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

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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 "tPA" 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 datasheet 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 registry 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 symptom 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 after discharge 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. Five series reported 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.
Table 1. Baseline Characteristics of All Included Cervical Artery Dissection Patients: Individual Patient Data

<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>
</tbody>
</table>

Stroke severity

| Presenting NIHSS score, mean±SD (range) | 15.8±6.9 (1–36) |
| Median NIHSS score (IQR)               | 16 (11–20) |
| Mild stroke (NIHSS score 1–7), n (%)   | 21 (15) |
| Moderate stroke (NIHSS score 8–14), n (%) | 42 (25) |
| Severe stroke (NIHSS score ≥15), n (%) | 86 (60) |

Location of dissection

| Carotid artery, n (%) | 131 (73) |
| Vertebral artery, n (%) | 48 (27) |
| Both, n (%)           | 1 (1) |

Occlusion before treatment, n (%) 107 (83)

Intracranial extension, n (%) 16 (10)

Onset-to-treatment time, mean SD (range) 195±123

Onset-to-treatment time, median (IQR) 165 (125–225)

Treatment

| IVT, n (%) | 121 (67) |
| IAT, n (%) | 59 (33) |

Median duration of follow-up (mo) (range) 3.0 (0.2–18)

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.

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.

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 (3.1%; 95% CI, 1.3 to 7.2), of which 2 occurrences were fatal. In the IVT group, 4 patients experienced SICH (3.3%; 95% CI, 1.2 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).

Other complications after thrombotic 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.

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 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 (2.1–8.7)</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 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>6/86</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>8/118</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.
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 score = 0 to 1) and favorable (mRS score = 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.

### 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

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**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: SICH</th>
<th>N/n</th>
<th>% (95% CI)</th>
<th>n</th>
<th>% (95% CI)</th>
<th>End Point</th>
<th>n</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICH per NINDS†</td>
<td>170</td>
<td>5.9 (3.0–10.9)</td>
<td>160</td>
<td>8.8 (5.1–14.5)</td>
<td>159</td>
<td>37.4 (30.3–45.8)</td>
<td>159</td>
</tr>
</tbody>
</table>

IVT indicates intravenous thrombolysis; SITS-ISTR, Safety Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register; SICH, symptomatic intracranial hemorrhage; NINDS, National Institutes of Neurological Disorders and Stroke definition; ECASS II, European-Australian Acute Stroke Study II; mRS, modified Rankin Scale score; CI, confidence interval.

*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.

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1. **Comparison With SITS-ISTR**

2. **Publication Bias**

3. **Regression Models**

4. **Discussion**

5. **Table 4**

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<table>
<thead>
<tr>
<th>CAD Patients</th>
<th>Stroke From All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>IVT</td>
</tr>
<tr>
<td>N/n</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>End point: SICH</td>
<td>180</td>
</tr>
<tr>
<td>Mortality at ≤3 mo</td>
<td>144</td>
</tr>
<tr>
<td>mRS=0–1 at ≤3 mo</td>
<td>144</td>
</tr>
<tr>
<td>mRS=0–2 at ≤3 mo</td>
<td>144</td>
</tr>
</tbody>
</table>

**End point: SICH**

- n = 170 (95% CI, 3.0–10.9)
- n = 160 (95% CI, 5.1–14.5)
- n = 159 (95% CI, 30.3–45.8)

**SICH per NINDS†**

- n = 170 (95% CI, 5.9–10.9)
- n = 160 (95% CI, 8.8–14.5)
- n = 159 (95% CI, 37.4–45.8)

**SICH per ECASSII‡**

- n = 170 (95% CI, 5.9–10.9)
- n = 160 (95% CI, 8.8–14.5)
- n = 159 (95% CI, 37.4–45.8)
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.

Acknowledgments

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Disclosures

None.

