Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke
A Meta-Analysis of Individual Patient Data

Sanne M. Zinkstok, MD; Mervyn D.I. Vergouwen, MD; Stefan T. Engelter, MD; Philippe A. Lyrer, MD; Leo H. Bonati, MD; Marcel Arnold, MD; Heinrich P. Mattle, MD; Urs Fischer, MD; Hakan Sarikaya, MD; Ralf W. Baumgartner, MD; Dimitrios Georgiadis, MD; Céline Odier, MD; Patrik Michel, MD; Jukka Putaala, MD; Martin Griebe, MD; Nils Wahlgren, MD; Niaz Ahmed, MD; Nan van Geloven, MSc; Rob J. de Haan, PhD; Paul J. Nederkoorn, MD

Background and Purpose—The safety and efficacy of thrombolysis in cervical artery dissection (CAD) are controversial. The aim of this meta-analysis was to pool all individual patient data and provide a valid estimate of safety and outcome of thrombolysis in CAD.

Methods—We performed a systematic literature search on intravenous and intra-arterial thrombolysis in CAD. We calculated the rates of pooled symptomatic intracranial hemorrhage and mortality and indirectly compared them with matched controls from the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register. We applied multivariate regression models to identify predictors of excellent (modified Rankin Scale=0 to 1) and favorable (modified Rankin Scale=0 to 2) outcome.

Results—We obtained individual patient data of 180 patients from 14 retrospective series and 22 case reports. Patients were predominantly female (68%), with a mean±SD age of 46±11 years. Most patients presented with severe stroke (median National Institutes of Health Stroke Scale score=16). Treatment was intravenous thrombolysis in 67% and intra-arterial thrombolysis in 33%. Median follow-up was 3 months. The pooled symptomatic intracranial hemorrhage rate was 3.1% (95% CI, 1.3 to 7.2). Overall mortality was 8.1% (95% CI, 4.9 to 13.2), and 41.0% (95% CI, 31.4 to 51.4) had an excellent outcome. Stroke severity was a strong predictor of outcome. Overlapping confidence intervals of end points indicated no relevant differences with matched controls from the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register.

Conclusions—Safety and outcome of thrombolysis in patients with CAD-related stroke appear similar to those for stroke from all causes. Based on our findings, thrombolysis should not be withheld in patients with CAD. (Stroke. 2011;42:2515-2520.)

Key Words: carotid artery □ cerebral infarct □ dissection □ outcome □ thrombolysis □ safety

Approximately 2% of all ischemic strokes are caused by cervical artery dissection (CAD). In patients <50 years of age, CAD accounts for 10% to 25% of all ischemic strokes.1-2 CAD is characterized by the presence of an intramural hematoma due to an intimal tear in the carotid or vertebral artery wall. Subsequent ischemic stroke is believed to be caused by thromboembolism in most cases rather than by hemodynamic factors.3 Randomized controlled trials to investigate thrombolysis in acute ischemic stroke did not exclude patients with CAD.4 However, safety and efficacy have not been investigated for this particular group in these randomized controlled trials. Therefore, it remains unknown whether thrombolysis can be given in acute ischemic stroke attributable to CAD.

The most serious complication of thrombolysis is symptomatic intracranial hemorrhage (SICH), which occurs in 2% to 9%.4 In patients with CAD, an additional concern is the risk of enlargement of the intramural hematoma. Small retrospective case series suggested that thrombolysis in CAD patients is safe.5-6 The aim of the current meta-analysis was to
pool all available case reports and series using individual patient data (IPD) and thus provide a valid estimate of safety and outcome of thrombolysis in patients with CAD-related stroke. In addition, predictors of outcome after thrombolysis in CAD patients were evaluated.

Methods

Study Selection
We systematically searched the PubMed and EMBASE database up to March 2010 for publications on thrombolysis in patients with CAD-related ischemic stroke by using the following combination of variables: "[dissection]" AND "[carotid" or "vertebral" or "cervical" or "extracranial" or "stroke" or "brain ischemia" or "brain infarction"] AND "[thrombolysis]" or "recombinant tissue plasminogen activator" or "rtPA" or "tissue plasminogen activator" or "tPA" or "urokinase" or "pro-urokinase"). In addition, we searched for relevant studies in the Cochrane Library and Cochrane Central Register of Controlled Trials and hand-searched citations from the retrieved studies. Finally, experts in the field were consulted.

We included studies that investigated thrombolysis in patients with CAD-related stroke, either as the main focus of research or as a subgroup analysis. Because the number of publications on this topic is scarce, we did not set a minimum to the number of patients per study. We included publications written in English, German, French, and other languages if an abstract in English, German, or French was available. Patients with a dissection limited to the intracranial part of the vessel(s) only or with an aortic dissection extending into the cervical arteries were excluded. The diagnosis of CAD needed to be confirmed with appropriate imaging tests: color duplex sonography, computed tomography angiography, magnetic resonance angiography, or conventional angiography. Confirmation of the dissection before or after thrombolysis was allowed. Because most studies did not systematically assess the degree of both extracranial and intracranial stenosis before and after treatment, recanalization was not included in our analysis. We analyzed 2 treatment groups: intravenous thrombolysis (IVT) and intra-arterial thrombolysis (IAT). IAT was defined as treatment with IAT only, IVT followed by IAT, or IAT in combination with any endovascular procedure, such as mechanical thrombectomy or stent placement. Thrombolytic therapy had to be administered within 24 hours after stroke symptom onset. The subgroups of patients treated within 3 hours and within 4.5 hours were analyzed separately.

Data Extraction
We collected the following baseline characteristics: sex, age, preceding trauma, stroke severity at presentation as assessed on the National Institutes of Health Stroke Scale (NIHSS), location of the dissected artery (carotid or vertebral), vessel occlusion before treatment, intracranial extension, time from symptom onset to treatment, treatment type (IVT or IAT), and duration of follow-up.

As safety variables, we analyzed SICH, mortality, and recurrent stroke. For the present study, we defined SICH as any intracranial bleeding documented on computed tomography or magnetic resonance imaging that was temporally related to deterioration in the patients' clinical condition. In the included studies, different definitions were used for clinical deterioration. Additional adverse events as reported by the authors were collected and described. We assessed functional outcome by means of the level of dependency at follow-up. Excellent functional outcome was defined as 0 to 1 on the modified Rankin Scale (mRS), and favorable functional outcome, as an mRS score of 0 to 2. Finally, we performed a subgroup analysis to investigate whether patients with carotid or vertebral artery occlusion had a higher risk of poor functional outcome (mRS = 3 to 6).

Two independent observers (S.Z., P.N.) extracted all data. Disagreements were resolved by consensus. When the mRS was unavailable, the same observers reconstructed the score if this could clearly be deducted from the case description, according to the mRS criteria.

Individual Patient Data
We sent a uniform dataset to the authors of all case series with aggregated data only. To prevent double counting of patients who were reported in case series, only the IPD were used for analysis. Authors of case reports were contacted only when the IPD needed for the analysis were incompletely described in the manuscript.

Statistical Analyses
We used the IPD to construct mixed models with the lme4 package of R. We adjusted for the heterogeneity across studies by including a random intercept per study in these models. Pooled proportions were calculated for SICH and mortality, for recurrent stroke and for excellent and favorable outcome. SICH and mortality rates were calculated for the subgroup treated within 3 and within 4.5 hours according to IVT guidelines. These proportions were also calculated for all patients treated with IVT. The following variables were included in univariate models as predictors of excellent and favorable outcome: sex, age, preceding trauma, location of dissected artery, onset-to-treatment time, stroke severity (NIHSS score), and treatment modality. Onset-to-treatment time was analyzed as both a continuous and categorical variable, the latter based on empirically defined cutoff values (<120 minutes, 120 to 180 minutes, and ≥180 minutes). In the multivariate analyses, we adjusted for predictors that were significantly (P < 0.05) associated with excellent and favorable outcomes in the univariate analyses. A subgroup analysis was performed after excluding data from the case reports.

