk factors for periprocedural MI remain unknown. We have recently shown that a simple rule (sex, contralateral occlusion, age, and restenosis [SCAR] rule) could help selecting patients with a similar risk of periprocedural stroke or death after CAS and CEA, but risk factors for MI might also need to be considered. Therefore, we updated our systematic review to (1) assess the absolute risk of periprocedural MI and the absolute risk of periprocedural death after CAS and CEA and (2) identify whether risk factors for these outcomes differ between the 2 interventions.

Methods
We updated our previous systematic reviews or reports of procedural risks of CEA and CAS, for the period October 1, 2011, until June 30, 2014, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations for reporting. Selection Criteria
Eligible studies were those that enrolled patients with symptomatic or asymptomatic stenosis in the region of the carotid bifurcation, treated by CAS or CEA, and in which the numbers of MI or death could be extracted for any subgroup among 9 predefined risk factors: age (≥75–80 versus <75–80 years), contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex (men versus women), hypertension, peripheral artery disease, type of stenosis (restenosis after CEA versus primary atherosclerotic disease), and clinical presentation (symptomatic versus asymptomatic stenosis). Studies were considered irrespective of setting and language. We excluded studies that enrolled only specific populations (eg, postradiation stenosis, restenosis after CEA, and patients treated in an emergency context) and case reports.

For estimation of relative risks (RRs), we included all studies that reported periprocedural risk (that could be periprocedural, intrahospital, or within 30 days after intervention). For estimation of absolute risks, we included studies that reported the risks at 30 days only.

Search Strategy
The search strategy was based primarily on electronic searches of 3 databases (Medline, Embase, and Cochrane Library database) from 1980 to June 30, 2014 (Table I in the online-only Data Supplement). We hand-searched the references of all included studies and any relevant reviews. We also searched books of abstracts from recent conferences that are available online, the US Food and Drug Administration and the European Medicines Agency databases. We contacted 17 authors of studies published after 2003 with data on the risk of periprocedural MI but with data unavailable on subgroups. We also added a retrospective registry from the Department of Vascular Surgery of our hospital (Caen University Hospital, France) of all patients treated by CEA from 2000 to 2013. In case of multiple publications referred to the same population, we retained that with the largest sample or the most relevant for the studied subgroup.

Analysis
Absolute Risk
Proportions of MI and death were calculated after CAS and CEA. Each individual proportion was first transformed into a quantity with the Freeman–Tukey variance stabilizing transformation. A weighted mean of the transformed proportions was computed by using a DerSimonian–Laird random-effects model. The combined proportion was calculated as the back-transform of this weighted mean. We estimated the median year of the period of inclusion (midcohort year) and analyzed the evolution of the absolute risks over time by metaregressions.

Relative Risks
For each of the 9 potential risk factors and separately for studies of CAS and CEA, we calculated the RR of a periprocedural event in patients with versus those without the risk factor. Because of differences between studies in which the risk factor data were reported, the numbers of studies (and patients) included in each meta-analysis differed. When zero cell count was observed in 1 or both groups (ie, patients with and without the risk factor), we used a continuity correction, by adding a factor proportional to the reciprocal of the size of the contrasting study group to all cells. Homogeneity of RR 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. For each risk factor, we assessed whether the effect on the risk of periprocedural event differed between CAS and CEA by performing an interaction test using random-effects metagressions. As recommended for such analyses, we considered a value of P ≤ .10 as evidence for statistically significant interaction. Statistical analyses were performed with SAS 9.2, STATA 11.0 and R.

Results
Of the 1584 articles identified from our update of the electronic searches, 147 abstracts were screened, 140 references were retrieved for assessment in full text, and 96 references were finally eligible (Figure II in the online-only Data Supplement).

In addition, we added 202 references obtained from other sources: (1) 200 references from our previous systematic review; (2) 1 reference from our own registry from the Department of Vascular Surgery (2000–2013); (3) 1 reference for which unpublished data were obtained (ie, the only author who replied). First, these 202 references and the 96 references obtained from electronic searches were screened, and second, we excluded 25 references corresponding to duplicated publications referring to same population. Therefore, 273 references were included corresponding to 120 independent populations. The list of all references included in the systematic review is available in the online-only Data Supplement.

