Periprocedural risk of myocardial infarction after carotid endarterectomy and carotid angioplasty and stenting

Risque périprocédural d’infarctus du myocarde après endartériectomie et angioplastie et stenting carotidiennes

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Carotid artery stenosis is the causative factor in 15–20% of patients with ischaemic stroke or transient ischaemic attack. In clinical trials, carotid endarterectomy (CEA) reduces the absolute risk of ischaemic stroke by about 50% in patients with symptomatic or asymptomatic carotid stenosis compared with medical treatment [1–3]. Carotid angioplasty and stenting (CAS) has been evaluated as an alternative to CEA for several years. However, randomized controlled trials (RCTs) have established that the 30-day risk of stroke or death is higher after CAS than after CEA in patients with symptomatic and asymptomatic stenosis [4,5]. Thus, although outcomes after CEA and CAS on long-term follow-up are similar, the overall stroke risk with CAS remains higher due to the excess initial periprocedural risk [4–7].

An intriguing observation found in most RCTs comparing CEA with CAS is an excess risk of periprocedural myocardial infarction after CEA (pooled odds ratio 2.23, 95% confidence interval [CI] 1.37–3.63; six studies, 5725 patients; 7 = 0%; Fig. 1 [1,4,8–13]). Until now, this excess of myocardial infarction after CEA has not been well understood, and the clinical importance of these events has been questioned, mainly because some asymptomatic events manifesting as small elevations of cardiac enzymes were counted as outcomes in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) study [14]. On the other hand, small elevations of cardiac enzymes after non-cardiac and cardiac procedures are associated with increased future mortality [4,15–17]. While stroke is correlated with functional impairment, myocardial infarction could be an important cause of periprocedural death. Although the effect size was similar across all trials, the total number of events observed was small (< 100), and risk factors for periprocedural myocardial infarction remain unknown.

Abbreviations: CAS, carotid angioplasty and stenting; CEA, carotid endarterectomy; CI, confidence interval; $P_{int}$, $P$ interaction; RCT, randomized controlled trial.

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Systematic reviews of observational studies can help to decipher unexpected findings from RCTs. Thus, we recently updated a previous systematic review of risks after carotid intervention, in order to assess the absolute risk of periprocedural myocardial infarction and to identify whether risk factors could be identified [18]. We screened studies published from January 1980 to June 2014 that enrolled patients with symptomatic or asymptomatic stenosis in the region of the carotid bifurcation, who were treated by CAS or CEA. Data on nine predefined risk factors (age, contralateral carotid occlusion, coronary artery disease, diabetes mellitus, sex, hypertension, peripheral artery disease, type of stenosis and clinical presentation [i.e. symptomatic or asymptomatic stenosis]) were extracted.

This meta-analysis indicated that the 30-day absolute risk of myocardial infarction is not significantly higher after CEA than after CAS (0.87%, 95% CI 0.69–1.07, 52 studies, 62,336 patients vs. 0.70%, 95% CI 0.54–0.88, 68 studies, 31,843 patients; P interaction [P_int] = 0.38). Regarding the risk factors for periprocedural myocardial infarction, symptomatic stenosis and restenosis were associated with a higher risk of myocardial infarction, whereas men were at lower risk of myocardial infarction after CAS (Fig. 2). Older age, coronary artery disease, peripheral artery disease and restenosis increased the risk of myocardial infarction after CEA. Only the effect of sex differed between CAS and CEA, with men being at lower risk of myocardial infarction than women after CAS, whereas there was no difference after CEA (P_int = 0.01) (Fig. 2).

The absolute risk of myocardial infarction after CEA in this analysis was lower than that found in the pooled analysis restricted to RCTs only (1.87%). By contrast, the absolute risk of myocardial infarction after CAS was similar to that observed in RCTs (0.75%). The risk of myocardial infarction after CEA could have been underestimated because retrospective registries were included, but a similar underestimation should have been found for CAS. Overall, CEA registries were carried out earlier than CAS registries, and the definition of myocardial infarction has changed over time, so there is a possibility that myocardial infarction was less likely to be diagnosed in the past. However, no changes in risks were found over time.