Comparison With SITS-ISTR
We compared our findings with the results of the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register (SITS-ISTR), an ongoing, prospective, international stroke register of patients treated with IVT. Our pooled rates for SICH and functional outcome (including mortality) were indirectly compared with the same end points of selected controls from SITS-ISTR; that is, matched for age and stroke severity (NIHSS score). When a complete match did not exist (allowing a deviation of 1 year or 1 point on the NIHSS score), a control patient was recorded as missing. In SITS-ISTR, SICH was reported according to the definition of both the National Institute of Neurological Diseases and Stroke (any hemorrhage with any neurologic deterioration <7 days after sympotm onset) and the European-Australian Acute Stroke Study II (any hemorrhage with a ≥4-point increase on the NIHSS and likely to be the cause of the clinical deterioration). Functional outcome (mRS) in SITS-ISTR was assessed at 3 months, whereas follow-up duration in our meta-analysis differed among studies. From our IPD, we therefore selected only patients with outcome assessed within 3 months of follow-up.

Results

Studies
Our search strategy yielded 186 citations; 36 publications about 190 patients fulfilled our predefined criteria. All studies were retrospective series or single case reports; no randomized controlled trials were identified. Fourteen case series (160 patients) presented data on thrombolysis in dissection-related stroke.5,6,10–21 Nine series used data from stroke registries10,14,18,21 or thrombolysis registries,5,11,16,22 and 1 was based on a nondefined hospital registry.15 Of these, 3 studies were multicenter studies,5,10,22 Supplemental Table I (http://stroke.ahajournals.org) gives an overview of the study characteristics of the case series. In addition, 22 case reports were retrieved describing another 24 patients,23–44 IPD were available from 33 publications (72 patients). IPD from 108 patients were provided by the authors from the remaining 3 publications that contained aggregated data of 118 patients.
The median NIHSS score was 16 (11–20), and most patients (60%) presented with severe stroke symptoms (NIHSS score ≥15). Median onset-to-treatment time was 165 minutes (interquartile range, 125 to 225). Treatment was IVT in 67% and IAT in 33%. Six percent of the IVT patients were treated beyond the therapeutic window of 4.5 hours after symptom onset.

In the IVT group, 4 patients experienced SICH (3.3%; 95% CI, 1.0–8.5). Recurrent stroke occurred in 4.5% (95% CI, 2.3–8.7) and in 6.8% (95% CI 3.4 to 13.0) of the patients treated with IVT (Tables 2 and 3). Other complications after thrombolytic treatment were asymptomatic ICH in 26 patients. One patient with right vertebral artery dissection treated with IVT experienced hematoma expansion (unpublished data), with excellent recovery (mRS score=1 at 3 months). Pseudoaneurysm at follow-up was reported in 8 of the 133 patients for whom this information was available. One asymptomatic subarachnoid bleeding event occurred. Progression of the infarct defined as worsening of the NIHSS score with intracranial hemorrhage excluded on imaging was reported in 13 of 161 patients.

### Safety

The pooled mortality was 8.1% (95% CI, 4.9 to 13.2). However, in 7 patients (4%), survival status was unavailable. Pooled mortality in 121 patients treated with IVT was 6.7% (95% CI, 3.4 to 13.8). SICH occurred in 8 of 180 patients (4.4% (95% CI, 1.3 to 8.5). Recurrent stroke occurred in 4.5% (95% CI, 2.3 to 8.7) and in 6.8% (95% CI 3.4 to 13.0) of the patients treated with IVT (Tables 2 and 3).

### Baseline Characteristics

Patients were predominantly female (68%) with a mean ± SD age of 46 ± 11 years. The median NIHSS score was 16 (interquartile range, 11 to 20), and most patients (60%) presented with severe stroke symptoms (NIHSS score ≥15). Median onset-to-treatment time was 165 minutes (interquartile range, 125 to 225). Treatment was IVT in 67% and IAT in 33%. Six percent of the IVT patients were treated beyond the therapeutic window of 4.5 hours after symptom onset. Baseline characteristics are summarized in Table 1.

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>IPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
<td>180</td>
</tr>
<tr>
<td>Men, n (%)</td>
<td>57 (32)</td>
</tr>
<tr>
<td>Age, mean±SD, y</td>
<td>46 ± 11</td>
</tr>
<tr>
<td>Preceding trauma, n (%)</td>
<td>31 (17)</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
</tr>
<tr>
<td>Presenting NIHSS score, mean±SD (range)</td>
<td>15.8±6.9 (1–36)</td>
</tr>
<tr>
<td>Median NIHSS score (IQR)</td>
<td>16 (11–20)</td>
</tr>
<tr>
<td>Mild stroke (NIHSS score 1–7), n (%)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Moderate stroke (NIHSS score 8–14), n (%)</td>
<td>42 (25)</td>
</tr>
<tr>
<td>Severe stroke (NIHSS score ≥15), n (%)</td>
<td>86 (60)</td>
</tr>
<tr>
<td>Location of dissection</td>
<td></td>
</tr>
<tr>
<td>Carotid artery, n (%)</td>
<td>131 (73)</td>
</tr>
<tr>
<td>Vertebral artery, n (%)</td>
<td>48 (27)</td>
</tr>
<tr>
<td>Both, n (%)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Occlusion before treatment, n (%)</td>
<td>107 (83)</td>
</tr>
<tr>
<td>Intracranial extension, n (%)</td>
<td>16 (10)</td>
</tr>
<tr>
<td>Onset-to-treatment time, mean±SD, min</td>
<td>195 ± 123</td>
</tr>
<tr>
<td>Onset-to-treatment time, median (IQR)</td>
<td>165 (125–225)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
</tr>
<tr>
<td>IVT, n (%)</td>
<td>121 (67)</td>
</tr>
<tr>
<td>IAT, n (%)</td>
<td>59 (33)</td>
</tr>
<tr>
<td>Median duration of follow-up (mo) (range)</td>
<td>3.0 (0.2–18)</td>
</tr>
</tbody>
</table>

NIHSS indicates National Institutes of Health Stroke Scale; IQR, interquartile range; IVT, intravenous thrombolysis; IAT, intra-arterial thrombolysis; IPD, individual patient data; SD, standard deviation.

and from unpublished cases. In total, IPD from 180 patients, all treated with IVT or IAT, were available for the analysis.

### Functional Outcome

The mRS score was available for 156 patients. In 17 cases, the mRS score could be reliably deduced from the description of functional status. In total, 41.0% (95% CI, 31.4 to 51.4) made an excellent recovery (mRS score=0 to 1), and 59.5% (95% CI, 51.8 to 66.6) had a favorable outcome (mRS score=0 to 2). In the IVT group, 33.3% (95% CI, 25.5 to 42.2) had an excellent outcome, and 60.8% (95% CI, 51.8 to 69.1) had a favorable outcome (Tables 2 and 3).

Median follow-up was 3 months (range, 5 days to 18 months), but 137 patients had their functional outcome

### Table 1. Baseline Characteristics of All Included Cervical Artery Dissection Patients: Individual Patient Data

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion</th>
<th>Crude Estimates, % (95% CI)</th>
<th>Adjusted for Heterogeneity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>8/180</td>
<td>4.4 (2.1–8.7)</td>
<td>3.1 (1.3–7.2)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>3/98</td>
<td>3.0 (0.7–9.0)</td>
<td>3.1 (0.1–9.1)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>5/137</td>
<td>3.7 (1.3–8.5)</td>
<td>3.6 (1.5–8.5)</td>
</tr>
<tr>
<td>Mortality</td>
<td>14/173</td>
<td>8.1 (4.8–13.1)</td>
<td>8.1 (4.9–13.2)</td>
</tr>
<tr>
<td>0–180 min*</td>
<td>8/96</td>
<td>8.3 (4.1–15.8)</td>
<td>8.3 (4.2–15.8)</td>
</tr>
<tr>
<td>0–270 min*</td>
<td>9/135</td>
<td>6.7 (3.4–12.3)</td>
<td>6.7 (3.5–12.3)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>8/177</td>
<td>4.5 (2.2–8.8)</td>
<td>4.5 (2.3–8.7)</td>
</tr>
<tr>
<td>mRS=0–1</td>
<td>63/173</td>
<td>36.4 (29.6–43.8)</td>
<td>41.0 (31.4–51.4)</td>
</tr>
<tr>
<td>mRS=0–2</td>
<td>103/173</td>
<td>59.5 (52.1–66.6)</td>
<td>59.5 (52.1–66.6)</td>
</tr>
</tbody>
</table>

SICH indicates symptomatic intracranial hemorrhage; mRS, modified Rankin Scale score; CI, confidence interval.