Thirty-Day Absolute Risk of MI
We included 52 independent studies of CEA (62 336 patients) and 68 of CAS (31 843 patients) for the calculation of the 30-day absolute risk of MI. The characteristics of these studies and those of the 1609 patients from our own registry and the list of all references included in the systematic review are shown in Tables II and III in the online-only Data Supplement.

Only 29 (56%) of the 52 CEA studies and 13 (19%) of the 68 CAS studies provided an explicit definition of MI. The Table shows that MI definitions varied across studies, being based on clinical parameters (chest pain suggestive of coronary ischemia), biology (elevation of myocardial necrosis enzymes levels such as creatine kinase, creatine kinase-MB, or troponin), and ECG changes (development of pathological Q waves, new significant ST-segment changes or T-wave changes, or new left bundle branch block). Definitions did not differ between CEA and CAS studies although they tended to be more specific in CAS studies. In our registry, MI is defined as a chest pain associated with ECG changes (development of pathological Q waves, new significant ST-segment changes or T-wave changes, or new left bundle branch block) and elevation of troponin higher than the laboratory limit.

The pooled absolute risk of MI was 0.87% (95% CI, 0.69–1.07; $I^2$ = 81%) after CEA and 0.70% (95% CI, 0.54–0.88;
CI, 0.79–1.08; \( I^2 = 24\% \) after CEA studies (\( I^2 = 35\% \) after CEA studies; \( F = 59\% \) after CAS (\( P_{int} = 0.38 \)).

In metaregression analyses using the midcohort year as covariate, the absolute risk of MI did not vary over time in either CEA studies (since 1980; \( P = 0.54 \)) or CAS studies (since 1990; \( P = 0.87 \); Figure III in the online-only Data Supplement).

### Thirty-Day Absolute Risk of Death

We included 99 independent studies of CEA (274765 patients) and 83 of CAS (39184 patients) for the calculation of the 30-day absolute risk of death. The pooled absolute risk of death was 0.92% (95% CI, 0.79–1.08; \( I^2 = 25\% \)) after CEA and 1.03% (95% CI, 0.83–1.26; \( F = 70\% \)) after CAS (\( P_{int} = 0.62 \)). In metaregression analyses, the risk of death slightly decreased over time in CEA studies (\( P < 0.001 \)) but did not change in CAS studies (\( P_{int} = 0.81 \)). There was no interaction in these time-trends between CAS and CEA (\( P_{int} = 0.17 \); figure not shown).

#### Thirty-Day Proportion of Death Related to Stroke and MI

Thirty-five independent CEA studies (24690 patients) and 21 CAS studies (7321 patients) recorded the 30-day proportions of death attributable to stroke (stroke death) or death attributable to MI (MI death). The proportion of stroke death was 35% (95% CI, 25–46; \( F = 53\% \)) after CEA and 42% (95% CI, 25–60; \( F = 67\% \)) after CAS. The proportion of MI death was 24% (95% CI, 17–31; \( F = 30\% \)) after CEA and 18% (95% CI, 8–29; \( F = 47\% \)) after CAS.

#### Risk Factors for Periprocedural MI

Figure 1 shows the RR of periprocedural MI according to the 9 potential risk factors. Symptomatic stenosis and restenosis were associated with a higher risk of MI, whereas male sex was associated with a lower risk of MI after CAS. Older age, coronary artery disease, peripheral...
artery disease, and restenosis increased the risk of MI after CEA. Only the effect of sex differed between CAS and CEA with men being at lower risk of MI than with women after CAS, whereas there was no difference after CEA ($P_{int}$ = 0.01).

