Intravenous Thrombolysis in Stroke Attributable to Cervical Artery Dissection

Stefan T. Engelter, MD; Matthieu P. Rutgers, MD; Florian Hatz, MD; Dimitrios Georgiadis, MD; Felix Fluri, MD; Lucka Sekoranja, MD; Guido Schwegler, MD; Felix Müller, MD; Bruno Weder, MD; Hakan Sarikaya, MD; Regina Luethy, MD; Marcel Arnold, MD; Krassen Nedeltchev, MD; Marc Reichhart, MD; Heinrich P. Mattle, MD; Barbara Tettenborn, MD; Hansjörg J. Hungerbühler, MD; Roman Sztajzfel, MD; Ralf W. Baumgartner, MD; Patrik Michel, MD; Philippe A. Lyrer, MD

Background and Purpose—Intravenous thrombolysis (IVT) for stroke seems to be beneficial independent of the underlying etiology. Whether this is also true for cervical artery dissection (CAD) is addressed in this study.

Methods—We used the Swiss IVT databank to compare outcome and complications of IVT-treated patients with CAD with IVT-treated patients with other etiologies (non-CAD patients). Main outcome and complication measures were favorable 3-month outcome, intracranial cerebral hemorrhage, and recurrent ischemic stroke. Modified Rankin Scale score ≤1 at 3 months was considered favorable.

Results—Fifty-five (5.2%) of 1062 IVT-treated patients had CAD. Patients with CAD were younger (median age 50 versus 70 years) but had similar median National Institutes of Health Stroke Scale scores (14 versus 13) and time to treatment (152.5 versus 156 minutes) as non-CAD patients. In the CAD group, 36% (20 of 55) had a favorable 3-month outcome compared with 44% (447 of 1007) non-CAD patients (OR, 0.72; 95% CI, 0.41 to 1.26), which was less favorable after adjustment for age, gender, and National Institutes of Health Stroke Scale score (OR, 0.50; 95% CI, 0.27 to 0.95; P = 0.03). Intracranial cerebral hemorrhages (asymptomatic, symptomatic, fatal) were equally frequent in CAD (14% [7%, 7%, 2%]) and non-CAD patients (14% [9%, 5%, 2%]; P = 0.99). Recurrent ischemic stroke occurred in 1.8% of patients with CAD and in 3.7% of non-CAD patients (P = 0.71).

Conclusion—IVT-treated patients with CAD do not recover as well as IVT-treated non-CAD patients. However, intracranial bleedings and recurrent ischemic strokes were equally frequent in both groups. They do not account for different outcomes and indicate that IVT should not be excluded in patients who may have CAD. Hemodynamic compromise or frequent tandem occlusions might explain the less favorable outcome of patients with CAD. (Stroke. 2009;40:3772-3776.)

Key Words: carotid artery ■ cervical artery dissection ■ complications ■ dissection ■ outcome ■ thrombolysis

Intravenous thrombolysis (IVT) for acute ischemic stroke using recombinant tissue plasminogen activator has been shown to be safe and efficacious.1,2 Treatment response seems to be independent of the underlying stroke mechanism.3 However, whether this observation includes patients with strokes attributable to cervical artery dissection (CAD) has not been studied. CAD is characterized by intramural accumulation of blood. Theoretically, IVT might promote and increase the intramural bleeding in CAD and cause progressive hemodynamic worsening and infarct growth. In patients with stroke with aortic dissection extending to the cervical arteries, IVT might be dangerous as it is in patients with IVT for myocardial infarction.4–6 According to recent pilot data, the outcome of 7 IVT-treated patients with CAD tended to be worse than that of 7 patients with CAD not treated with IVT.7

In turn, patients with CAD have not been excluded from randomized, placebo-controlled trials1,8,9 of IVT in stroke. Treatment guidelines10 do not advise against IVT in such patients, but randomized, placebo-controlled trial-based data about IVT versus placebo in patients with CAD are not available. Only information of case series without control groups and small sample sizes (ie, 30,11 11,12 6,13 and 214 is available, which suggests low complications rates of IVT for patients with CAD.11–14

With these considerations in mind, we aimed at evaluating whether the variable “stroke etiology CAD” has a prognostic meaning in IVT-treated patients. Specifically, we analyzed

Received April 21, 2009; final revision received August 12, 2009; accepted August 25, 2009.

From the Stroke Units and Departments of Neurology, University Hospitals Basel (S.T.E., F.H., F.F., P.A.L.), Bern (M.A., K.N., H.P.M.), Geneva (L.S., R.S.), Lausanne (M.P.R., M.R., P.M.), and Zurich (D.G., H.S., R.W.B.), Cantonal Hospitals Aarau (G.S., H.J.H.), Thurgau (Muensterlingen; F.M.), St Gallen (B.W., B.T.), and the Department of Internal Medicine Triemli Hospital (Zurich; R.L.), Switzerland.