*Minutes from symptom onset to thrombolytic treatment.
Table 4. Indirect Comparison of Thrombolysis in Patients With Cervical Artery Dissection–Related Stroke (Current Meta-Analysis) With Matched* Patients With Stroke From All Causes Treated With IVT (Data From SITS-ISTR)*

<table>
<thead>
<tr>
<th>End Point</th>
<th>N/n</th>
<th>% (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>180</td>
<td>3.1 (1.3–7.2)</td>
<td>121</td>
<td>3.3 (1.2–8.5)</td>
</tr>
<tr>
<td>Mortality at ≤3 mo</td>
<td>144</td>
<td>9.0 (5.3–14.9)</td>
<td>110</td>
<td>7.3 (3.7–13.9)</td>
</tr>
<tr>
<td>mRS=0–1 at ≤3 mo</td>
<td>144</td>
<td>31.2 (24.2–39.3)</td>
<td>110</td>
<td>30.9 (23.0–40.1)</td>
</tr>
<tr>
<td>mRS=0–2 at ≤3 mo</td>
<td>144</td>
<td>55.6 (47.4–63.5)</td>
<td>110</td>
<td>58.2 (48.8–67.0)</td>
</tr>
</tbody>
</table>

*Controls were matched for age and stroke severity.
†Any hemorrhage plus any neurologic deterioration.
‡Any hemorrhage plus ≥4-point increase on the National Institutes of Health Stroke Scale.

Discussion

This meta-analysis of IPD comprises the largest published number of CAD patients treated with thrombolysis to date and suggests that thrombolysis in acute ischemic stroke due to CAD is safe. The pooled SICH rate of 3% and overall mortality of 8% (3% and 7%, respectively, in IVT) in CAD patients are apparently similar to those of stroke from all causes. In particular, the indirect comparison between our population and matched controls from SITS-ISTR did not show relevant differences for these important end points. We did not perform statistical testing of differences between our population and SITS-ISTR, as both studies were not designed beforehand to be compared. We therefore present this comparison only in a descriptive way. However, because placebo-controlled trials on thrombolysis in patients with CAD-related stroke may not be ethical anymore, the presented data may be the best available evidence for clinical guidelines to date.

Expansion of the intramural hematoma during thrombolysis seems to be a rather theoretical concern. In our study, only 1 patient with an intramural hematoma expansion was described but had an excellent outcome. We realize that most studies did not systemically report on this direct complication. However, given the overall safety end points and functional outcome, direct bleeding complications from thrombolysis are apparently not a major issue.

In our population, 31% of all CAD patients had an excellent outcome (mRS=0 to 1), compared with 37% in SITS-ISTR. However, a favorable outcome seemed slightly higher in our population (58%, versus 52% in SITS-ISTR). For both outcome measures, the CIs largely overlapped. Therefore, given the fact that we can only make an indirect comparison, the outcome after IVT in patients with stroke due to CAD is in the same range as observed in IVT after stroke from all causes. The subgroup of patients with a priori proven carotid or vertebral artery occlusion may have a higher risk for poor outcome. Because of the small numbers and wide CIs, we could not prove this, and the possible association was not significant. If a higher risk would be found in a larger study in the future, this could imply a different and possibly

assessment at 3 months exactly. Proportions per follow-up period are reported in Supplemental Table II.

The odds ratio (OR) for poor functional outcome (mRS=3 to 6) for the subgroup of patients with proven carotid artery occlusion (n=79) was 1.47 (95% CI, 0.41 to 5.51); for patients with vertebral artery occlusion (n=28), this OR was 1.57 (95% CI, 0.19 to 15.41). The small numbers precluded a valid or meaningful multivariate analysis.

Regression Models

Predictors of excellent (mRS=0 to 1) and favorable (mRS=0 to 2) outcome are presented in Supplemental Table III. In the univariate analyses, only stroke severity (NIHSS score on admission) was inversely associated with both excellent and favorable outcome. The OR for excellent outcome was 0.9 (95% CI, 0.8 to 0.9) for each 1-point increase on the NIHSS. For favorable outcome, this OR was also 0.9 (95% CI, 0.8 to 0.9). Vertebral artery dissection was significantly associated with excellent outcome compared with carotid artery dissection (OR=2.6; 95% CI, 1.2 to 5.6) but not with favorable outcome (univariate analysis). Other variables were not associated with outcome. In the multivariate models, we adjusted for stroke severity only. In these models, vertebral artery dissection remained associated with an excellent outcome (OR=3.9; 95% CI, 1.4 to 11.1). None of the other variables examined were associated with outcome.

Publication Bias

Leaving out the data from case reports did not alter the main findings. Apparently, there was no publication bias in favor of case reports compared with the results of the larger studies.

Comparison With SITS-ISTR

Selection of controls from SITS-ISTR, matched for age and stroke severity, resulted in 170 eligible cases. Point estimates for the main outcomes of our study compared with SITS-ISTR are shown in Table 4. Overlapping CIs indicated no relevant differences in SICH rates, mortality, and functional outcome.
more aggressive therapeutic approach in this particular subgroup. This still needs to be investigated.

Our study has some limitations. First, no randomized trials were available for this meta-analysis. The pooled estimates are based on retrospective and mostly uncontrolled series and case reports only. Although leaving out the case reports did not change our findings, the possibility of publication bias in included series cannot be excluded and might still have influenced the results of this meta-analysis. Another limitation is that we used a pragmatic instead of a strict definition of SICH because the criteria for SICH in the studies contributing to our meta-analysis were heterogeneous. This makes a comparison with SICH rates in other studies difficult. However, our rate with mixed definitions of SICH falls within the rates from SITS-ISTR according to the National Institute of Neurological Diseases and Stroke and European-Australian Acute Stroke Study II definitions. This strongly suggests that the risk of SICH is not increased in patients with CAD-related stroke.

Another point of concern in this study is diagnostic uncertainty in patients with presumed CAD. However, the largest published series included in our analysis excluded patients with “possible” CAD, thereby reducing the diagnostic uncertainty. The type of antithrombotic agents used after thrombolysis was not assessed, which might influence the rate of SICH as well as the outcome. One could argue that we applied a wide treatment window of 24 hours after symptom onset, which is beyond the current guidelines of 4.5 hours for IVT. Median treatment time in our study was 165 minutes (interquartile range, 125 to 225) after symptom onset, indicating that thrombolytic therapy was mostly administered in the very acute phase of the stroke, which was the focus of our study. In the subgroup analysis, we showed that safety and outcome did not differ between patients treated within 3 and within 4.5 hours after symptom onset, in comparison with the entire study population. Finally, the follow-up duration varied among the included studies. Therefore, we present subgroups according to follow-up duration. Moreover, the majority of patients had their follow-up at 3 months exactly, which is similar to that in SITS-ISTR.

Conclusions
In conclusion, thrombolysis appears to be safe in acute ischemic stroke due to CAD. Mortality and SICH rate, as well as outcome, after thrombolysis in these patients appear to be similar to the rates in stroke patients from all causes treated with thrombolysis. Although our analysis is based on retrospective data with small numbers of patients, our results give no evidence that thrombolysis should be withheld in patients with ischemic stroke caused by CAD.

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Disclosures
None.