**Risk Factors for Periprocedural Death**

Figure 2 shows the RR of periprocedural death according to the 9 potential risk factors. There were no statistically significant differences between risk factors in studies of CAS versus studies of CEA, and all trends were in the same directions. However, statistical power was much greater in studies of CEA, and so only older age and symptomatic stenosis were significantly associated with a higher risk of death after CAS; older age, contralateral occlusion, coronary heart disease, diabetes mellitus, peripheral artery disease, and symptomatic stenosis were associated with a higher risk of death after CEA.

**Discussion**

We found that the 30-day absolute risk of MI was not significantly higher after CEA than after CAS (0.87% versus 0.70%), and that there were no major risk factors that could help to identify patients with a differential risk of MI after CEA versus CAS.

The absolute risk of MI we found after CEA was lower than the one found in the pooled analysis restricted to RCTs only (1.87%). By contrast, the absolute risk of MI after CAS was comparable with that observed in RCTs (0.75%). The risk of MI after CEA could have been underestimated because we included retrospective registries, but a similar underestimation should have been found for CAS. As overall, CEA registries were performed earlier than CAS registries, and because definition of MI has changed over time, there is a possibility that MI was less likely to be diagnosed in the past. However, we did not find any change in risks over time. Although RCTs have shown a 2x higher risk of MI after CEA than after CAS, the absolute difference is small and the reasons remain unclear. First, the use of combined antiplatelet therapy (aspirin/clopidogrel for at least 1 month) in CAS but not in CEA might explain the absolute difference between CAS and CEA. Combined antiplatelet therapy is less commonly used in patients scheduled for CEA because it seems to increase the risk of bleeding and to slow down healing. Second, the type of anesthesia differs between CEA and CAS. CAS is performed under local anesthesia, whereas, depending on centers, CEA is performed under general or locoregional anesthesia. The risk of stroke and death at 30 days does not differ between the 2 types of anesthetic techniques after CEA; however, there are few data on the risk of MI. In a large multicenter RCT, proportion of MI at 30 days after CEA was higher under local than under general anesthesia (0.5% versus 0.2%), but the difference did not significantly differ. Thus, considering the few number of studies, it remains difficult to know the exact influence of anesthesia technique on the risk of MI after CEA and CEA. Combined antiplatelet therapy induces local inflammation, stress, and liberation of proinflammatory cytokines, which