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section: intra-arterial thrombolysis through an occipital vertebral anas-
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successfully managed by endovascular treatment. No Shinkei Geka. 2003;
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therapy for acute extra-cranial artery dissection: report of two cases. Arg
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Safety and Functional Outcome of Thrombolysis in Dissection-Related Ischemic Stroke: A Meta-Analysis of Individual Patient Data

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Safety and functional outcome of thrombolysis in dissection-related ischemic stroke: a meta-analysis of individual patient data

Zinkstok et al.

Supplemental Tables: 4
### 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. (2010)</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. (2009)</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. (2009)</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. (2009)</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. (2008)</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. (2008)</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. (2007)</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. (2007)</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>Author(s)</td>
<td>Study Design</td>
<td>Study Details</td>
<td>Number</td>
<td>Thrombolytic Therapy</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Georgiadis et al. (2005)⁹</td>
<td>retrospective, multicentre</td>
<td>33 consecutive patients with stroke due to spontaneous carotid dissection treated with IVT</td>
<td>33</td>
<td>IVT</td>
</tr>
<tr>
<td>Arnold et al. (2002)¹⁰</td>
<td>retrospective, single centre</td>
<td>9 patients with cervical artery dissection treated with thrombolysis</td>
<td>9</td>
<td>IVT, IAT</td>
</tr>
<tr>
<td>Bin Saeed et al. (2000)¹¹</td>
<td>retrospective, single centre</td>
<td>26 patients with vertebral artery dissection</td>
<td>2</td>
<td>IAT</td>
</tr>
<tr>
<td>Derex et al. (2000)¹²</td>
<td>retrospective, single centre</td>
<td>11 consecutive patients with acute ischemic stroke related to internal carotid artery dissection treated with IVT</td>
<td>11</td>
<td>IVT</td>
</tr>
<tr>
<td>Ahmad et al. (1999)¹³</td>
<td>retrospective, multicentre</td>
<td>18 patients with cervicocerebral artery dissections</td>
<td>2</td>
<td>IAT</td>
</tr>
<tr>
<td>Rudolf et al. (1999)¹⁴</td>
<td>retrospective, single centre</td>
<td>15 consecutive patients with internal carotid artery occlusion treated with IVT</td>
<td>6</td>
<td>IVT</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></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 outcome unknown</td>
<td>11</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>0.75 (0.36-1.57)</td>
<td>0.44</td>
<td>0.74 (0.32-1.71)</td>
<td>0.47</td>
</tr>
<tr>
<td>120-180 minutes</td>
<td>0.63 (0.15-2.58)</td>
<td>0.52</td>
<td>0.27 (0.03-2.83)</td>
<td>0.27</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>UniversitätsMedizin 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


動脈解離に関連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, MD3; Philippe A. Lyrer, MD4; Leo H. Bonati, MD1; Marcel Arnold, MD1; Heinrich P. Mattle, MD3; Urs Fischer, MD5; Hakan Sarikaya, MD6; Ralf W. Baumgartner, MD8; Dimitrios Georgiadis, MD9; Céline Odier, MD7; Patrik Michel, MD7; Jukka Putaala, MD5; Martin Grieben, MD5; Nils Wahlgren, MD9; Niaz Ahmed, MD5; Nan van Geloven, MSc7; Rob J. de Haan, PhD7; Paul J. Nederkoorn, MD8

1Department of Neurology, 2Experimental Vascular Medicine, and 3Clinical Research Unit, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; Departments of Neurology, 4University Hospital Basel, 5University Hospital Bern, 6University Hospital Zürich, 7University Hospital of Lausanne, Switzerland; 8Helsinki University Central Hospital, Helsinki, Finland; 9Universitätsmedizin Mannheim, University of Heidelberg, Heidelberg, Germany; and 10Department 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）における血栓溶解療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であった。

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な文献検索を行った。統合した症候性頭蓋内出血率および死亡率を算定し、Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR)から抽出した、患者と方法を一致させた対照群との間隔比較を行った。多変量回帰モデルを適用し、きわめて良好な転帰(変改Rankin尺度=0～1)および良好な転帰(変改Rankin尺度=0～2)の予測因子を同定した。