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### Supplemental Tables

#### S1. Characteristics of included series (case-reports are not listed)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Population</th>
<th>No. of patients included in meta-analysis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelter et al.</td>
<td>retrospective, multicenter</td>
<td>55 consecutive patients with stroke due to cervical artery dissection treated with IVT</td>
<td>55</td>
<td>IVT</td>
</tr>
<tr>
<td>Vergouwen et al.</td>
<td>retrospective, single centre</td>
<td>8 consecutive patients with stroke due to extracranial artery dissection</td>
<td>6</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Putaala et al.</td>
<td>retrospective, single centre</td>
<td>48 consecutive patients with stroke aged 16-49 treated with IVT</td>
<td>12</td>
<td>IVT</td>
</tr>
<tr>
<td>Huang et al.</td>
<td>retrospective, single centre</td>
<td>73 patients with cervicocranial arterial dissection</td>
<td>1</td>
<td>IAT</td>
</tr>
<tr>
<td>Cerrato et al.</td>
<td>retrospective, single centre</td>
<td>3 patients with vertebral artery dissection and basilar artery occlusion treated with IAT</td>
<td>3</td>
<td>IAT.</td>
</tr>
<tr>
<td>Baumgartner et al.</td>
<td>retrospective, single centre</td>
<td>18 consecutive patients with internal carotid artery dissection and a symptomatic middle cerebral artery occlusion</td>
<td>18</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Lavallée et al.</td>
<td>retrospective, single centre</td>
<td>10 patients with tandem internal carotid and middle cerebral artery occlusion with internal carotid dissection</td>
<td>5</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Dabitz et al.</td>
<td>retrospective, single centre</td>
<td>10 consecutive patients with cerebral ischemia associated with proximal carotid artery occlusion</td>
<td>3</td>
<td>IAT</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Study Design</td>
<td>Number of Patients</td>
<td>Description of Patients</td>
<td>Number</td>
</tr>
<tr>
<td>--------------------</td>
<td>--------------</td>
<td>--------------------</td>
<td>-------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Georgiadis et al. (2005)</td>
<td>retrospective, multicentre</td>
<td>33</td>
<td>Consecutive patients with stroke due to spontaneous carotid dissection treated with IVT</td>
<td>33</td>
</tr>
<tr>
<td>Arnold et al. (2002)</td>
<td>retrospective, single centre</td>
<td>9</td>
<td>Patients with cervical artery dissection treated with thrombolysis</td>
<td>9</td>
</tr>
<tr>
<td>Bin Saeed et al. (2000)</td>
<td>retrospective, single centre</td>
<td>26</td>
<td>Patients with vertebral artery dissection</td>
<td>2</td>
</tr>
<tr>
<td>Derex et al. (2000)</td>
<td>retrospective, single centre</td>
<td>11</td>
<td>Consecutive patients with acute ischemic stroke related to internal carotid artery dissection treated with IVT</td>
<td>11</td>
</tr>
<tr>
<td>Ahmad et al. (1999)</td>
<td>retrospective, multicentre</td>
<td>18</td>
<td>Patients with cervicocerebral artery dissections</td>
<td>2</td>
</tr>
<tr>
<td>Rudolf et al. (1999)</td>
<td>retrospective, single centre</td>
<td>15</td>
<td>Consecutive patients with internal carotid artery occlusion treated with IVT</td>
<td>6</td>
</tr>
</tbody>
</table>

IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis
S2. Functional outcome per time period of follow-up

<table>
<thead>
<tr>
<th>Follow-up duration</th>
<th>All patients (n=180)</th>
<th>IVT (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mRS 0-1</td>
</tr>
<tr>
<td>0 - ≤10 days</td>
<td>4</td>
<td>2/4</td>
</tr>
<tr>
<td>&gt; 10 days - ≤1 month</td>
<td>1</td>
<td>1/1</td>
</tr>
<tr>
<td>&gt; 1 months - ≤3 months</td>
<td>139</td>
<td>42/139</td>
</tr>
<tr>
<td>3 months exactly</td>
<td>137</td>
<td>137</td>
</tr>
<tr>
<td>&gt; 3 months - ≤12 months</td>
<td>22</td>
<td>15/22</td>
</tr>
<tr>
<td>&gt;12 months - ≤18 months</td>
<td>3</td>
<td>1/3</td>
</tr>
<tr>
<td>Follow-up period or</td>
<td>11</td>
<td>--</td>
</tr>
<tr>
<td>outcome unknown</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mRS = modified Rankin Score; IVT = intravenous thrombolysis; CI = confidence interval
S3. Univariable and multivariable analysis. Odds for excellent and favourable outcome, multivariate analysis is adjusted for stroke severity by means of the NIHSS before start of treatment.

<table>
<thead>
<tr>
<th>Variables</th>
<th>mRS 0 - 1</th>
<th></th>
<th>mRS 0 - 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Adjusted for stroke severity</td>
<td>Univariate</td>
<td>Adjusted for stroke severity</td>
</tr>
<tr>
<td>Gender [female]</td>
<td>0.73 (0.37-1.43)</td>
<td>0.35</td>
<td>0.51 (0.22-1.15)</td>
<td>0.11</td>
</tr>
<tr>
<td>Age</td>
<td>1.01 (0.98-1.04)</td>
<td>0.91</td>
<td>1.00 (0.96-1.04)</td>
<td>0.99</td>
</tr>
<tr>
<td>Preceding trauma</td>
<td>1.79 (0.67-4.77)</td>
<td>0.24</td>
<td>0.43 (0.09-2.03)</td>
<td>0.29</td>
</tr>
<tr>
<td>Dissected artery [vertebral artery]</td>
<td>2.64 (1.24-5.62)</td>
<td>0.01</td>
<td>3.94 (1.40-11.12)</td>
<td>0.01</td>
</tr>
<tr>
<td>Onset to treatment time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous</td>
<td>1.0 (1.00-1.00)</td>
<td>0.72</td>
<td>1.00 (0.99-1.00)</td>
<td>0.42</td>
</tr>
<tr>
<td>&lt; 120 minutes</td>
<td>reference</td>
<td>0.75 (0.36-1.57)</td>
<td>0.44</td>
<td>0.74 (0.32-1.71)</td>
</tr>
<tr>
<td>120-180 minutes</td>
<td>reference</td>
<td>0.63 (0.15-2.58)</td>
<td>0.52</td>
<td>0.27 (0.03-2.83)</td>
</tr>
<tr>
<td>&gt;180 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.88 (0.82-0.93)</td>
<td>&lt;0.001</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVT</td>
<td>reference</td>
<td>1.66 (0.80-3.43)</td>
<td>0.17</td>
<td>2.36 (0.86-6.53)</td>
</tr>
<tr>
<td>IAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

mRS = modified Rankin Score; OR = odds ratio; CI = confidence interval; NIHSS = National Institutes of Health Stroke Scale; IVT = intravenous thrombolysis; IAT = intra-arterial thrombolysis
S4. Overview of centers providing individual patient data

<table>
<thead>
<tr>
<th>Centre</th>
<th>No of patients with individual patient data (per treatment modality)</th>
</tr>
</thead>
<tbody>
<tr>
<td>University Hospital Lausanne, Switzerland</td>
<td>27 patients (22 IVT, 5 IAT)</td>
</tr>
<tr>
<td>University Hospital Bern, Switzerland</td>
<td>25 patients (9 IVT, 16 IAT)</td>
</tr>
<tr>
<td>University Hospital Zürich, Switzerland</td>
<td>24 patients (21 IVT, 3 IAT)</td>
</tr>
<tr>
<td>University Hospital Basel, Switzerland</td>
<td>22 patients (20 IVT, 2 IAT)</td>
</tr>
<tr>
<td>University Hospital Helsinki, Finland</td>
<td>12 patients (12 IVT)</td>
</tr>
<tr>
<td>Universität Medizin Mannheim, Germany</td>
<td>7 patients (7 IVT)</td>
</tr>
<tr>
<td>Academic Medical Centre, University of Amsterdam, the Netherlands</td>
<td>6 patients (4 IVT, 2 IAT)</td>
</tr>
</tbody>
</table>

IVT = intravenous thrombolysis only, IAT = intra-arterial thrombolysis only
References


動脈解離に関係した虚血性脳卒中における血栓溶解療法の安全性および機能的転帰 — 患者の個別データのメタアナリシス

Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke

— A Meta-Analysis of Individual Patient Data

Sanne M. Zinkstok, MD1; Mervyn D.I. Vergouwen, MD2; Stefan T. Engelert, MD1; Philippe A. Lyser, MD1; Leo H. Bonati, MD1; Marcel Arnold, MD3; Heinrich P. Mattle, MD4; Urs Fischer, MD5; Hakan Sarikaya, MD6; Ralf W. Baumgartner, MD7; Dimitrios Georgiadis, MD8; Céline Odier, MD9; Patrik Michel, MD10; Jukka Putaala, MD10; Martin Griebe, MD11; Nils Wahlgren, MD12; Niaz Ahmed, MD12; Nan van Geloven, MSc13; Rob J. de Haan, PhD13; Paul J. Nederkoorn, MD1

