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Article in European Journal of Vascular and Endovascular Surgery · September 2014
DOI: 10.1016/j.ejvs.2014.08.012

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Safety of Carotid Intervention Following Thrombolysis in Acute Ischaemic Stroke

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WHAT THIS PAPER ADDS
Urgent carotid intervention is indicated for stroke resulting from significant carotid stenosis, but performing such intervention soon after thrombolysis may be associated with increased risk of bleeding and other complications. By analysing the 30-day stroke or death rates in published series of patients who have undergone carotid intervention within 14 days of thrombolysis, this systematic review concludes that early carotid endarterectomy post-thrombolysis appears to be safe, with stroke or death rates similar to that of surgery without thrombolysis.

Objectives: Thrombolysis is effective in improving clinical outcome in the treatment of acute ischaemic stroke. However, thrombolysis results in low recanalisation rates, particularly in the event of carotid occlusion. Carotid intervention is indicated in stroke resulting from significant carotid atherosclerosis, but intervention soon after thrombolysis may be associated with increased risks. This study aims to assess the safety of carotid intervention post-thrombolysis for acute ischaemic stroke.

Design: Systematic review.

Materials and methods: MEDLINE and EMBASE were searched on 29 May 2014. Inclusion criteria were (i) intra-arterial or intravenous thrombolysis for acute ischaemic stroke; (ii) carotid intervention within 14 days of thrombolysis; and (iii) derivable primary outcome. The primary outcome was 30-day stroke or death. A meta-analysis of incidence was completed for the 30-day stroke or death rates using Freeman—Tukey arcsine transformations and assuming random effects. Point estimates with confidence intervals (CIs) were generated and heterogeneity was assessed. The strength of recommendations and quality of underlying evidence were assessed using the American College of Chest Physicians (ACCP) grading system.

Results: Nine included publications recorded 114 carotid endarterectomy (CEA) and four angioplasty interventions. The point estimate of 30-day stroke or death for CEA was 4.93% (95% CI 1.83—9.44), representing four of 114. The strength of recommendation and quality of underlying evidence for CEA as per the ACCP grading system was determined as 1C. There were no cases of stroke or death in patients undergoing angioplasty post-thrombolysis (0/4).

Conclusions: Early CEA post-thrombolysis appears safe, with stroke or death rates similar to that of the operation without thrombolysis. However, the wide CI obtained highlights the uncertainty of this result. Further, we emphasise that this recommendation is supported by low-quality evidence. Additional data are required to confirm the safety of surgery and early endovascular therapy post-thrombolysis.

INTRODUCTION
Acute ischaemic stroke is a leading cause of death and disability worldwide. According to the World Stroke Organization, one in six people will have a stroke in their lifetime, with a mortality rate of 25% in the first year. Thrombolysis has revolutionised ischaemic stroke therapy with the potential to acutely reverse symptomatology and permit complete recovery. The most well-studied drugs for thrombolysis, including streptokinase, urokinase, and recombinant tissue plasminogen activator, work by converting plasminogen to plasmin to break down fibrin in blood clots.
While thrombolysis has become established as the standard therapy in acute ischaemic stroke,\textsuperscript{7} partial or complete recanalisation following thrombolysis only occurs in approximately 10% of occluded internal carotid arteries and in 25% of occluded proximal middle cerebral arteries.\textsuperscript{5,6} Further, more than 80% of stroke patients with a National Institutes of Health Stroke Scale score of $\geq 10$ have persistent arterial occlusion despite thrombolysis.\textsuperscript{7} In such circumstances, and/or in the presence of significant carotid stenosis, it is important to consider early operative intervention.

Carotid intervention, including carotid endarterectomy (CEA) and angioplasty, is indicated in symptomatic carotid stenosis of 50–99%, according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria,\textsuperscript{8} or 70–99%, according to the European Carotid Surgery Trialists’ (ECST) \textsuperscript{9} Collaborative Group criteria, within 2 weeks of onset of stroke or transient ischaemic attack symptoms.\textsuperscript{10} With the risk of recurrent ischaemic attack being highest within the days following the first episode,\textsuperscript{11} there has been a recent move towards performing carotid intervention as soon as possible after the onset of symptoms.\textsuperscript{12–14} Recent evidence suggests no additional procedural risk if the intervention is performed in the hyperacute period, whether this time period is defined as $<48$ h, $<7$ days, or $<14$ days.\textsuperscript{15}