結果：14件の後向き症例集積研究および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%)、平均年齢士SDは46±11歳であった。受診時にほとんどの患者に重度頭蓋内出血が認められた(ニッセスコアの中央値=16)。治療は、動注血栓溶解療法が67%，静注血栓溶解療法が33%であった。追跡調査期間の中央値は3ヶ月であった。統合した症候性頭蓋内出血率は3.1%(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%)をきわめて良好な転帰を示した。脳卒中重症度は有効な転帰予測因子であった。患者群と対照群における評価項目の信頼区间は重視しており、SITS-ISTRから抽出した対照群との間に関与する重要性はみられなかった。

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れる。本研究に基づくと、CAD患者への血栓溶解療法は推奨されるべきではない。

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表
頭部動脈解離に関連した脳卒中患者（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></th>
<th>全患者</th>
<th>IVT症例</th>
<th>あらゆる原因による脳卒中（SITS-ISTR）*</th>
</tr>
</thead>
<tbody>
<tr>
<td>事由</td>
<td>例数</td>
<td>% (95%CI)</td>
<td>例数</td>
</tr>
<tr>
<td>評価項目：SICH</td>
<td>180</td>
<td>31.3 (1.3～7.9)</td>
<td>121</td>
</tr>
<tr>
<td>3ヶ月以内の回帰率</td>
<td>144</td>
<td>9.0 (5.3～14.9)</td>
<td>110</td>
</tr>
<tr>
<td>3ヶ月以内のmRS=0</td>
<td>144</td>
<td>31.2 (24.2～39.3)</td>
<td>110</td>
</tr>
<tr>
<td>3ヶ月以内のmRS=0</td>
<td>144</td>
<td>55.6 (47.4～63.5)</td>
<td>110</td>
</tr>
</tbody>
</table>

注：このメタ解析に用いられた症例は73%が頭動脈で、27%が椎骨動脈の解離であった。頭蓋内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 Putaala, MD; Martin Grieb, 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

배경과 목적: 경부동맥박리(cervical artery dissection, CAD)에서 혈전응해술(thrombolysis)의 안전성 및 효능에 대하여 논란이 많다. 본 메타분석은 모든 개별환자자료를 통합하여 CAD 환자에서 혈전응해술의 안전성과 결과에 대한 타당한 평가를 제공하고자 하였다.

방법: 저자들은 CAD에서 경맥내(intravenous), 동맥내(intra-arterial) 혈전응해술에 대한 체계적 문헌 검색을 시행하였다. 통합(pooled) 증상성두께내출혈(symptomatic intracranial hemorrhage) 발생률과 사망률을 계산하고 SITS–ISTR (Safe Implementation of Thrombolysis in Stoke–International Stroke Thrombolysis Register) 연구로부터 환자는 대조군과 간결 비교를 하였다. 탁월한 결과(수정Rankin척도(modified Rankin Scale, mRS)=0~1)와 양호한 결과(mRS=0~2)의 예측인 자를 찾기 위해 다변량 회귀 모델을 적용하였다.

결과: 14개의 후향 연구와 22개의 증례 보고서에서 180명의 개별환자자료를 얻었다. 환자들은 여성이 많았고(68%), 평균 연령은 46±11세였다. 대부분의 환자들이 중증 뇌졸중(NIH뇌졸중점수 중앙값=10)을 보였다. 환자들의 67%가 경맥내 혈전응해술, 33%가 동맥내 혈전응해술을 받았다. 추적 기간 중앙값은 3개월이었다. 통합 증상성두께내출혈 발생률은 3.1% (95% CI, 1.3~7.2)였다. 전체 사망률은 8.1% (95% CI, 4.9~13.2)였고, 41.0% (95% CI, 31.4~51.4)의 환자들이 혈전응해술을 보였다. 뇌졸중 중증도는 간결한 결과 예측인자였다. 종말점(end point)의 신뢰구간이 겹쳐 SITS–ISTR 연구로부터 환자는 대조군과 유의한 차이가 없었다.

결론: CAD 관련 뇌졸중 환자에서 혈전응해술의 안전성과 결과는 모든 원인에 의한 뇌졸중 환자의 안전성 및 결과와 유사하였다. 저자들의 결과에 근거할 때, CAD 환자에서 혈전응해술을 보유화하여는 안된다.