Although RCTs have shown a two times higher risk of myocardial infarction after CEA than after CAS, the absolute difference is small and the reasons remain unclear. A few potential explanations can be suggested. First, combined antiplatelet therapy (aspirin/clopidigrel for at least 1 month) is commonly used in CAS but not in CEA (as it seems to increase the risk of bleeding and slow healing in this situation). Second, the type of anaesthesia differs between CEA and CAS: CAS is performed under local anaesthesia, while CEA is performed under general or locoregional anaesthesia, depending on the centre. The risk of stroke and death at 30 days does not differ between the two types of anaesthetic techniques after CEA, but there are few data on the risk of myocardial infarction. In a large multicentre RCT, no statistically significant differences were identified in the proportions of myocardial infarctions at 30 days after CEA between local and general anaesthesia [19]. However, given the small number of studies, it remains difficult to know the exact influence of anaesthesia technique on the risk of myocardial infarction after CEA and CAS. Third, cervical incision induces local inflammation, stress and liberation of pro-inflammatory cytokines, which cause a prothrombotic state and could favour atherothrombotic events.

Compared with what we found for stroke and death in our previous meta-analysis, sex was also the only factor that differed between the two techniques [20]; however, men were at lower risk of periprocedural stroke or death after CEA, whereas sex had no significant influence on the
Myocardial infarction after carotid intervention

Figure 2. Meta-analyses of the relative risk (RR) of myocardial infarction after carotid angioplasty stenting (CAS) and carotid endarterectomy (CEA) according to nine potential risk factors. N: number of studies; n0: number of events in patients without clinical factor; N0: number of patients without clinical factor; n1: number of events in patients with clinical factor; N1: number of patients with clinical factor; \( P_{\text{het}} \): Cochrane homogeneity test probability value; \( P_{\text{int}} \): P interaction; \( P_{\text{sig}} \): P significance.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>n1/N1</th>
<th>n0/N0</th>
<th>Summary RR</th>
<th>Psig</th>
<th>12, % (Phet)</th>
<th>Pint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (&gt; 75-80 vs &lt;75-80 years)</td>
<td>CAS</td>
<td>25</td>
<td>18/3223</td>
<td>53/12138</td>
<td>1.28</td>
<td>0.37</td>
<td>0 (0.97)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>29</td>
<td>58/4101</td>
<td>269/25224</td>
<td>2.02</td>
<td>&lt;0.001</td>
<td>9.40 (0.32)</td>
</tr>
<tr>
<td><strong>Contralateral occlusion</strong> (yes vs no)</td>
<td>CAS</td>
<td>7</td>
<td>2/457</td>
<td>6/4177</td>
<td>2.02</td>
<td>0.40</td>
<td>0 (0.97)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>15</td>
<td>14/1176</td>
<td>74/12449</td>
<td>2.06</td>
<td>0.17</td>
<td>45.9 (0.03)</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong> (yes vs no)</td>
<td>CAS</td>
<td>6</td>
<td>0/465</td>
<td>0/447</td>
<td>1.00</td>
<td>1</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>8</td>
<td>26/2453</td>
<td>15/3897</td>
<td>2.90</td>
<td>&lt;0.01</td>
<td>0 (43)</td>
</tr>
<tr>
<td><strong>Diabetes</strong> (yes vs no)</td>
<td>CAS</td>
<td>7</td>
<td>16/1114</td>
<td>14/2030</td>
<td>1.78</td>
<td>0.09</td>
<td>0 (0.91)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>13</td>
<td>18/2267</td>
<td>38/7682</td>
<td>1.66</td>
<td>0.06</td>
<td>0 (0.98)</td>
</tr>
<tr>
<td><strong>Sex</strong> (male vs female)</td>
<td>CAS</td>
<td>22</td>
<td>61/9894</td>
<td>68/6005</td>
<td>0.60</td>
<td>&lt;0.01</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>27</td>
<td>168/5407</td>
<td>95/7750</td>
<td>1.03</td>
<td>0.83</td>
<td>0 (0.97)</td>
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<td><strong>Hypertension</strong> (yes vs no)</td>
<td>CAS</td>
<td>5</td>
<td>1/618</td>
<td>0/164</td>
<td>1.28</td>
<td>0.83</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
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<td>7</td>
<td>21/3364</td>
<td>18/2350</td>
<td>0.77</td>
<td>0.46</td>
<td>0 (0.68)</td>
</tr>
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<td><strong>Peripheral artery disease</strong> (yes vs no)</td>
<td>CAS</td>
<td>2</td>
<td>0/108</td>
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<td>1.00</td>
<td>1</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>3</td>
<td>9/546</td>
<td>15/2701</td>
<td>3.22</td>
<td>0.04</td>
<td>27.9 (0.25)</td>
</tr>
<tr>
<td><strong>Restenosis</strong> (yes vs no)</td>
<td>CAS</td>
<td>9</td>
<td>13/979</td>
<td>5/4023</td>
<td>3.97</td>
<td>&lt;0.01</td>
<td>0 (0.94)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>8</td>
<td>11/668</td>
<td>105/15522</td>
<td>3.18</td>
<td>&lt;0.001</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Symptomatic stenosis</strong> (sympt vs asympt)</td>
<td>CAS</td>
<td>49</td>
<td>96/10026</td>
<td>159/22928</td>
<td>1.35</td>
<td>0.02</td>
<td>0 (1)</td>
</tr>
<tr>
<td></td>
<td>CEA</td>
<td>34</td>
<td>218/2403</td>
<td>223/76292</td>
<td>1.11</td>
<td>0.31</td>
<td>0 (0.50)</td>
</tr>
</tbody>
</table>