1. Department of Neurology, 1 Experimental Vascular Medicine, and 1 Clinical Research Unit, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; Departments of Neurology, 2 University Hospital Basel, 3 University Hospital Bern, 4 University Hospital Zurich, and 3 University Hospital of Lausanne, Switzerland; 5 Helsinki University Central Hospital, Helsinki, Finland; 6 Universitätsmedizin Mannheim, University of Heidelberg, Heidelberg, Germany; and 13 Department of Neurology, Karolinska University Hospital and Department of Clinical Neurosciences, Karolinska Institutet, Stockholm, Sweden

背景および目的：頭部動脈解離 (CAD) における血栓溶解除法の安全性および有効性については意見が分かれる。本メタアナリシスの目的は、患者の個別データをすべて集積し、CAD における血栓溶解療法の安全性および転帰について、妥当な推定を行うことをあった。

方法：CAD における静注および動注血栓溶解療法について体系的文献検索を行った。統合した症候性頭蓋内出血率および死亡率を推定し、Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) や他の調査から抽出した、患者条件を絞った特定の対照群と対照群の比較を行った。削減された危険因子を適用し、きわめて良好な転帰（Rankin スコア 0～2）および良好な転帰（Rankin スコア 0～1）の症例を同定した。

結果：14 件の症例（122 件）の集積研究および 22 件の症例報告から患者 180 例の個別データを入手した。患者は女性が多く（68%）、平均年齢 67 岁で 46 ± 11 歳であった。受診時にはほとんどの患者に徹底脳卒中が認められた（NIHSS スコアの平均値 = 16）。治療は、静注血栓溶解療法が 67%、動注血栓溶解療法が 33% であった。脳卒中発症後 3 倍月で、統合した症候性頭蓋内出血率が 31%（95% CI：1.3 ～7.2%）、全死亡率は 8.1%（95% CI：4.9 ～13.2%）で、41.0%（95% CI：31.4 ～51.4%）はきわめて良好な転帰を示した。脳卒中重症度は有意に転帰予測因子であった。患者群と対照群における治療の内容と脳卒中重症度間には関與がみられなかった。

結論：CAD に関連した脳卒中患者に対する血栓溶解療法の安全性および転帰は、あらゆる原因による脳卒中患者の場合と変わらないように思わせる。本研究に基づくと、CAD 患者に対する血栓溶解療法は検討するべきではない。

Stroke 2011; 42: 2515-2520

表 4
頭部動脈解離に関係した脳卒中患者（本メタアナリシス）と IVT を実施したあらゆる原因による脳卒中患者（本患者群と条件を一致させた* SITS-ISTR のデータ）における血栓溶解療法の間隔比較

<table>
<thead>
<tr>
<th>評価項目</th>
<th>全患者</th>
<th>IVT 症例</th>
<th>あらゆる原因による脳卒中合計</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>例数</td>
<td>% (95% CI)</td>
<td>例数</td>
</tr>
<tr>
<td>評価項目：SICH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>180</td>
<td>3.1 (1.3 ～7.2)</td>
<td></td>
</tr>
<tr>
<td>3カ月以内の死亡率</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3カ月以内の mRS = 0 ～1</td>
<td>121</td>
<td>3.3 (1.2 ～8.5)</td>
<td>110</td>
</tr>
<tr>
<td>3カ月以内の mRS = 0 ～2</td>
<td>144</td>
<td>9.0 (5.3 ～14.7)</td>
<td>110</td>
</tr>
<tr>
<td>3カ月以内の mRS = 0 ～2</td>
<td>144</td>
<td>9.0 (5.3 ～14.7)</td>
<td>110</td>
</tr>
<tr>
<td>3カ月以内の mRS = 0 ～2</td>
<td>144</td>
<td>5.56 (43.7 ～63.5)</td>
<td>110</td>
</tr>
</tbody>
</table>

IVT：静注血栓溶解療法。SITS-ISTR：Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register。SICH：脳卒中重症度。
NINDS：米国国立神経疾患・脳卒中研究所の定義、ECASS III：European-Australian Acute Stroke Study II。mRS：Rankin スコア。CI：信頼区間。
* 一致させた対照群は、本研究と一致させた。

* あらゆる出血 + あらゆる神経学的悪化。
* あらゆる出血 + NIHSS スコア 4 以上上昇。

注：このメタ解析に用いられた症例は 73% が頭動脈解離で、27% が椎骨動脈の解離であった。頭動脈に限局した症例と大動脈解離を伴う症例は除外されている。
Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke
A Meta-Analysis of Individual Patient Data

Sanne M. Zinkstok, MD; Mervyn D.I. Vergouwen, MD; Stefan T. Engelter, MD; Philippe A. Lyrer, MD; Leo H. Bonati, MD; Marcel Arnold, MD; Heinrich P. Mattle, MD; Urs Fischer, MD; Hakan Sarikaya, MD; Ralf W. Baumgartner, MD; Dimitrios Georgiadis, MD; Céline Odier, MD; Patrik Michel, MD; Jukka Putsala, MD; Martin Griebe, MD; Nils Wahlgren, MD; Niaz Ahmed, MD; Nan van Geloven, MSc; Rob J. de Haan, PhD; Paul J. Nederkoorn, MD

(Stroke. 2011;42:2515-2520.)

Key Words:  carotid artery ■ cerebral infarct ■ dissection ■ outcome ■ thrombolysis ■ safety

From the Department of Neurology (S.M.Z., P.J.N.), Experimental Vascular Medicine (M.D.I.V.), and Clinical Research Unit (N.v.G., R.J.d.H.), Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; Departments of Neurology, University Hospital Basel (S.T.E., P.A.L., L.H.B.), University Hospital Bern (M.A., H.P.M., U.F.), University Hospital Zürich (H.S., R.W.B., D.G.), and University Hospital of Lausanne (C.O., P.M.), Switzerland; Helsinki University Central Hospital (J.P.), Helsinki, Finland; Universitätspoliklinik Mannheim (M.G.), University of Heidelberg, Heidelberg, Germany; and the Department of Neurology, Karolinska University Hospital and Department of Clinical Neurosciences, Karolinska Institutet (N.W., N.A.), Stockholm, Sweden.

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Correspondence to Paul J. Nederkoorn, MD, Department of Neurology, H2.216, Academic Medical Center, PO Box 22600, 1100 DD Amsterdam, the Netherlands. E-mail p.j.nederkoorn@ama.uma.nl

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전체 혈관출혈(ischemic stroke)의 약 2%는 경부동맥박리(cervical artery dissection, CAD)에 의하여 발생한다. 50세 미만의 환자에서 CAD는 전체 혈관출혈의 10~25% 정도를 차지한다. 4) CAD는 경동맥 혹은 척추동맥의 내막 파열에 의한 백내혈증(intramural hematoma)이 특징이다. CAD에 의한 혈관출혈은 대부분 혈류학적 요인보다는 혈전색증(thromboembolism)에 의하여 발생하는 것으로 여겨진다. 4) 급성 혈관출혈에서 혈관출혈(thrombolysis)을 연구한 무작위대조사연구들에서 CAD 환자를 제외하지 않았다. 5) 그러나 이 무작위대조사연구들에서 CAD 환자에 대하여 별도로 혈관출혈의 안전성과 결과를 연구하지는 않았다. 따라서 CAD에 의한 급성 혈관출혈에서 혈관출혈의 시행 여부는 아직 알려져 있지 않다.

혈관출혈의 가장 심각한 합병증은 증상성두개내출혈(symptomatic intracranial hemorrhage, SICH)로, 2~9%에서 발생한다. 4) CAD 환자에서는 백내혈증의 확인 위험에 대한 추가가 요구가 있다. 적은 규모의 후향 исслед연구들에서 CAD 환자에서의 혈관출혈은 안전한 것으로 제시되었다. 5) 본 메타 분석의 목적은 얻을 수 있는 모든 증례 보고(case report)와 증례 연구(case series)들의 개별환자자료(individual patient data)를 통합하여 CAD 관련 뇌출혈 환자에서 혈관출혈의 안전성과 결과에 대한 타당한 평가를 제공하는 것이다. 주가적으로 혈관출혈의 결과 예측인자도 평가하였다.