However, thrombolysis up to 6 h after the onset of stroke has been found to increase the risk of symptomatic and fatal intracranial haemorrhage approximately fourfold within the first 7 days, even after the clearance of thrombolysis.\textsuperscript{15} Data from a recent meta-analysis have identified an incidence of symptomatic intracranial haemorrhage of 7.7% in patients treated with alteplase alone within 6 h for acute ischaemic stroke.\textsuperscript{16} Therefore, while early carotid intervention is indicated in stroke resulting from carotid stenosis, performing carotid intervention soon after thrombolysis may be associated with an increased risk of bleeding and other complications.

This systematic review aims to assess the safety of carotid intervention post-thrombolysis by analysing the 30-day stroke or death rates in published series of patients who have undergone carotid intervention post-thrombolysis.

**MATERIALS AND METHODS**

**Search strategy**

A systematic review adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was performed.\textsuperscript{17} MEDLINE and EMBASE were searched using the Ovid portal. The databases were searched on 29 May 2014, for articles published between 1947 and 2014. The search string used was: [stroke and thrombolysis and carotid and endarterectomy] or [stroke and thrombolysis and carotid and [stent or angioplasty or intervention or thrombectomy]].

Two authors (R.M. and M.I.Q.) searched independently and compared results at each stage. A third author (A.H.D) arbitrated disagreements. Authors of cases presented in conference proceedings were contacted where further details were required. Data abstraction and quality assessment were conducted by two independent investigators (R.M. and M.I.Q.).

**Inclusion and exclusion criteria**

Studies were considered for summation analysis according to the following inclusion criteria: intra-arterial or intravenous thrombolysis for acute ischaemic stroke; carotid intervention within 14 days of thrombolysis; derivable primary outcome; intervention conducted on internal carotid artery; and internal carotid stenosis confirmed on imaging. Studies were excluded based on the following exclusion criteria: case series with fewer than five cases; review articles; non English-language studies; intraoperative thrombolysis; and intervention conducted on middle cerebral artery.

**Primary and secondary outcomes**

The primary outcome measure was 30-day stroke or death. Secondary outcome measures included bleeding complications; cranial nerve injury; and wound complications (defined as delayed healing or infection, or wound haematoma at site of surgery).

**Analysis**

The quality of studies was assessed in domains of study design; study duration; sample size; inclusion and exclusion criteria; diagnosis and follow-up by stroke neurologist; operative technical details; postoperative control of blood pressure; and source of funding. The strength of recommendations and quality of underlying evidence were assessed using the American College of Chest Physicians (ACCP) grading system, which is a modified approach to the international GRADE group.\textsuperscript{17} The grading scheme classifies recommendations as strong (grade 1) or weak (grade 2), according to the balance between benefits, risks, burdens, and the degree of confidence in estimates of benefits, risks, and burdens. The system classifies the quality of evidence as high (grade A), moderate (grade B), or low (grade C) according to factors that include study design, consistency of the results, and directness of evidence.

A meta-analysis of incidence was completed for the 30-day stroke or death rates using Freeman—Tukey arcsine transformations and assuming random effects as described by DerSimonian and Laird.\textsuperscript{18} Point estimates with confidence intervals (CIs) were generated and heterogeneity was assessed. $I^2$ is reported, which is a measure of the degree of inconsistency in study results. $I^2$ describes the percentage of total variation across studies that is due to heterogeneity rather than chance with values ranging from 0 to 100%. The $I^2$ value is proportional to the heterogeneity across studies, with a value of 0% representing no heterogeneity and larger values demonstrating increasing heterogeneity. $I^2$ is reported with 95% uncertainty intervals. Calculations were performed using MedCalc for Windows, version 13.1.2.0 (MedCalc Software, Mariakerke, Belgium).
RESULTS
After duplicates were removed, 588 articles were screened, of which nine studies (eight full-text articles and one conference abstract) were included for summation analysis (Fig. 1).

The characteristics of the included studies are displayed in Table 1, including reported 30-day stroke or death data. The quality assessment of included studies can be seen in Table 2. All included studies were performed retrospectively with a mean sample size of 13 patients (range 5—52; SD 14.6).