Correspondence to Stefan T. Engelter, MD, Department of Neurology and Stroke Unit, University Hospital Basel, Petersgraben 4, CH-4031 Basel, Switzerland. E-mail sengelter@uhbs.ch

© 2009 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.109.555953
and compared outcome and complications of CAD and non-CAD patients using pooled data of Swiss stroke centers.

Methods

As a joint initiative of 9 stroke centers in Switzerland, we designed a study about the significance of CAD as an underlying stroke etiology in IVT-treated patients. All participating centers (5 university, 4 community hospitals) used IVT according to current guidelines. None of the centers excluded patients with CAD.

Data were collected with a standardized form with predefined variables because it was also used in a previous study with similar methodology. Local study investigators filled in the forms systematically using prospectively ascertained in-hospital stroke databases or thrombolysis registries. The completed forms of all centers were compiled in the coordinating center, Basel, where the analyses of the pooled data were performed.

The following variables were ascertained prospectively: age, gender, functional independence before thrombolysis, time to treatment, stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) score (ascertained by certified raters), etiology according to the Trial of Org 10172 in Acute Treatment (TOAST) criteria, vascular risk factors according to predefined criteria, blood pressure, temperature, and blood glucose level obtained before IVT. Functional outcome was assessed by outpatient visits or telephone calls using the modified Rankin Scale (mRS) at 3 months. Patients who died during follow-up were given a mRS score of 6. Patients without 3-month outcome were excluded. All intracranial hemorrhages (ICHs) were ascertained on follow-up CT or MRI obtained within 72 hours after IVT and additional scans in case of clinical deterioration. Applying the National Institute of Neurological Diseases and Stroke criteria, symptomatic ICH was defined as any CT/MRI-documented ICH temporally related to any deterioration in the patient’s clinical condition. Fatal hemorrhage was defined as any symptomatic ICH leading to death.

Each center reported on the period for which they had prospectively ascertained data on consecutive patients up to December 31, 2007. The Appendix provides detailed data about the number of patients and the study period for each center.

For the current study, all IVT-treated patients with stroke were categorized according to the underlying etiology as CAD and non-CAD patients. In general, the etiologic diagnoses were established after IVT.

The investigators of the local study centers were asked to repropose the etiologic diagnoses of CAD by applying at least one of the following widely accepted diagnostic criteria: (1) mural hematoma visible on MRI or CT; (2) a nonatherosclerotic string-like stenosis or a tapered, flame-shaped arterial occlusion, which shows after recanalization a pseudoaneurysm or a long filiform stenosis, or a double lumen; or (3) intimal flap visible on carotid ultrasound. To prevent false-positive inclusions in the CAD group, patients with just suspected CAD, thus not meeting the aforementioned criteria, were excluded. Patients with solely intracranial dissections were excluded, because it is still under debate whether CAD and intracranial dissections can be regarded as one entity. The non-CAD patients group included all patients with stroke causes other than CAD.

Outcome measures were (1) favorable 3-month outcome; and (2) death of all causes. Complication measures were (1) ICH (asymptomatic, symptomatic, fatal); and (2) recurrent ischemic stroke within 3 months.

Statistical Analysis

After data pooling, comparisons of CAD and non-CAD patients were done using t and χ² tests. Data were given as mean and SD or median with interquartile range where appropriate. The prognostic importance of the variable “CAD” was estimated by calculating ORs with 95% CIs for each outcome and complication variable. In a second step, the OR for favorable 3-month outcome was adjusted for age, gender, and NIHSS scores by multivariable regression analysis.

Results

Study Population

One thousand sixty-two (98%) of 1085 IVT-treated patients were eligible for this study.

Nineteen patients (1.8%) were lost to follow-up; all of them belonged to the non-CAD group. Three patients with pure intracranial dissection were excluded. (Two patients had mRS scores ≤1, one patient had mRS 2 at 3 months.) One patient with intraluminal thrombus and suspected CAD was excluded, because he did not adhere to the aforementioned diagnostic criteria. Among study patients, CAD was the underlying etiology in 55 (5.2%) of them. Fifty-two of 55 patients with CAD (94.5%) had internal carotid artery and 3 (5.5%) vertebral artery dissections. In the non-CAD group, cardioembolism was the most frequent etiology (47%; Table 1).

Extracranial arterial occlusion was present in 89.6% (26 of 29) of the patients with CAD of whom information about arterial patency was available. Twelve of them (46.2%) had accompanying intracranial occlusions (ie, tandem occlusions).