방법

환자 선택

저작들은 PubMed와 EMBASE 데이터베이스에서 ‘dissection’ AND (′carotid’ or ‘vertebral’ or ‘cervical’ or ‘extracranial’ or ‘stroke’ or ‘brain ischemia’ or ‘brain infarction’) AND (′thrombolysis’ or ‘recombinant tissue plasminogen activator’ or ‘rtPA’ or ‘tissue plasminogen activator’ or ‘tPA’ or ‘urokinase’ or ‘pro-urokinase’ ′) 변수들을 조합하여 2010년 3월까지 출판된 CAD 관련 뇌출혈 환자에 대한 연구들을 제계적으로 검색하였다. 또한 Cochrane Library, 혹은 Cochrane Central Register of Controlled Trials에서 기준에 일치하는 연구들을 찾아보고, 최근 한국에서 수시로 인용 문헌들을 조사하였고, 마지막으로 이 분야 전문가들에게 자문을 얻었다.

저작들은 CAD 관련 뇌출혈에서 혈관출혈을 주목적으로 연구하였으나, 이들에 대한 하위 집단 분석을 한 연구들을 포함시켰다. 이 수혜에 대한 연구가 드물기 때문에 각 연구당 최소 환자를 기준을 정하는 것 없었다. 영어, 독일어, 프랑스어로 출판된 연구를 포함하였고, 다른 언어라도 초록이 이들 언어로 쓰여진 경우는 포함하였다. 두개내 혈관에 국한된 혈관박리, 혹은 대동맥박리(aortic dissection)가 경부동맥까지 확장된 경우는 제외하였다. CAD의 진단은 클러스터초음파활영술 (color duplex sonography), 컴퓨터단층혈관조영술(computed tomography angiography), 자기공명혈관조영술 (magnetic resonance angiography), 또는 고식적 혈관조영술을 통해 확인한 경우였다. 혈관출혈 발생 전 혹은 후의 혈관박리 확인을 모두 인정하였으며, 대부분의 연구에서 경도 및 치료 후 두개내 혈관 협착에 대하여 체계적으로 평가하지 않았기 때문에 제계 통계는 분석에서 제외하였다. 저작들은 2 개 치료군(경부내 혈관출혈(intravenous thrombolysis, IVT)과 두개내 혈관출혈(intra-arterial thrombolysis, IAT))으로 나누어 분석하였다. IAT는 IAT만 시행한 경우, IVT 이후 IAT를 시행한 경우, 또는 IAT와 기계적 혈관폐쇄술 혹은 스탠드술과 같은 혈관내 시술을 병행한 경우로 정의하였다. 혈관출혈은 증상 발생 이후 24시간 이내에 시행되어야 했다. 3시간 이내와 4.5시간 이내에 치료받은 환자들을 구분하여 하위 집단 분석을 하였다.

자료 추출

저작들은 성별, 연령, 성행 외상력, NIH뇌출혈체도(National Institutes of Health Stroke Scale)로 평가한 내원 시 뇌졸 중 중증도, 혈관박리의 위치(경동맥 또는 척추동맥), 치료 전 혈관 폐색, 두개내 협착 여부, 증상 발생 후 치료까지 소요 시 간, 치료 종류(IVT 또는 IAT) 및 추적 관찰 기간에 대한 정보를 수집하였다.

안전성 변수로 SICH, 사망률 및 뇌졸중 재발을 평가하였다. SICH는 환자의 임상적 약화와 시간적 연관성을 가지면서 컴퓨터단층촬영, 혹은 자기공명영상에서 확인된 모든 두개내출혈로 정의하였다. 포 함된 연구들에서 임상적 약화와 생명의 독립성은 다양하였다. 저작들이 보고한 추가적인 부작용 자료도 수집하여 기술하였다. 기능적 결과는 추적 기간 중 기능적 독립성인도 정도로 평가하였다. 블랙의 기능적 결과는 수정Rankin척도(modified Rankin Scale, mRS)가 0~1인 경우로, 양호한 기능적 결과는 mRS 0~2로 정의하였다. 마지막으로 창추동맥 혹은 경동맥 폐색 중에서 어느 것이 더 뚜렷한 결과(mRS =3~6)를 보이는지에 대하여 하위 집단 분석을 시행하였다.

두 명의 독립적인 판찰자들(S.Z., P.N.)이 모든 자료를 추출하였다. 의견이 일치하지 않은 경우에는 협의에 의해 해결하였 다. mRS 정보가 없는 경우에는, 증례 기술을 통해 명확히 유추할 수 있는 경우를 동일한 판찰자가 mRS 판단 기준에 따라 재구성하였다.

개별환자자료

저작들은 모든 증례 연구 저작들에게 수집된 자료만 포함된 동일한 데이터 시트를 보냈다. 증례 연구에 보고된 환자들의
중복 집계를 피하기 위해 개별환자자료만 분석에 사용하였다. 중대 보고의 경우 분석에 필요한 개별환자자료의 기술이 불완전한 경우에는 자료와 접촉하였다.

통계 분석

R Ime4 패키지로 개별환자자료를 이용한 통합 모형을 만들었다. 이 모델에서는 각 연구들의 무작위 절편(random intercept)을 포함함으로써 연구들의 어질성을 보정하였다. SICH, 사망률, 뇌졸중 재발, 탁월한 결과 및 양호한 결과에 대한 통합 비율(pooled proportion)를 계산하였다. SICH의 사망률은 IVT 가이드라인에 따라 3시간 이내와 4.5시간 이내의 하위 집단으로 나누어 계산하였고, IVT 치료를 받은 모든 환자들에 대하여서도 계산하였다. 탁월한 결과와 양호한 결과의 예측인자를 보기 위한 단변량 모델을 생성, 나이, 성별, 혈관박리의 위치, 중상 발생-치료 시간, 뇌졸중 중증도(NIH뇌졸중등도 점수), 치료 종류를 변수로 포함하였다. 중상 발생-치료 시간은 연속 변수와 범주형 변수로 분석하였다. 범주형 변수 분석에서 범주 구분을 위한 차단값(cutoff value)은 경험적으로 120분 미만, 120~180분 및 180분 초과의 경우로 나누었다.

SITS-ISTR과의 비교

저자들은 분석 결과를 현재 진행 중인 IVT 치료를 받은 환자들의 전향적 국제적 뇌졸중 등록 체계인 SITS-ISTR (Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register)의 결과와 비교하였다. 연구에서 얻은 SICH와 사망률을 포함한 기능적 결과의 통합 비율 (pooled rate)을 SITS-ISTR에서 연령과 뇌졸중 중증도를 추가한 선택적 대조군의 같은 통합결과 비교하였다. 완벽한 핫아웃 기가 이루어지지 않기 때문에(나이 1년 혹은 NIH뇌졸중등도 점수 1점 이내의 페어는 허용), 대조 환자는 각각에 기록되었다. SITS-ISTR에서 SICH는 National Institute of Neurological Diseases and Stroke (중앙 발생 7일 이내 어떠한 신경학적 악화와 연관된 모든 출혈)와 European–Australian Acute Stroke Study II (NIH뇌졸중등도 점수 4점 이상의 신경학적 악화와 연관된 임상적 악화의 원인으로 판단되는 모든 출혈) 정의에 따라 보고되었다. SITS–ISTR에서는 3개월에 기능적 결과(mRS)를 평가한 방법, 본 메타분석에서의 추적 관찰 기간은 연구마다 달랐다. 따라서 저자들의 개별환자자료에서 3개월 이내에 예후가 평가되었던 환자들만을 선택하였다.