risk after CAS. Given the huge number of studies (n = 22; 15,889 patients) included for this subgroup, and the absence of heterogeneity in our analyses on myocardial infarction, this 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 myocardial infarction after angioplasty/stenting and surgery in other atherosclerotic territories.

Despite potential limitations (variation in myocardial infarction definitions over time and studies, lack of validation in RCTs, lack of accurate data on periprocedural medication), the findings have several practical implications. First, the overall periprocedural risk of myocardial infarction after CEA and CAS in routine clinical practice is low, and the potential excess risk after CEA is likely to have marginal effect. Second, the selection of individual patients between CEA and CAS should be based on the risk factors for periprocedural stroke and death, as stroke remains the main cause of periprocedural death after carotid revascularization [1,18]. In addition, although we found that male sex is associated with a lower risk of periprocedural myocardial infarction compared with female sex after CAS, this should not be considered a major criterion for selecting candidates for CAS, because myocardial infarction is far less common than stroke, myocardial infarction accounts for relatively few periprocedural deaths, and male sex is a strong risk factor for periprocedural stroke or death after CAS.

In view of the burden of stroke, although most of the risk factors for periprocedural myocardial infarction and stroke or death found in our analyses are non-modifiable, future
work should be undertaken to establish whether potential modifiable risk factors could be identified. Further research, including information on periprocedural medication, will be helpful, not only for improving our understanding of the association between carotid intervention and periprocedural myocardial infarction and stroke, but also for identifying effective intervention to reduce these excesses of risk. Obtaining data on carotid plaque characteristics — in particular carotid intima-media thickness, as it has been shown to be a surrogate of atherosclerosis and cardiovascular outcomes — may also be beneficial to help predict the likelihood of periprocedural myocardial infarction and stroke events.

Disclosure of interest

The authors declare that they have no competing interest.

References