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전체 허혈뇌졸증(ischemic stroke)의 약 2%는 경부동맥판리(cervical artery dissection, CAD)에 의하여 발생한다. 50세 미만의 환자에서 CAD는 전체 허혈뇌졸증의 10~25% 정도를 차지한다. 1 CAD는 경동맥 혹은 세주동맥의 내막 파열에 의한 백내혈증(intramural hematoma)이 특징이다. CAD에 의한 허혈뇌졸증은 대부분 헤모락학적 요인보다는 혈전석증(thromboembolism)에 의하여 발생하는 것으로 여겨진다. 1 급성 허혈뇌졸증에서 혈전해해(thrombolysis)를 연구한 무작위대조시험에서 CAD 환자를 재외치는 않았다. 2 그러나 이 무작위대조시험에서 CAD 환자에 대하여 별도로 혈전해해의 안전성과 결과를 연구하는 않았다. 따라서 CAD에 의한 급성 허혈뇌졸증에서 혈전해해의 시행 여부는 아직 알려져 있지 않다. 

혈전해해의 가장 심각한 합병증은 증상성두개뇌출혈(symptomatic intracranial hemorrhage, SICH)으로, 2~9%에서 발생한다. 3 CAD 환자에서는 백내혈증의 확대 위험에 대한 추가 우려가 있다. 적은 규모의 후향 중재 연구들에서 CAD 환자에서의 혈전해해는 안전한 것으로 제시되었다. 4 본 메타 분석은 영향을 줄 수 있는 모든 증례 보고(case report)와 중재 연구(case series)들의 개별환자자료(individual patient data)를 통합하여 CAD 관련 뇌졸중 환자에서 혈전해해의 안전성과 결과에 대한 타당한 평가를 제공하는 것이다. 추가적으로 혈전해해의 결과 예측인자도 평가하였다.

방법
환자 선택
저자들은 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 허혈뇌졸중 환자에 대한 연구들을 체계적으로 검색하였다. 또한 Cochrane Library, 혹은 Cochrane Central Register of Controlled Trials에서 기준에 일치하는 연구들을 찾았고, 찾아낸 연구들에서 수기로 인용 문헌들을 조사하였다. 마지막으로 이 분야 전문가들에게 자문을 얻었다. 저자들은 CAD 관련 뇌졸중에 혈전해해를 주목적으로 연구하였으나, 이들에 대한 하위 집단 분석을 한 연구들을 포함시켰다. 이 주제에 대한 연구가 드물기 때문에 각 연구당 최소 환자 수 기준을 정정치는 않았다. 영어, 독일어, 프랑스어로 출판된 연구를 포함하였고, 다른 언어라도 초록이 이들 언어로 쓰여진 경우는 포함하였다. 두개뇌 혈관에 국한된 혈관판리, 혹은 대동맥판리(aortic dissection)가 경부동맥까지 확장된 경우는 제외하였다. CAD의 진단은 헤모락중초음파촬영술(color duplex sonography), 컴퓨터단층혈관조영술(computed tomography angiography), 자기공명혈관조영술(magnetic resonance angiography), 또는 고식적 혈관조영술을 통해 확인한 경우였다. 혈전해해 시행 전 혹은 후의 혈관판리 확진을 모두 인정하였다. 대부분의 연구에서 치료 전과 치료 후 두개뇌 혈관 혈착에 대하여 체계적으로 평가하지 않았기 때문에 재재해 영역은 분석에서 제외하였다. 저자들은 2개 치료군(경동맥 혈전해해(intravenous thrombolysis, IVT)과 두개뇌 혈전해해(intra-arterial thrombolysis, IAT))으로 나누어 분석하였다. IAT는 IAT만 시행한 경우, IVT 이후 IAT를 시행한 경우, 또는 IAT와 기계적 혈관재건술 혹은 스펜트슘과 같은 혈관내 시술을 병행한 경우로 정의하였다. 혈전해해는 증상 발생 이후 24시간 이내에 시행되어야 했다. 3시간 이내와 4.5시간 이내에 치료받은 환자를 구분하여 하위 집단 분석을 하였다.