결론

연구

검색 결과 186개의 인용을 찾았고, 36건의 출판물에서 190명의 환자들이 본 연구에 정의된 기준을 충족하였다. 모든 연구들은 후향 보고, 혹은 단일 중재 보고였으며, 무작위대조시험은 없었다. 14개의 중재 연구들(환자 160명)에서 혈관박리 관련 뇌졸증에서의 혈전유해해술에 대한 자료를 제시하였다.5,6,10–21 9개의 중재 연구는 뇌졸중 등록 체계,20,21 혹은 혈전유해해술 등록 체계11,12,21의 자료를 이용하였으며, 1개 연구는 특별히 정의하지 않은 병원 등록 체계를 이용하였다.23 이 중 3개는 다기관 연구였다.20,21,22 연구의 개요와 중재 연구들의 특성을 분석 Table 1에 제시하였다(http://stroke.ahajournals.org). 추가로 24명의 환자를 보고한 22개의 중재 보고를 얻었다.20,44 33개의 출판물에서 72명 환자의 개별환자자료를 얻었다. 118명의 환자 자료가 포함된 나머지 3개의 출판물과 출판되지 않은 중재들에서 108명 환자의 개별환자자료를 저자로부터 제공받았다. 총 180명의 IVT 혹은 IAT을 받은 환자들로부터 얻은 개별환자자료가 본격에 이용되었다.

기본 특성

환자들은 주로 여성이었고(68%), 평균 연령은 46 ±11세었다. NIH뇌졸중등도 점수 중증은 16점(사분위수 범위: 11~20)이었으며, 60%가 중증의 뇌졸중 중증을 보였다(NIH뇌졸중등도 점수 15점 이상). 중상 발생-치료 시간의 중앙값은 165분(사분위수 범위: 11~20). 120% 돌연 흐름이 등록된 환자들은 73명(40%)었다. 사망률은 10%였다. 사망은 사망률이 0%였고, 사망은 사망률이 0%였다. 사망은 사망률이 0%였다.
위수 범위: 125~225였다. 67%에서 IVT, 33%에서 IAT 치료를 받았다. IVT 환자들 중 6%가 증상 발생 후 4.5시간 이후에 치료를 받았다. Table 1에 환자들의 기본 특성이 요약되어 있다.

Table 2. Safety and Outcome in Cervical Artery Dissection Patients Treated With Thrombolytic Therapy (N=180)

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion</th>
<th>Crude Estimates, % (95% CI)</th>
<th>Adjusted for Heterogeneity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>8/180</td>
<td>4.4 (2.1~6.7)</td>
<td>3.1 (1.3~7.2)</td>
</tr>
<tr>
<td>0~180 min*</td>
<td>3/88</td>
<td>3.0 (0.7~9.0)</td>
<td>3.1 (0.1~9.1)</td>
</tr>
<tr>
<td>0~270 min*</td>
<td>5/137</td>
<td>3.7 (1.3~8.5)</td>
<td>3.6 (1.5~8.5)</td>
</tr>
<tr>
<td>Mortality</td>
<td>14/173</td>
<td>8.1 (4.8~13.1)</td>
<td>8.1 (4.9~13.2)</td>
</tr>
<tr>
<td>0~180 min*</td>
<td>9/86</td>
<td>8.3 (4.1~15.8)</td>
<td>8.3 (4.2~15.8)</td>
</tr>
<tr>
<td>0~270 min*</td>
<td>9/135</td>
<td>6.7 (3.4~12.3)</td>
<td>6.7 (3.5~12.3)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>8/177</td>
<td>4.5 (2.2~8.8)</td>
<td>4.5 (2.3~8.7)</td>
</tr>
<tr>
<td>mRS=0–1</td>
<td>63/173</td>
<td>36.4 (28.6~43.8)</td>
<td>41.0 (31.4~51.4)</td>
</tr>
<tr>
<td>mRS=0–2</td>
<td>103/173</td>
<td>59.5 (52.1~66.8)</td>
<td>59.5 (52.1~66.6)</td>
</tr>
</tbody>
</table>

SICH indicates symptomatic intracranial hemorrhage; mRS, modified Rankin Scale score; CI, confidence interval.

*Minutes from symptom onset to thrombolytic treatment.

안전성
통합 사망률은 8.1% (95% CI, 4.9~13.2)였다. 그러나 7명 (4%)의 사망 여부는 확인할 수 없었다. IVT를 받은 121명에서 통합 사망률은 6.7% (95% CI, 3.4~13.8)였다. 180명 중 8명 (3.1%: 95% CI, 1.3~7.2)에서 SICH가 발생하였으며, 이 중 2명에서 치명적이었다. IVT군은 4명(3.3%: 95% CI, 1.2~8.5)에서 SICH가 발생하였다. 뇌출혈 증상은 4.5% (95% CI, 2.3~8.7)있었고, IVT 치료 환자 중 6.8% (95% CI, 3.4~13.0)에서 있었다(Table 2, 3).

혈전용해 후 다른 혈관으로서 무중상두대뇌졸이 28명에 서 있었다. 우측 축추동맥바리에 IVT를 받은 환자 중 혈중 증가가 있었으나(비출혈 자료), 탁월한 회복을 보였다(3개월 mRS=1). 자료를 얻을 수 있는 133명 중 8명에서 추적 관할 중 저점동맥류(pseudoaneurysm)가 발생하였다. 한 명에서 무중 상가미막술이 실시되었다. 뇌경색의 정도는 영상 검사에 서 두개내혈 열이 신경학적 악화를 보이는 경우로 정의하였는데, 161명 중 13명에서 보고되었다.

기능적 결과
156명의 환자에서 mRS를 얻을 수 있었다. 17명에서 기능적 상태에 대한 기술을 통해 신뢰성 있는 mRS를 추정하였다. 전체 환자 중 41.0% (95% CI, 31.4~51.4)에서 탁월한 회복(mRS=0~1)을 보였고, 59.5% (95% CI, 52.1~66.6)에서 양호한 결과(mRS=0~2)를 보였다. IVT군에서는 33.3% (95% CI, 25.5~42.2)가 탁월한 결과를, 60.8% (95% CI, 51.8~69.1)가 양호한 결과를 보였다(Table 2, 3).

추적 관찰 중 3개월(범위, 2~6개월)이었으나, 3개월에 정확한 기능적 결과 평가가 된 환자는 137명이었다. 추적 관찰 기간별 비율은 부록 Table II에 있다. 불량한 기능적 결과(mRS=3~6)에 대한 교차비(OR)는 경동맥 폐색 환자(79명)에서 1.47 (95% CI, 0.41~5.51)이었고, 척추동맥 폐색 환자에서는 1.57 (95% CI, 0.19~15.41)이었다. 숫자가 작아 타당한 혹은 유의한 다변량 분석은 시행할 수 없었다.

Table 3. Adverse Events and Outcome in Cervical Artery Dissection Patients Treated With Intravenous Thrombolysis (n=121)

<table>
<thead>
<tr>
<th>Event</th>
<th>Proportion</th>
<th>Crude Estimates, % (95% CI)</th>
<th>Adjusted for Heterogeneity, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH</td>
<td>4/121</td>
<td>3.3 (1.0~8.5)</td>
<td>3.3 (1.2~8.5)</td>
</tr>
<tr>
<td>0~180 min*</td>
<td>2/87</td>
<td>2.3 (0.1~8.5)</td>
<td>2.3 (0.6~8.7)</td>
</tr>
<tr>
<td>0~270 min*</td>
<td>3/110</td>
<td>2.7 (0.6~8.6)</td>
<td>2.7 (0.9~8.1)</td>
</tr>
<tr>
<td>Mortality</td>
<td>8/120</td>
<td>6.7 (2.2~11.1)</td>
<td>6.7 (3.4~13.8)</td>
</tr>
<tr>
<td>0~180 min*</td>
<td>6/66</td>
<td>7.0 (3.0~14.7)</td>
<td>7.0 (3.2~14.7)</td>
</tr>
<tr>
<td>0~270 min*</td>
<td>6/109</td>
<td>5.5 (2.3~11.7)</td>
<td>5.5 (2.5~11.7)</td>
</tr>
<tr>
<td>Recurrent stroke</td>
<td>8/181</td>
<td>6.8 (3.3~13.0)</td>
<td>6.8 (3.4~13.0)</td>
</tr>
<tr>
<td>mRS=0–1</td>
<td>40/120</td>
<td>33.3 (25.5~42.2)</td>
<td>33.3 (25.5~42.2)</td>
</tr>
<tr>
<td>mRS=0–2</td>
<td>73/120</td>
<td>60.8 (51.9~69.1)</td>
<td>60.8 (51.8~69.1)</td>
</tr>
</tbody>
</table>

SICH indicates symptomatic intracranial hemorrhage; mRS, modified Rankin Scale score; CI, confidence interval.