**Primary outcome**
The point estimate of 30-day stroke or death for CEA using a random effects meta-analysis model was 4.93% (95% CI 1.83—9.44). This represents four cases in 114. The $I^2$ was 0.00% (95% CI 0.00—34.95).

In one of these cases, a 49-year-old woman who was administered intravenous thrombolysis for an initial combined intracranial internal carotid artery (ICA)—middle cerebral artery occlusion was operated upon 33 h after stroke onset for residual ICA stenosis. She developed a haemorrhagic stroke 24 h postoperatively.

The second case involved a 66-year-old woman who underwent a CEA within 12 days of intravenous thrombolysis. She suffered a postoperative intracranial haemorrhage on the same day following CEA.

The third and fourth cases involved two 81-year-old men treated with CEA within 5 days of thrombolysis and who suffered a retinal infarction and minor hemispheric stroke, respectively, post-CEA.

There were four included cases of angioplasty (without stenting) post-thrombolysis, in which there was no stroke or death. No studies reported stroke or death in patients undergoing angioplasty (without stenting) post-thrombolysis.

**Secondary outcome**
Only one of nine included studies reported on cranial nerve injury, in which no patient experienced cranial nerve injury. Bleeding complications were documented in two studies investigating CEA post-thrombolysis, with two out of 27 patients experiencing bleeding (7%). Wound complications
Table 1. Characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study design</th>
<th>Patients meeting inclusion criteria (n)</th>
<th>Age (years) mean/median (range)</th>
<th>Male: female ratio</th>
<th>Intervention: CEA/angioplasty</th>
<th>Onset-to-IVT/IAT (h)</th>
<th>Thrombolysis to intervention time (mean/median) (range)</th>
<th>Onset to intervention time (mean/median) (range)</th>
<th>30-day stroke (n)</th>
<th>30-day death (n)</th>
<th>30-day stroke or death (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rathenborg et al., 2013</td>
<td>Denmark</td>
<td>R</td>
<td>22</td>
<td>71 (66–77)</td>
<td>18:4</td>
<td>IVT CEA</td>
<td>≤4.5</td>
<td>NR</td>
<td>11 d (7–13)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leseche et al., 2012</td>
<td>France</td>
<td>R</td>
<td>7</td>
<td>NR</td>
<td>NR</td>
<td>IVT CEA</td>
<td>≤3.0</td>
<td>NR</td>
<td>&lt;14 d</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bartoli et al., 2009</td>
<td>France</td>
<td>R</td>
<td>9</td>
<td>60 (49–79)</td>
<td>7:2</td>
<td>IVT CEA</td>
<td>≤3.0</td>
<td>Within 12 d</td>
<td>≤12 d</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>McPherson et al., 2001</td>
<td>America</td>
<td>R</td>
<td>5</td>
<td>59 (75–72)</td>
<td>4:1</td>
<td>All patients had IVT, 3 patients also had IAT</td>
<td>CEA NR</td>
<td>&lt;48 h</td>
<td>Mean = 24.6 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endo et al., 1998</td>
<td>Japan</td>
<td>R</td>
<td>5</td>
<td>64 (49–76)</td>
<td>5:0</td>
<td>IAT Angioplasty (n = 4); CEA (n = 1)</td>
<td>≤6.0</td>
<td>CEA performed 8 h later. Angioplasty all performed immediately</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Shalhoub et al., 2011</td>
<td>England</td>
<td>R</td>
<td>6</td>
<td>69 (51–75)</td>
<td>4:2</td>
<td>IVT CEA</td>
<td>NR</td>
<td>5.5 d (4–9)</td>
<td>NR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yong et al., 2013</td>