자료 추출
저자들은 성별, 연령, 성행 외상력, NIH뇌졸중척도(National Institutes of Health Stroke Scale)로 평가한 내원 시 뇌졸중 증중도, 혈관판리의 위치(경동맥 또는 세주동맥), 치료 전 혈관 폐쇄, 두개뇌 침범 여부, 증상 발생 후 치료까지 소요 시간, 치료 종류(IVT 또는 IAT) 및 추적 관찰 기간에 대한 정보를 수집하였다.

안전성 변수로 SICH, 사망률 및 뇌졸중 재발을 평가하였다. SICH는 환자의 임상적 악화와 시간적 연관성을 가지면서 컴퓨터단층촬영, 혹은 자기공명영상에서 확인된 모든 두개뇌출혈로 정의하였다. 포함된 연구들에서 임상적 악화로 정의는 다양하였다. 저자들이 보관한 추가적인 부작용 자료도 수집하여 기술하였다. 기능적 결과는 추적 기간 중 기능적 독립성의 정도로 평가하였다. 탁월한 기능적 결과는 수정Rankin척도(modified Rankin Scale, mRS)가 0~1인 경우로, 양호한 기능적 결과는 mRS 2~3로 정의하였다. 마지막으로 최추동맥 혹은 경동맥 폐쇄 중에서 어느 것이 더 불량한 결과(mRS = 3~6)를 보이는지에 대하여 하위 집단 분석을 시행하였다.

두 명의 독립적인 관찰자(S.Z., P.N.)가 모든 자료를 추출하였다. 의견이 일치하지 않은 경우에는 합의에 의해 해결하였 다. mRS 정보가 없는 경우에는, 증례 기술을 통해 명확히 유추할 수 있는 경우에 동일한 관찰자가 mRS 판단 기준에 따라 재구성하였다.

개별환자자료
저자들은 모든 중재 연구 저자들에게 수집된 자료만 포함된 동일한 데이터 시트를 보냈다. 중재 연구에 보고된 환자의
중복 집계를 피하기 위해 개별환자자료만 분석에 사용하였다. 중재 보고의 경우 분석에 필요한 개별환자자료의 기수는 불완전한 경우에도 제외하고 간주하였다.

통계 분석
R Lime4 패키지로 개별환자자료를 이용한 훈합 모형을 만들었다. 이 모델에서는 각 연구들의 무작위 절편(random intercept)을 포함함으로써 연구들의 이질성을 보정하였다. SICH, 사망률, 뇌졸중 재발, 탁발한 결과 및 양호한 결과에 대한 동합 비율(pooling proportion)을 계산하였다. SICH와 사망률은 IVT 가이드라인에 따라 3시간 이내와 4.5시간 이내의 하위 집단으로 나누어 계산하였고, IVT 치료를 받은 모든 환자들에 대하여서도 계산하였다. 탁발한 결과와 양호한 결과의 예측인자들 보이기 위한 단변량 모델에 성별, 나이, 선형 외상, 혈관박리의 위치, 증상 발생-치료 시간, 뇌졸중 중증도(NIH뇌졸중척도 점수), 치료 종류를 변수로 포함하였다. 증상 발생-치료 시간은 연속 변수와 범주형 변수로 분석하였다. 범주형 변수 분석에서 범주 구분을 위한 차단값(cutoff value)은 정합적으로 120분 미만, 120~180분 및 180분 초과의 경우로 나누었다.