<table>
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<th>Subgroup</th>
<th>s</th>
<th>n1/p1</th>
<th>n0/p0</th>
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<th>Psig</th>
<th>I2% (Phet)</th>
<th>Pint</th>
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<tr>
<td>CAS</td>
<td>31</td>
<td>45/3852</td>
<td>89/14263</td>
<td>1.73 [1.21; 2.49]</td>
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<td>51</td>
<td>295/29900</td>
<td>934/104537</td>
<td>1.63 [1.42; 1.87]</td>
<td>&lt;0.001</td>
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<td>38/5527</td>
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<td>258/31702</td>
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<tr>
<td>CAS</td>
<td>7</td>
<td>6/364</td>
<td>3/812</td>
<td>2.81 [0.74; 10.72]</td>
<td>0.13</td>
<td>0 (0.63)</td>
<td>0.34</td>
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<td>57/572</td>
<td>101/1824</td>
<td>1.42 [1.06; 1.90]</td>
<td>0.02</td>
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<td>Diabetes (yes vs. no)</td>
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<td></td>
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<tr>
<td>CAS</td>
<td>10</td>
<td>22/1373</td>
<td>272/778</td>
<td>1.50 [0.88; 2.57]</td>
<td>0.13</td>
<td>0 (1)</td>
<td>0.48</td>
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<tr>
<td>CEA</td>
<td>25</td>
<td>214/12741</td>
<td>379/42530</td>
<td>1.85 [1.56; 2.18]</td>
<td>&lt;0.001</td>
<td>0 (0.99)</td>
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<tr>
<td>Sex (male vs. female)</td>
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<tr>
<td>CAS</td>
<td>23</td>
<td>114/10757</td>
<td>73/6341</td>
<td>0.94 [0.70; 1.26]</td>
<td>0.68</td>
<td>0 (1)</td>
<td>0.58</td>
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<tr>
<td>CEA</td>
<td>42</td>
<td>936/138551</td>
<td>378/79539</td>
<td>1.03 [0.91; 1.17]</td>
<td>0.66</td>
<td>0 (0.57)</td>
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<tr>
<td>Hypertension (yes vs. no)</td>
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<tr>
<td>CAS</td>
<td>8</td>
<td>9/773</td>
<td>0/230</td>
<td>2.49 [0.32; 19.63]</td>
<td>0.39</td>
<td>0 (0.99)</td>
<td>0.42</td>
</tr>
<tr>
<td>CEA</td>
<td>16</td>
<td>172/21353</td>
<td>82/10403</td>
<td>1.05 [0.80; 1.38]</td>
<td>0.74</td>
<td>0 (0.48)</td>
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<tr>
<td>CAS</td>
<td>3</td>
<td>1/74</td>
<td>1/357</td>
<td>-</td>
<td>-</td>
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<td>-</td>
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<tr>
<td>CEA</td>
<td>9</td>
<td>62/12013</td>
<td>120/12064</td>
<td>1.96 [1.37; 2.53]</td>
<td>&lt;0.001</td>
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<td>CAS</td>
<td>12</td>
<td>6/1160</td>
<td>32/5000</td>
<td>1.29 [0.53; 3.19]</td>
<td>0.57</td>
<td>0 (0.94)</td>
<td>0.82</td>
</tr>
<tr>
<td>CEA</td>
<td>9</td>
<td>19/1238</td>
<td>423/32774</td>
<td>1.46 [0.93; 2.29]</td>
<td>0.10</td>
<td>0 (0.84)</td>
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<td>Symptomatic stenosis (sympto vs. asympto)</td>
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<tr>
<td>CAS</td>
<td>65</td>
<td>197/12438</td>
<td>233/25744</td>
<td>1.80 [1.48; 2.19]</td>
<td>&lt;0.001</td>
<td>0 (0.98)</td>
<td>0.14</td>
</tr>
<tr>
<td>CEA</td>
<td>66</td>
<td>1036/87642</td>
<td>1121/232862</td>
<td>1.37 [1.13; 1.65]</td>
<td>&lt;0.01</td>
<td>44 (&lt;0.001)</td>
<td></td>
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</tbody>
</table>

Figure 2. Meta-analyses of the relative risk (RR) of death after carotid angioplasty and stenting (CAS) and carotid endarterectomy (CEA) according to the 9 potential risk factors. n0 indicates number of events in patients without clinical factor; n1, number of events in patients with clinical factor; p0, number of patients with clinical factor; p1, number of patients with clinical factor; $P_{int}$ Cochrane homogeneity test probability value; $P_{sgr}$ P interaction; $P_{sgr}$ P significance; and s, number of studies.
causes prothrombotic state. This prothrombotic state could favor the risk of periprocedural MI after CEA.29

Noncardiac vascular surgery (carotid artery, lower extremity artery, and abdominal aortic aneurysm) is associated with a risk of periprocedural MI, mainly because atherosclerosis is a systemic disease. In a meta-analysis, this risk has been estimated to vary between 1% and 26%.26 As expected, in our study, the main risk factor for periprocedural MI was a history of coronary artery disease. The risk of periprocedural MI has never been compared in lower extremity artery between surgery and angioplasty/stenting; only few studies30–32 reported this risk after surgery and only 133 after angioplasty/stenting. Thus, uncertainty remains on whether our results are specific or not of the carotid artery.

Sex had a differential association with the risk of MI between CAS and CEA. When compared with what we found for stroke and death, sex was the only factor that differed between the two techniques.19 Men were at lower risk of MI than women after CAS. On the contrary, in our previous meta-analysis, male sex was associated with a lower risk of periprocedural stroke or death after CEA, whereas sex had no significant influence on the risk after CAS. Considering the huge number of studies included for this subgroup and the absence of heterogeneity in our analyses on MI, the association is likely to be genuine. However, it remains difficult to explain. No data are available on the influence of sex on the risk of periprocedural MI after angioplasty/stenting and surgery in other atherosclerotic arteries.