<td>England</td>
<td>R</td>
<td>7</td>
<td>71 (62–84)</td>
<td>5:2</td>
<td>IVT CEA</td>
<td>≤4.5</td>
<td>NR</td>
<td>7 d (2–12)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Koraen-Smith et al., 2014</td>
<td>Sweden</td>
<td>R</td>
<td>52</td>
<td>NR</td>
<td>NR</td>
<td>IVT CEA</td>
<td>≤6.0</td>
<td>&lt;14 d</td>
<td>NR</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Benes et al. 2014</td>
<td>Czech Republic</td>
<td>R</td>
<td>5</td>
<td>63 (54–68)</td>
<td>1:4</td>
<td>IVT CEA</td>
<td>≤4.5</td>
<td>&lt;5 h</td>
<td>&lt;6 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Note. R = retrospective; NR = not reported; IAT = intra-arterial thrombolysis; IVT = intravenous thrombolysis; CEA = carotid endarterectomy.
### Table 2. Quality assessment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Study duration (y)</th>
<th>Patients (n)</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Diagnosis by stroke neurologist</th>
<th>Operation technical details given</th>
<th>Measures taken to prevent high blood pressure in the postoperative period</th>
<th>Follow-up examination performed by neurologist</th>
<th>Source of funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rathenborg et al., 2013</td>
<td>R</td>
<td>5</td>
<td>22</td>
<td>IVT before CEA for stroke</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Nil</td>
</tr>
<tr>
<td>Leseche et al., 2012</td>
<td>R</td>
<td>8</td>
<td>7</td>
<td>All patients with stroke in evolution and ipsilateral high-grade ICA stenosis and who underwent operation ≤ 2 weeks of index event</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
</tr>
<tr>
<td>Bartoli et al., 2009</td>
<td>R</td>
<td>NR</td>
<td>9</td>
<td>IVT before CEA for stroke</td>
<td>Persistent severe neurological deficit; previous radical neck dissection; cervical irradiation; expectation of poor surgical risk</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Nil</td>
</tr>
<tr>
<td>McPherson et al., 2001</td>
<td>R</td>
<td>3</td>
<td>5</td>
<td>Patients who met all the inclusion criteria and none of the exclusion criteria for thrombolysis</td>
<td>NR</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Endo et al., 1998</td>
<td>R</td>
<td>6</td>
<td>5</td>
<td>Acute ICA occlusion, treated with thrombolysis within 6 h</td>
<td>Age &gt; 80 y; deep coma; gradually improving symptoms; critical condition; known contraindication to fibrinolysis; inability to obtain informed consent</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Shalhoub et al., 2011</td>
<td>R</td>
<td>2</td>
<td>6</td>
<td>CEA within 2 weeks of thrombolysis</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yong et al., 2013</td>
<td>R</td>
<td>3</td>
<td>7</td>
<td>Patients operated within 30 days of stroke onset</td>
<td>NR</td>
<td>NR</td>
<td>No</td>
<td>Yes</td>
<td>NR</td>
<td>Nil</td>
</tr>
<tr>
<td>Koraen-Smith et al., 2014</td>
<td>R</td>
<td>4</td>
<td>52</td>
<td>Patients with carotid intervention post-stroke</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>Declared</td>
</tr>
<tr>
<td>Benes et al., 2014</td>
<td>R</td>
<td>3</td>
<td>5</td>
<td>Patients with ischaemic stroke with NIHSS &gt; 5 and ICA occlusion</td>
<td>NR</td>
<td>Yes</td>
<td>Yes</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
</tr>
</tbody>
</table>