CAD- Versus Non-CAD Patients

Baseline Characteristics

Patients with CAD were younger than non-CAD patients with a median age (interquartile range) of 50 years (43 to 57) versus 70 years (57 to 77). NIHSS scores (median 14 versus 13), median time to treatment (150 versus 156 minutes), and gender ratios (66% versus 61% males) were similar in both groups. Hypertension, hypercholesterolemia, and coronary artery disease were more frequent among non-CAD than among CAD patients (P=0.05; Table 1).

Outcome and Complications

In the CAD group, 5.5% (3 of 55) died within 3 months compared with 10.8% (109 of 1007) non-CAD patients (P=0.22). After 3 months, 36% (20 of 55) of the patients with CAD and 44% (447 of 1007) of the non-CAD patients had recovered to mRS≤1 (OR, 0.72; 95% CI, 0.41 to 1.26; P=0.25). If the CAD group was compared with the subgroup of non-CAD patients with the same upper age limit (n=650; ie, all non-CAD patients who are older than the oldest patient with CAD were excluded), the OR for a favorable outcome was 0.57 (95% CI, 0.32 to 1.01; P=0.05). Compared with patients with cardioembolic etiology (n=217) within this subgroup, the CAD group had an OR of 0.68 (95% CI, 0.36 to 1.26; P=0.22) for recovery to mRS≤1 at 3 months. Two of the 3 patients with vertebral artery dissections (ie, 66% with 95% CI 9% to 99%) and 18 of the 52 patients (ie, 35% with 95% CI 22% to 49%) with dissections of the internal carotid artery had mRS>1. The rate of ICH (asymptomatic, symptomatic, fatal) did not differ between CAD (7%, 2%, and non-CAD patients (9%, 5%, 2%; P=0.99). Among patients with symptomatic ICH, the NIHSS scores did not differ between the CAD group (mean NIHSS score 13.3±6.6) and the non-CAD group (15.5±5.2; P=0.5). Recurrent ischemic events occurred in one of the patients with CAD (1.8%) versus 24 of the 649 non-CAD patients (3.7%) for whom this information was available (P=0.71; Table 2).
Table 1. Clinical Characteristics of IVT-Treated Patients With Stroke Attributable to CAD Versus Those Attributable to Another Cause (Non-CAD)

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Patients With CAD</th>
<th>Non-CAD Patients</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean, years (±SD)</td>
<td>50 (±10)</td>
<td>67 (±13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>50 (42–57)</td>
<td>70 (59–77)</td>
<td></td>
</tr>
<tr>
<td>Male sex, % (no.)</td>
<td>66% (36)</td>
<td>61% (613)</td>
<td>0.57</td>
</tr>
<tr>
<td>Independence prior to stroke, %</td>
<td>98%</td>
<td>96%</td>
<td>0.87</td>
</tr>
<tr>
<td>Stroke severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean NIHSS score (±SD)</td>
<td>13.5 (±6.3)</td>
<td>12.9 (±6.0)</td>
<td>0.40</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>14 (8–19)</td>
<td>13 (8–18)</td>
<td></td>
</tr>
<tr>
<td>Laboratory findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose level, mmol/L</td>
<td>6.5 (±1.6)</td>
<td>7.1 (±2.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>C-reactive protein, mmol/L</td>
<td>5.0 (±6.6)</td>
<td>6.7 (±12.6)</td>
<td>0.11</td>
</tr>
<tr>
<td>Vital signs before lysis mean (±SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>137 (±22.6)</td>
<td>157 (±27.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature, °C†</td>
<td>36.6 (±0.61)</td>
<td>36.5 (±0.66)</td>
<td>0.13</td>
</tr>
<tr>
<td>Time to treatment, mean (±SD) minutes</td>
<td>149 (±35.0)</td>
<td>153 (±36.5)</td>
<td>0.46</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>152.5 (124–175)</td>
<td>156 (130–180)</td>
<td></td>
</tr>
<tr>
<td>Stroke etiology,* %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>47%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large-artery atherosclerosis</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small artery occlusion</td>
<td>7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (except CAD)</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other (CAD)</td>
<td>100%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Undetermined</td>
<td>26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular risk factors, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>36%</td>
<td>63%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>15%</td>
<td>26%</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>15%</td>
<td>30%</td>
<td>0.03</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>6%</td>
<td>15%</td>
<td>0.16</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6%</td>
<td>17%</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*According to the TOAST-classification.17
†Data about temperature were only available on 25 of 58 patients with CAD and 405 of 1007 non-CAD patients. IQR indicates interquartile range.

After adjustment for age, gender, and NIHSS score, the OR to recover to mRS≤1 was 0.50 (95% CI, 0.27 to 0.95; P=0.030) for patients with CAD compared with non-CAD patients (Table 3).