Our analysis has several potential limitations. First, the numbers of events were sometimes small and because of the population case-mix, our results on absolute risks were heterogeneous. However, this heterogeneity is common in meta-analyses of absolute risks. We consequently used random-effects models. In contrast, there was no or little heterogeneity in analyses of risk factors. Second, MI definitions have varied over time and between studies, especially the use of cardiac biomarkers has changed (creatine kinase appeared first then creatine kinase-MB, and troponin have now been used for over a decade). However, this has probably not substantially affected the estimate of the risk of MI. Diagnosis of MI in studies was based, when available, on the presence of several parameters (clinical symptoms and at least 1 biomarker or ECG changes). Because it is common knowledge that elevation of cardiac biomarkers can occur after carotid procedure, biomarkers elevation without symptoms suggestive of coronary ischemia or ECG changes were not included in the calculation of the absolute risk of MI. Furthermore, in spite of changes in MI definition over time, the absolute risk of MI has not changed over time. Third, we were unable to validate our results on sex in RCTs. Few RCTs have reported data on MI by sex. Moreover, the total number of events in these trials was too small to assess the validity of our results. Fourth, we only included studies that reported events in at least 1 of the 9 predefined subgroups for the calculation of the absolute risk of MI and death. However, this should not have introduced selection bias. On the one hand, we excluded some RCTs; on the other hand, the ones retained were the RCTs with larger sample size than those excluded and had, therefore, more precise estimations of absolute risks. In addition, only 8% of total of references eligible (from our previous systematic review and update) were excluded because of the absence of data on subgroup. Finally, apart dual antiplatelet therapy almost always used in CAS, we were unable to assess whether periprocedural medication differed between CEA and CAS because this information was scarcely reported. RCTs have shown that stroke is the main cause of periprocedural death after carotid revascularization.23–26 Our results confirm this finding. Risk factors for periprocedural stroke and death will, therefore, have most potential clinical utility in selecting the most appropriate intervention for individual patients. Although we found that male sex is associated with a lower risk of periprocedural MI than female sex after CAS, this should not be considered as a major criteria to select candidates for CAS, because MI is far less common than stroke, MI accounts for relatively few periprocedural deaths, and male sex is a strong risk factor for periprocedural stroke or death after CAS.

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Disclosures
None.

References


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Supplementary table I - Search Strategy.
(((carotid stenosis[MeSH Terms]) AND stenting[MeSH Terms]) OR angioplasty[MeSH Terms]) OR endarterectomy[MeSH Terms]) AND myocardial infarction[MeSH Terms]) AND outcome[MeSH Terms]) OR death[MeSH Terms]) AND humans[MeSH Terms] AND ("2011/10"[Date - Publication] : "2014/07"[Date - Publication])
Supplementary table II - Characteristics of studies included for the calculation of the 30-day absolute risk of MI.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CAS 68 studies (31,843 patients)</th>
<th>CEA 52 studies (62336 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value N (%)*</td>
<td>N studies with data available</td>
</tr>
<tr>
<td>Mean number of patients per study (min/max)</td>
<td>468 (20/3,737)</td>
<td>68</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.4</td>
<td>61</td>
</tr>
<tr>
<td>Male</td>
<td>18,818 (67)</td>
<td>59</td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>11,066 (46)</td>
<td>60</td>
</tr>
</tbody>
</table>

*Except where stated otherwise in the table
Supplementary table III - Characteristics of the patients treated by CEA at Caen University Hospital from 2000 to 2013.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caen University Hospital registry</td>
<td>(N= 1609)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>71.8</td>
</tr>
<tr>
<td>Minimal /Maximal age (years)</td>
<td>43/97</td>
</tr>
<tr>
<td>Age &gt; 80 ans</td>
<td>400 (25)</td>
</tr>
<tr>
<td>Males</td>
<td>1170 (73)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1317 (82)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>574 (36)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>397 (25)</td>
</tr>
<tr>
<td>Symptomatic stenosis</td>
<td>578 (36)</td>
</tr>
</tbody>
</table>

*Except where stated otherwise in the table
Supplementary figure I - Risk of periprocedural MI in all randomized controlled trials comparing CAS (carotid angioplasty stenting) and CEA (carotid endarterectomy).