SITS-ISTR과의 비교
저자들은 본문 결과를 현재 진행 중인 IVT 치료를 받은 환자의 치료 집단으로 SITS-ISTR (Safe Implementation of Thrombolysis in Stroke—International Stroke Thrombolysis Register)의 결과와 비교하였다. 연구에서 얻은 SICH와 사망률을 포함한 가능성 결과의 동합 비율 (pooled rate)은 SITS-ISTR에서 얻어낸 뇌졸중 중증도를 평가한 전체의 대조군의 같은 방식과 비교하였다. 완벽한 학적 기기가 이루어지지 않을 경우(나이 1년 혹은 NIH뇌졸중척도 점수 1점 이내의 페퍼는 하위), 대조 환자는 결정적으로 기록되었다. SITS-ISTR에서 SICH는 National Institute of Neurological Diseases and Stroke (증상 발현 7일 이내 어떠한 신경학적 악화와 관련된 모든 출혈)와 European–Australian Acute Stroke Study II (NIH뇌졸중척도 점수 4점 이상의 신경학적 악화와 연관되고 임상적 악화의 원인으로 판단되는 모든 출혈 정의에 따라 보고되었다. SITS-ISTR에서는 계절에 기능적 결과(mRS)를 평가한 반면, 본 메타분석에서의 주관적 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 연구는 후향 보고, 혹은 단일 중재 보고였으며, 무작위대조실험은 없었다. 14개의 중재 연구(환자 160명)에서 혈관박리 관련 뇌졸중에서의 혈전응해술에 대한 자료를 제시하였다. 4,5,18-21 9개의 중재 연구는 뇌졸중 중증도 점수, 12,16,18,21 혹은 혈전응해술 중증도 점수의 자료를 이용하였으며, 1개 연구는 특별히 정의하지 않은 범위로 중증도 점수를 이용하였다.23 이 중 3개는 다기관 연구였다.23,24,25 연구의 개요와 중재 연구들의 특징을 Table 1에 제시하였다(http://stroke.ahajournals.org). 추가로 24명의 환자를 보고한 22개의 중재 보고를 얻었다. 24-24 33개의 출판물에서 72명 환자의 개별환자자료를 얻었다. 118명의 환자 자료가 포함된 나머지 3개의 출판물로 올바르지 않은 증례들에서 108명 환자의 개별환자자료를 저자로부터 제공받았다. 총 180명의 IVT 혹은 IAT를 받은 환자들로부터 얻은 개별환자자료가 분석에 이용되었다.

기본 특성
환자들은 주로 여성이었고(68%), 평균 연령은 46±11세였다. NIH뇌졸중척도 점수 중앙값은 16점(사분위수 범위: 11~20)이었으며, 60%가 중증의 뇌졸중 중증도 보였다(NIH뇌졸중척도 점수 15점 이상), 증상 발생-치료 시간의 중앙값은 165분(사분위수 범위: 15~225분)이었다. 희리트로 치료를 받은 환자들은 120분 미만과 120~180분의 시간과 180분 이상의 시간으로 분류되었다. 중재는 혈관을 포함한 육중의 자료들이 165개의 환자들로부터 얻은 자료들에 해당하였다. 165개의 환자들로부터 얻은 자료들은 120분 미만, 120~180분 및 180분 초과의 경우로 나누어졌다.
위수 범위: 125~225이었다. 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.

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. IVT군에서 4명 (3.3%; 95% CI, 1.2~8.5)에서 SICH가 발생하였다. 뇌졸중 재발은 4.5% (95% CI, 2.3~8.7)에서 있었고, IVT 치료 환자 중 6.8% (95% CI, 3.4~13.0)에서 있었다 (Table 2, 3).

혈전용해 후 다른 혈압증중으로 무증상 두개내출혈이 28명에서 있었다. 우측 척추동맥관으로 IVT를 받은 환자 중 4명에서 혈종 증가가 있으면서 (비슷한 자료), 탈혈한 희박을 보였다 (3개월 mRS=1). 자료를 얻을 수 있는 133명 중 8명에서 추적 관찰 중 저직동맥류(pseudoaneurysm)가 발생하였다. 한 명에서 무증상 기해막혈종이 발생하였다. 노경석의 경우는 영상 검사에서 두개내출혈 없이 신경학적 약화를 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 탈혈한 희박(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 탈혈한 결과를, 60.8% (95% CI, 51.8~69.1)가 양호한 결과를 보였다 (Table 2, 3).