*Minutes from symptom onset to thrombolytic treatment.

희귀 모델
탁월한 결과(mRS=0~1)와 양호한 결과(mRS=0~2)에 대한 예측인자는 부록 Table III에 제시되어 있다. 단변량 분석에서 뇌출혈 증가등증도(임원 시 NIH뇌졸중점도 점수)에 비해 판찰한 결과 및 양호한 결과와 약한 연관관계가 있었다. NIH뇌졸중점도 점수가 1점 증가시 탁월한 결과에 대한 OR은 0.9 (95% CI, 0.8~0.9)였고, 양호한 결과에 대한 OR 역시 0.9 (95% CI, 0.8~0.9)이었다. 경동맥바리에 비교 시 축추동맥바리가 탁월한 결과와 유의하게 연관성을 보였으나(OR=2.6, 95% CI, 1.2~5.6), 양호한 결과는 연관이 없었다(단변량 분석). 다른 변수들은 결과와 연관성이 없었다. 각각들은 다변량 로지스틱에서 뇌출혈 증가등증도를 보정하였다. 이 모델에서 축추동맥바리가 탁월한 결과와 연관성이 있었다(OR=3.9, 95% CI, 1.4~11.1). 나머지 다른 변수들은 결과와 연관이 없었다.
출판 치우침

증례 보고 자료를 제외하여도 주요 결과는 변하지 않았다. 큰 연구와 비교하여 증례 보고에 유리한 출판 치우침은 분명히 없었다.

SITS–ISTR과의 비교

SITS–ISTR로부터 나와 및 뇌졸중 증증도를 적은 대조군 170명을 선별하였다. Table 4에 본 연구의 주요 결과를 SITS–ISTR과 비교한 점 추정(point estimation)이 나와 있다. 신뢰구간이 검정 SICH 발생률, 사망률과 기능적 결과에 차이가 없음을 의미하였다.

고찰

개별환자자료를 이용한 본 메타분석은 현재까지 출판된 혈전응해출 치료를 받은 CAD 환자들을 가장 많이 포함하여, CAD에 의한 급성 혈관뇌졸중에서 혈전응해출이 안전하다는 것을 제시한다. CAD 환자에서 3%의 혈관 SICH 발생률과 8%의 전체 사망률(IVT에서는 각각 3%, 7%)은 모든 원인으로 인한 뇌졸중에서의 결과와 비슷하다. 특히 본 연구의 환자들과 SITS–ISTR로부터 적은 대조군과의 간접적인 비교에 이러한 주요 종합점에 대한 차이는 유의하지 않았다. 본 연구와 SITS–ISTR 연구는 사전에 비교가 가능하도록 설계한 것은 아니기 때문에, 두 연구들의 차이에 대한 통계적 검증은 시행하지 않았다. 따라서 저자는 두 연구에 대한 비교를 기술적으로 진행하였다. 그러나 CAD 관련 뇌졸중 환자에 대한 혈전응해출의 수용적대조연구는 더 이상 윤리적이지 않기 때문에, 본 자료는 현재까지의 기아트리에 대한 가장 최신의 증거가 될 수 있다.

혈전응해출 중 범뇌혈증의 확장은 이론적으로 상당한 우려가 될 수 있다. 본 연구에서 한 명에서 범뇌혈증의 확장이 보고되었고, 이 화자 또한 탁월한 결과를 보였다. 자료들은 대부분의 연구에서 이러한 직접적 합병증에 대한 체제적인 보고가 없음을 알차였다. 그러나 최적의 안전성과 가능한 결과를 고려한 혈전응해출로 인정한 직접적인 출혈 합병증은 분명히 주요 족점 사항이다.

본 연구에서 모든 CAD 환자 중 31%가, SITS–ISTR에서는 37%가 탁월한 결과(mRS=0~1)를 보였다. 그러나 양호한 결과를 보이던 본 연구에서 조금 더 많은 듯 하였다(58% vs. 52% in SITS–ISTR). 두 가지 결과 모두에 대해 신뢰구간이 크게 겹쳤다. 그러므로 두 연구의 간접적 비교만이 가능했던 다른 고려하여 CAD로 인한 뇌졸중 환자들에서 IVT의 결과는 모든 환이로 인하여 발생한 뇌졸중 환자들에서 관찰된 IVT 치료의 결과와 같은 범위 내에 있다. 추정적으로 확인된 경동맥 혹은 척추동맥 폐색을 가진 환자들은 브레인 결과의 위험이 더 높을 수 있다. 환자 수가 적고 신뢰구간이 넓어 저자는 이들 을 임상적으로 사용할 수 없으며 신뢰성도 유의하지 않았다. 추가된 요소의 연구에서 고위험군을 확인할 수 있다면, 이러한 하위 집단 환자들에게는 다른, 아마도 더 적극적인 치료가 필요함을 의미할 수 있다.

본 연구는 몇 가지 한계점을 가지고 있다. 첫째, 무작위대조시험 자료가 없어 본 메타분석에 포함되지 않았다. 통합 추정치는 향후적 비대조연구의 증례 보고에 근거한 것이다. 증례보고 자료를 제외하여도 연구 결과가 변하지는 않았으나 출판 치우침의 가능성을 배제할 수 없어 이로 인하여 메타분석 결과가 영향을 받았을 수 있다. 또한 본 메타분석에 포함된 연구마
다 SICH의 정의가 서로 달랐기 때문에, 본 연구에서 SICH의 정의에 대하여 엄격한 기준이 아닌 실용적인 정의를 사용할 수밖에 없었다. 이로 인해 다른 연구의 SICH 발생률과 비교하기가 어렵다. 그러나 이러한 혼란된 정의에 따른 SICH의 발생률은 National Institute of Neurological Diseases and Stroke와 European–Australian Acute Stroke Study II의 정의에 따른 SITS–ISTR 연구에서의 발생률 내에 있다. 이는 CAD 관련 뇌졸중 환자들에게 SICH의 위험이 증가하지 않음을 강력히 시사한다.

본 연구의 또 다른 우려는 CAD가 추정되는 환자들에 대한 진단의 불확실성이다. 그러나 이 분석에 포함된 큰 규모의 연구들에서는 ‘가능한(possible)’ CAD를 가진 환자들을 제외하였으므로, 이러한 진단적 불확실성을 줄이 준다. 결과 뿐 아니라 SICH 발생에 영향을 줄 수 있는 혈전유해물 이외에 사용된 혈협전체의 종류가 평가되지 않았다. 본 연구에서 현재 IVT 가이드라인에 따른 4.5시간이 아닌 24시간이라는 넓은 치료창을 적용하였다는 점도 비판받을 수 있다. 본 연구에서의 치료 시작 중간값은 중장 발생 후 165분(사분위수 범위, 125~225)으로, 대부분의 혈전유해물이 뇌졸중의 초급상기 시에 시행되었다는 것을 의미한다. 하위 집단 분석에서 전체 연구 집단에 대한 결과와 3시간 이내에 4.5시간 이내에 치료받은 하위 집단에 서의 결과가 다르지 않았다. 마지막으로 연구마다 추적 관찰 기간이 상이하였다. 그러므로 저자들은 추적 관찰 기간에 따른 하위 집단을 제시하였다. 또한 대부분의 환자들은 SITS–ISTR의 경우와 유사하게 3개월째에 정확히 추적 관찰을 받았다.

결론
결론적으로, CAD로 인한 급성 혈원류중증에서의 혈전유해물은 안전한 것으로 보인다. 이 환자들에서 혈전유해물의 결과 뿐 아니라 사망률과 SICH 발생률은 모두 높이로 인하여 혈전유해물을 받은 뇌졸중 환자들에서의 발생률과 유사한 것으로 보인다. 비록 저자들의 분석이 적은 수의 환자들을 대상으로 한 후향 연구에 기반하고 있으나, 본 연구 결과 CAD에 의한 혈원류중증 환자들에게 혈전유해물을 보류해야 한다는 어머한 근거도 제공하지 않는다.

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Disclosures

None.

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