The risk of periprocedural MI was 0.75% (95% CI, 0.31-1.39) after CAS and 1.87% (95% CI,0.84-3.31) after CEA. The following trials CARESS, LEICESTER, SPACE, TESCAS, and WALLSTENT, did not assess periprocedural MI.
Supplementary figure II - Flow chart for selection of studies.

- Medline & Embase Update
  - 1584 titles screened
  - 147 abstracts screened
  - 140 references eligible for full review
    - 200 references from our previous systematic review
    - 1 reference from our own registry
    - 1 reference for which unpublished data was obtained
    - Excluded references = 44
      - No data on subgroup (3)
      - No outcome available (41)
  - 96 references eligible for the systematic review
    - Excluded references = 25
      - Duplication = non independent population
  - 298 references retrieved
  - 273 references included
Supplementary figure III - Evolution of the absolute risk of MI at 30 days according to the mid-cohort year in CAS and CEA studies from 1980 to 2014 by meta-regressions.

The size of each circle is inversely proportional to the variance of the absolute risk. The absolute risk of MI according to mid-cohort year did not vary over time either in CEA studies (since 1980, p=0.54) or in CAS studies (since 1990, p=0.87).
List of all references included in the systematic review.

References followed by (death) were included for the calculation of the risk of death
References followed by (MI) were included for the calculation of the risk of MI
References followed by (death and MI) were included for the calculation of the risk of death and MI

Sub-group: Age

CAS
Ahmadi R et al. J Endovasc Ther 2002;9:559-565. (death)
Arjomand H et al J Am Coll Cardiol 2008;52(suppl 2). (MI)
Langhoff R et al. Vasc Endovasc Surg 2014;48:317-324. (death and MI)
Safian RD et al. J Am Coll Cardiol 2006;47:2384-2389. (death and MI)
Takayama K et al. Radiat Med 2008; 26:348-354. (death and MI)
Tatli E et al. Postep Kardiol Inter 2013;9(33): 221–227. (death and MI)
Teitelbaum GP et al. Surgical Neurology1998;50:300-311. (death and MI)

CEA
ECST Lancet 1998; 351:1379-1387. (death and MI)
Goldstein LB et al. Stroke 1994;25:1116-1121. (death and MI)
Magnadottir HB et al. Neurosurgery 1999;45:786-791. (death and MI)
Menyhei G et al. Eur J Vasc Endovasc Surg 2011;41:735e740. (death)
Nunnelee JD et al. Geriatr Nurs 1995;15:121-123. (death and MI)
Ouriel K et al. Surg Gynecol Obst 1986;162:334-336. (death and MI)
Sternbergh WC et al. The Ochsner Journal 2003;5:23-29. (death)
Ting ACW et al. Cardiovascular Surgery, 2000;8:441-445. (death)
Tu JV et al. Stroke 2003;4:2568-2573. (death)
Young B et al. Stroke. 1996;27:2216-2224. (death and MI)

Sub-group: Contralateral occlusion
CAS
Hofmann R et al. Stroke 2006;37:2557-2561. (MI)
Kao HL et al. Cardiology 2002;97:89-93. (MI)
Mehta RH et al. Am J Cardiol 2009;104:725-731. (death and MI)

CEA
AbuRahma AF et al. Stroke 2000;31:1566-1571. (death and MI)
Ballotta E et al. Langenbeck’s Arch Surg 2002;387:216-221. (death and MI)
Supplemental data

ECST Lancet 1998;351:1379-1387. (death and MI)
Fitzpatrick CM et al. Mil Med 2005;170:1069-1074. (death and MI)
Magnadottir HB et al. Neurosurgery 1999;45:786-791. (death and MI)
Menyhei G et al. Eur J Vasc Endovasc Surg 2011;41:735e740. (death)
Tu JV et al. Stroke 2003;34:2568-2573. (death)
Young B et al. Stroke 1996;27:2216-224. (death and MI)