추적 관찰 중간 값은 3개월째 (범위, 5일~18개월)이었으나, 3개 월째 정확한 기능적 결과 평가가 되는 환자는 137명이었다. 추적 관찰 기간별 비율은 보통 Table II에 있다.

불량한 기능적 결과(mRS=3~6)에 대한 교차비(odds ratio, OR)는 정통맥 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 작아도 잘한 환자의 유의한 다변량 분석은 시행할 수 없었다.

회귀 모델
탈혈한 결과 (mRS=0~1)와 양호한 결과 (mRS=0~2)에 대한 예측인자를 부록 Table III에 제시되어 있다. 단변량 분석에서 뇌졸중 중증도 (일반 IVT/뇌졸중 중증도 점수)는 탈혈한 결과 및 양호한 결과와 역의 연관관계가 있었다. IVT뇌졸중 중증도 점수가 1점 증가 시 탈혈한 결과에 대한 OR은 0.9 (95% CI, 0.8~0.9)이었고, 양호한 결과에 대한 OR 역시 0.9 (95% CI, 0.8~0.9)였다. 정통맥 관리와 비교 시 척추동맥관리는 탈혈한 결과와 유의하게 연관성을 보였으나 (OR=2.6; 95% CI, 1.2~5.6), 양호한 결과와는 연관이 없었다 (단변량 분석). 다른 변수들은 결과와 연관이 없었다. 자각은 다변량 모델에서 뇌졸중 중증도만을 보정하였다. 이 모델에서 척추동맥관리는 탈혈한 결과와 연관성이 있었다 (OR=3.9; 95% CI, 1.4~11.1), 나머지 다른 변수들은 결과와 연관이 없었다.
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></th>
<th>CAD Patients</th>
<th>Stroke From All Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>IVT</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>n (% (95% CI))</td>
</tr>
<tr>
<td>End point: SICH</td>
<td>180</td>
<td>3.1 (1.3–7.2)</td>
</tr>
<tr>
<td></td>
<td>121</td>
<td>3.3 (1.2–8.5)</td>
</tr>
<tr>
<td>Mortality at ≤3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>9.0 (5.3–14.9)</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>31.2 (24.2–39.3)</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>55.6 (47.4–63.5)</td>
</tr>
<tr>
<td>mRS=0–1 at ≤3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>9.0 (5.3–14.9)</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>31.2 (24.2–39.3)</td>
</tr>
<tr>
<td></td>
<td>144</td>
<td>55.6 (47.4–63.5)</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.

출판 차우침

출판 차우침

중래 보고 자료를 제외하여도 주요 결과는 변하지 않았다. 근 연구와 비교하여 중래 보고에 유리한 출판 차우침은 분명히 없었다.

SITS–ISTR과의 비교

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

고찰

개별환자자료를 이용한 본 메타분석은 현재까지 출판된 혈전용해제 치료를 받은 CAD 환자를 가장 많이 포함하며, CAD에 의한 급성 혈栓뇌졸중에서 혈전용해제가 안전하다는 것을 제시한다. CAD 환자에서 3%의 통합 SICH 발생률과 8%의 전체 사망률(IVT에서는 각각 3%, 7%)은 모든 원인으로 인한 뇌졸중에서의 결과와 비교하였다. 특히 본 연구의 환자들보다 SITS–ISTR로부터 적은 대조군과의 간접적인 비교에 이론적 주요 증상점에 대한 차이는 유의하지 않았다. 본 연구와 SITS–ISTR 연구는 사전에 비교가 가능하도록 설계된 것은 아니기 때문에, 두 연구들의 차이에 대한 통계적 검증은 시행하지 않았다. 따라서 저자는 두 연구에 대한 비교를 기술적으로만 제시하였다. 그러나 CAD 관련 뇌졸중 환자에 대한 혈전용해율의 속임수영태연구는 더 이상 유효적이지 않기 때문에, 본 자료는 현재까지의 가이드라인에 대한 가장 최신의 증거가 될 수 있다.