_Note._ R = retrospective; NR = not reported; IVT = intravenous thrombolysis; CEA = carotid endarterectomy; ICA = internal carotid artery; NIHSS = National Institutes of Health Stroke Scale.
were recorded in one study investigating CEA; no wound complications were observed.

The strength of recommendation and quality of underlying evidence as per the ACCP grading system was determined as 1C.17 This represents a strong recommendation with low-quality or very low-quality evidence, and a recommendation that may change if/when higher quality evidence becomes available. This grade was established owing to (i) existing evidence clearly suggesting that early CEA within 14 days of thrombolysis is safe; and (ii) supporting evidence being observational studies or case series.

DISCUSSION

The aim of this systematic review was to assess the safety of early carotid intervention post-thrombolysis. All patients had confirmed significant ICA stenosis, underwent carotid intervention within 14 days of thrombolysis, and had 30-day stroke or death outcomes recorded. Two types of carotid intervention were included for analysis: CEA and angioplasty (without stenting).

CEA

In a pooled analysis of the NASCET and ECST trials, patients who underwent CEA had a 7.0% stroke or death rate at 30 days.10 Furthermore, two large trials—EVA-3S (‘Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis’)20 and SPACE (‘Stent-supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy’)21—reported 30-day stroke or death rates of 3.9% and 6.3%, respectively, post-CEA for symptomatic ICA stenosis. Similar rates were obtained by the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS; 5.9%),22 the Carotid Revascularization Endarterectomy Versus Stenting Trial (3.2%),23 and the International Carotid Stenting Study (3.4%).24

In this systematic review, the point estimate of 30-day stroke or death for CEA was 4.93% (95% CI 1.83–9.44), representing four cases in 114. While this may suggest that early CEA (≤14 days) appears safe, with stroke or death rates similar to that of the operation without thrombolysis, the wide CI highlights the uncertainty of this result. The I² was 0.00% (95% CI 0–34.95), indicating a low level of heterogeneity between studies concerning rates of stroke or death in patient with CEA.

Further, as highlighted by the ACCP grading system,17 this recommendation is supported by low-quality or very low-quality evidence, meaning that such a recommendation may change if/when higher quality evidence becomes available.

These findings are supported by a 2013 systematic review by Yong et al.,25 which reported a pooled 30-day stroke or death rate for CEA following thrombolysis for acute ischaemic stroke of 3.0% (2/77). However, it should be noted that this study included patients who underwent CEA within 30 days of stroke onset, thereby not assessing the safety of CEA in the acute period during which intervention is recommended for symptomatic disease (≤14 days).10

Further, this review had no minimum sample size inclusion criteria and was limited to studies published up to August 2012.

Angioplasty

The potential benefit of angioplasty as an alternative to CEA was highlighted by CAVATAS.22 Since the completion of CAVATAS, angioplasty with stenting has largely replaced angioplasty alone, with studies reporting fewer complications and improved outcomes.22 Despite the increasing utility of carotid stenting,24,26,27 no studies investigating the safety of such intervention post-thrombolysis were identified that met simple inclusion criteria.

Angioplasty soon after thrombolysis has been found to be safe in the management of acute myocardial infarction.28–30 In the Rescue Angioplasty versus Conservative Treatment or Repeat Thrombolysis (REACT) trial, Gershlick et al.31 highlighted the safety and efficacy of coronary angioplasty post-thrombolysis. In a randomised multicentre trial, Bonnefoy et al. obtained similar findings.29

In the present study, as no patients undergoing angioplasty (without stenting) suffered stroke or death in the small series published, the safety of this procedure post-thrombolysis could not be estimated.

The secondary outcomes obtained are difficult to interpret owing to the paucity of recorded surgical complications. It appears that there is a relatively low risk of bleeding and wound complications, but, again, prospective data from large cohorts or patients are required.

Despite the impetus to surgically treat significant carotid atherosclerosis as early as possible following cerebral insult, significant heterogeneity in reported intervention timings prohibited detailed analysis of safety if the intervention was performed in the hyperacute period (48 h) following thrombolysis.

Limitations

First, the included studies consisted of observational studies or case series with small sample sizes. The formal quality assessment implemented highlights the low-quality evidence available. Second, data concerning cranial nerve injury, and bleeding and wound complications were only partially available, limiting the ability to draw conclusions on the secondary outcomes. Finally, the presence of reporting bias must also be considered and, to address these limitations, prospective registry data are required to generate the required numbers to assess accurately the safety of carotid revascularization post-thrombolysis.

CONCLUSIONS

In situations of acute ischaemic stroke, where patients have residual carotid artery stenosis post-thrombolysis, early CEA (≤14 days) appears safe with stroke or death rates similar to that of the operation without thrombolysis. However, the wide CI obtained highlights the uncertainty of this result, which is supported by low-quality evidence. With no cases of stroke or death concerning angioplasty, the safety of this
intervention post-thrombolysis could not be estimated. Prospective registry data are required to verify these findings and accurately determine the optimal timing of carotid intervention post-thrombolysis.

CONFLICT OF INTEREST
None.

FUNDING
M.I.Q. is funded by The Circulation Foundation, The Graham Dixon Charitable Trust, The Rosetrees Trust, and The Royal College of Surgeons of England. BD has received funding from The Stroke Association, The European Venous Forum, and The Graham Dixon Charitable Trust. The study sponsors had no role in the study design, in the collection, analysis, and interpretation of data; in the writing of the manuscript; nor in the decision to submit the manuscript for publication.

REFERENCES