Sub-group: Coronary artery disease
CAS
Balashankar GS et al. Indian Heart J. 2008;60:325-329. (MI)
Gupta AK et al. Neurol India 2006;54:68-72. (death and MI)
Hofmann R et al. Stroke 2006;37:2557-2561. (MI)
Tatli E et al. Postep Kardiol Inter 2013;9:221-227. (death and MI)

CEA
ECST Lancet 1998;351:1379-1387. (death and MI)
Magnadottir HB et al. Neurosurgery 1999;45:786-791. (death and MI)
Tu JV et al. Stroke 2003;34:2568-2573. (death)
Young B et al. Stroke. 1996;27:2216-2224. (death and MI)

Sub-group: Diabetes
CAS
Balashankar GS et al. Indian Heart J. 2008;60:325-329. (MI)
Cridio E et al. Am J Cardiol 2006;98(suppl1). (death and MI)
Hofmann R et al. Stroke 2006;37:2557-2561. (MI)

CEA
Agiar ET et al. Sao Paulo Medical Journal 2001;119:206-211. (death and MI)
Ballotta E et al. Langenbeck’s Arch Surg 2002;387:216-221. (death and MI)
ECST Lancet 1998;351:1379-1387. (death and MI)
Debing E et al. Vas Endovasc Surg 2011;45:28-32. (death)
Magnetodit HB et al. Neurosurgery 1999;45:786-791. (death and MI)
Tu JV et al. Stroke 2003;4:2568-2573. (death)
Young B et al. Stroke. 1996;27:2216-2224. (death and MI)

Sub-group: Sex
CAS
Ardjmand H et al. J Am Coll Cardiol 2008;52(suppl2). (death and MI)
Balashankar GS et al. Indian Heart J. 2008;60:325-329. (MI)
Bayram N et al. Perfusion 2012;27:146-149. (death and MI)
Bisdas T et al. European J of Vase Endovasc Surg 2012;44:244-250. (death and MI)
Gupta AK et al. Neurol India 2006;54:68-72. (death and MI)
Howard VJ et al. Stroke 2009;40:1140-1147. (death and MI)
Kypja A et al. Am J Cardiol 2006;98(suppl1):244M. (death)
Langhoff R et al. Vase Endovasc Surg 2014;48:317-324. (death and MI)
Lihara K et al. J Neurosurg 2006;105:546-554. (death and MI)
Takayama K et al. Radiat Med 2008;26:348-354. (death and MI)
Tatli E et al. Postep Kardiol Inter 2013;9:221-227. (death and MI)
Tietke MW et al. Neuroradiology 2010;52:611-618. (death)
Teitelbaum GP et al. Surgical Neurology 1998;50:300-311. (death and MI)

CEA
Aguirar ET et al. Sao Paulo Medical Journal 2001;119:206-211. (MI)
Bisdas T et al. European J of Vasc Endovasc Surg 2012;44:244-250. (death and MI)
Chang JB et al. Vasc Endovasc Surg 2002;36:21-27. (death and MI)
ECST Lancet 1998;351:1379-1387. (death and MI)
Howard VJ et al. Lancet Neurol 2011;10:530-537. (death)
Kapral MK et al. Stroke 2003;34:1120-1124. (death)
Menyhei G et al. Eur J Vasc Endovasc Surg 2011;41:735e740. (death)
Zenonos G et al. Neurosurgery 2012;70:646-655. (MI)

Sub-group: Hypertension
CAS
Supplemental data

Balashankar GS et al. Indian Heart J. 2008;60:325-329. (MI)
Gupta AK et al. Neurol India 2006;54:68-72. (death and MI)
Hofmann R et al. Stroke 2006;37:2557-2561. (MI)

CEA
ECST Lancet 1998;351:1379-1387. (death and MI)
Tu JV et al. Stroke 2003;4:2568-2573. (death)
Young B et al. Stroke 1996;27:2216-2224. (death and MI)