혈전용해시 증 백내혈증 환자는 이론적으로 상당한 우려가 될 수 있다. 본 연구에서 한 명에서도 백내혈증의 확장이 보고되었고, 이 환자 또한 탁월한 결과를 보였다. 자료들은 대부분 분 연구들에서 이러한 직접적 합병증에 대한 체계적인 보고가 없음을 실감하였다. 그러나 전반적인 안전성과 합병증을 고려한 때 혈전용해시로 인한 직접적인 출혈 합병증은 분명히 주요 캐주징 사항이 아니다.

본 연구에서 모든 CAD 환자 중 31%가, SITS–ISTR에서는 37%가 탁월한 결과(mRS=0–1)를 보았다. 그러나 양호한 결과를 보인 경우는 본 연구에서 조금 더 많은 듯 하였다(58% vs. 52% in SITS–ISTR). 두 가지 결과 모두에 대해 신뢰구간이 크게 빨랐다. 그러므로 두 연구의 간접적 비교만이 가능하였다는 고려하여 CAD로 인한 뇌졸중 환자들에서 IVT의 결과는 모든 원인으로 인하여 발생한 뇌졸중 환자들에게 관련된 IVT 치료의 결과와 같은 범위 내에 있다. 추정한 결과검정은 보통은 이론적 기이산적인 비교에서 이러한 결과성을 잃을 수 있다. 환자수가 적고 신뢰구간이 넓어 저자는 이 를 엄중할 수 없었으며 상관성도 유의하지는 않았다. 추후 더 큰 규모의 연구에서 고위험군을 확인할 수 있다면, 이러한 하위 집단 환자들에게는 더, 아마도 더 적절적인 치료가 필요함을 의미할 수 있다.

본 연구는 몇 가지 한계점은 가지고 있다. 첫째, 무작위대조 시험 자료가 없어서 본 메타분석에 포함되지 않았다. 통합 추정치는 후향적 비대조연구와 중래 보고에 근거한 것이다. 중래 보고 자료를 제외하여도 연구 결과가 변하지는 않았으나 출판 차우침의 가능성을 배제할 수 없어 이로 인하여 메타분석 결과가 영향을 받았을 수 있다. 또한 본 메타분석에 포함된 연구마
da SICH의 정의가 서로 달랐기 때문에, 본 연구에서 SICH의 정의에 대하여 엄격한 기준이 아닌 실용적인 정의를 사용할 수 밖에 없었다. 이로 인해 다른 연구의 SICH 발생률과 비교하기가 어렵다. 그러나 이러한 혼합된 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 환자들에서 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 줄여 준다. 결과 뿐 아니라 SICH 발생에 영향을 줄 수 있는 혈전예방 침술 사용된 양혈전제의 종류가 평가되지 않았다. 본 연구에서 현재 IVT 가이드라인에 따른 4.5시간 이내의 뇌졸중 환자 치료용을 적용하였다는 점도 비판받을 수 있다. 본 연구에서의 치료 시작 중양값은 증상 발생 후 165분(사분위수 범위, 125~225)로, 대부분의 혈전용해술이 뇌졸중의 초급성기에 시행되었다는 것을 의미한다. 하위 집단 분석에서 전체 연구 집단에 대한 결과와 3시간 이내, 4.5시간 이내에 치료받은 하위 집단에서의 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 정확한 추적 관찰을 받았다.

결론

결론적으로, CAD로 인한 급성 혈栓성뇌졸중의 혈전예방 치료는 안전한 것으로 보인다. 이 환자들에서 혈전예방 치료의 결과 뿐 아니라 사망률과 SICH 발생률은 모든 환자들로 인하여 혈전예방 치료를 받은 뇌졸중 환자들에서의 발생률과 유사한 것으로 보인다. 비록 저자들의 분석이 적은 수의 환자들 대상으로 한 후향 연구에 기반하고 있으나, 본 연구 결과 CAD에 의한 혈栓성뇌졸중 환자들에게 혈전예방 치료를 보류해야 한다는 여타의 근거도 제공하지 않는다.

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Disclosures

None.

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