Sub-group: Peripheral artery disease
CAS
Hofmann R et al. Stroke 2006;37:2557-2561. (MI)

CEA
ECST Lancet 1998;351:1379-1387. (death and MI)
Tu JV et al. Stroke 2003;4:2568-2573. (death)

Sub-group: Restenosis
CAS
Gupta AK et al. Neurol India 2006;54:68-72. (MI)
Mehta RH et al. Am J Cardiol 2007;99:1288-1293. (death and MI)
Safian RD et al. J Am Coll Cardiol 2006;47:2384-2389. (death and MI)
Supplemental data


CEA
Maggadottir HB et al. Neurosurgery 1999;45:786-791. (death and MI)
Tu JV et al. Stroke 2003;34:2568-2573. (death)

Sub-group: Symptomatic stenosis
CAS
Arjomand H et al. J Am Coll Cardiol 2008;52(suppl2). (death and MI)
Bisadas T et al. European J of Vasc Endovasc Surg 2012;44:244-250. (death and MI)
Cernetti et al. Ital Herat J 2003;4:695-700. (death and MI)
Chiam PTL et al. Circulation 2009;119:2343-2348. (death and MI)
Criadio E et al. Am J Cardiol 2006;98(suppl1). (death and MI)
Grant A et al. Catheter Cardiovasc Interv 2010;75:651-655. (death and MI)
Howard VJ et al. Lancet Neurol 2011;10:530-537. (death and MI)
Ielasi A et al. J endovasc Ther 2010;17:298-307. (death and MI)
Kadkhodayan Y et al. Neurosurg Focus 2005;18:e1. (death and MI)
Kao HL et al. Cardiology 2002;97:89-93. (death and MI)
Katzen BT et al. Catheter Cardiovasc Interv 2007;70:316-323. (death and MI)
Kirsch EC et al. Radiology 2001;220:737-744. (death and MI)
Knur R et al. Herat Vessels 2011;26:125-130. (death and MI)
Koch C et al. Rofo 2002;174:1506-1510. (death and MI)
Krasniqi N et al. PLoS ONE 2012;7:e35300 (death and MI)
Langhoff R et al Vasc Endovasc Surg 2014;48:317-324. (death and MI)
Lihara K et al. J Neurosurg 2006;105:546-554. (death and MI)
Safian RD et al. J Am Coll Cardiol 2006;47:2384-2389. (death and MI)
Sztiria LK et al. Stroke 2004;35:2862-2866. (death and MI)
Takayama K et al. Radiat Med 2008;26:348-354. (death and MI)
Tatli E et al. Postep Kardiol Inter 2013;9:221-227. (death and MI)
Tietke MW et al. Neuroradiology 2010;52:611-618. (death)

CEA

Aguiar ET et al. Sao Paulo Medical Journal 2001;119:206-211. (MI)
Berger L et al. 2014 (unpublished). (death and MI)
Bisdas T et al. European J of Vasc Endovasc Surg 2012;44:244-250. (death and MI)
Boontje AH et al. Cardiovascular Surg 1994;5:549-554. (MI)
Brinjikji W et al. Stroke 2010;41:2186-2190. (death and MI)
Faggioli GL et al. Eur J Vasc Endovasc Surg 2011;41:238-248. (MI)
Feasby TE et al. Arch Neurol 2007;64:1496-1500. (death and MI)
Fode NC et al. Stroke 1986;17:370-376. (death and MI)
Goldstein LB et al. Stroke 1994;25:1116-1121. (death and MI)
Hagmuller GW et al. Aust J Cardiol 2004;11:206-211. (death)
Howard VJ et al. Lancet Neurol 2011;10:530-537. (death and MI)
Menyhe G et al. Eur J Vasc Endovasc Surg 2011;41:735e740. (death)
Rantner B et al. J stroke Cerebrovasc Dis 2006;15:114-120. (death and MI)
Till JS et al. Stroke 1987;18:823-829. (death and MI)
Tu JV et al. Stroke 2003;34:2568-2573. (death)
Zenonos G et al. Neurosurgery 2012;70:646-655. (MI)