Discussion
The Swiss multicenter study comprises the largest IVT-treated CAD cohort studied so far. By comparing IVT-treated patients with CAD with IVT-treated patients with a different underlying etiology, the following main findings were obtained: (1) IVT-treated patients with CAD had lower chances to recover favorably than IVT-treated non-CAD patients; and (2) the lower recovery rate was not caused by different intracranial bleeding or recurrent stroke rates between the 2 groups.

Only 36% of the IVT-treated patients with CAD did have a favorable outcome, that is, mRS≤1 after 3 months, which is in line with results obtained in smaller series (2 of 6,13 4 of 11,12 and 12 of 3311). The rate is slightly lower than that of the European Cooperative Acute Stroke Study (ECASS) (3-hour cohort; 40%),8 and the National Institute of Neurological Diseases and Stroke trial1 (39%), in which patients had comparable stroke severity to that of the current CAD cohort (median NIHSS = 13,8 14,1 to 14 [our study]). With regard to the considerably younger mean age of the latter (10 to 15 years younger), this finding is striking.

Several open series of patients with CAD reported a rate of approximately 80% of neither dead nor dependent patients with CAD; three fourths of the survivors were considered to have a “fairly good prognosis.”25 Differing eligibility criteria (inclusion of transient ischemic attack and nonischemic CAD symptoms) for the majority of these open series do, however, not allow for a one-to-one comparison with the current study and its less favorable outcome.

Adjustment for age, gender, and stroke severity entailed a statistically significant worse outcome for patients with CAD compared with non-CAD patients. This finding was somewhat surprising, because vascular risk factors, which one would expect to be associated with a less favorable outcome, were more frequent in non-CAD patients than in patients with CAD. Because the risk of ICH and the rate of recurrent stroke between CAD and non-CAD patients did not differ, the lower recovery rate of the patients with CAD cannot be ascribed to them. The rate of symptomatic ICH was similar to those reported in the National Institute of Neurological Diseases and Stroke (ie, 6.4%)3 and the ECASS-3 (ie, 7.9%)9 studies adhering to the same definition.

Ninety percent of the patients with CAD had occlusion of the dissected cervical artery before IVT. Thus, the theoretical concern that IVT could cause progression from stenotic CAD to occlusive CAD by promoting intramural bleeding proved inappropriate for the majority of patients with CAD.

A cohort of internal carotid dissections not treated with IVT9 showed differences in lesion size between patients with occlusive dissections compared with those with stenotic dissections. Because the first group of patients had larger ischemic lesions, the high rate of occlusive CAD in our study may be an important prognostic variable. In IVT-treated populations of miscellaneous stroke etiologies, internal carotid artery occlusion was a negative prognostic factor.26 In the current cohort, half of the patients with occlusive CAD had tandem occlusions, which is an independent predictor of unfavorable outcome after IVT in general.27 In IVT-treated
patients with CAD, the prognostic significance of arterial occlusions deserves further testing.

Important limitations of this study are due to the nonavailability of data on recanalization rates as prognostic variable or data on vessel patency for non-CAD patients. This disallowed us to study whether the high rate of arterial occlusions in the CAD group may be responsible for the lower recovery rate. In addition, data on medication before IVT (eg, statins, antihypertensive, or antiplatelet treatment) were not systematically collected in all centers contributing to the databank. Therefore, we cannot exclude confounding of the primary result of a worse functional outcome after IVT in patients with CAD by differences in pre-existing medication. Moreover, the lower recovery rate of IVT-treated patients with CAD in our study might erroneously lead to the questioning of any beneficial effect of IVT in patients with CAD at all. Yet, the lower recovery rate was not obtained by comparing IVT-treated patients with CAD with non-IVT-treated patients with CAD, but with IVT-treated non-CAD patients. In fact, the absence of excessive complications in patients with CAD compared with non-CAD patients suggests a certain safety of the IVT treatment also in patients with CAD.

As another limitation, most IVT-treated patients with CAD had internal carotid artery dissections rather than vertebral artery dissections. Thus, our observation of reduced recovery chances is based on patients with primarily internal carotid artery dissections. In how far this statement is also valid for the small number of patients with vertebral artery dissections is less clear.

The exclusion of intracranial dissections is debatable. Interestingly, the inclusion of these cases would have not altered our results substantially (ie, OR_{CAD+intracranial dissections} for favorable 3-month outcome = 0.51; 95% CI, 0.28 to 0.96 as compared with OR_{CAD} = 0.50; 95% CI, 0.27 to 0.95).

In conclusion, IVT-treated patients with CAD do not recover as well as IVT-treated non-CAD patients. However, intracranial bleedings and recurrent ischemic strokes were equally frequent in both groups. They do not account for different outcomes and indicate that IVT can be used safely for patients with CAD.

### Appendix

Participating centers (number of patients, study period) and contributors in alphabetical order: Kantonsspital Aarau (104, 8 years): H.J. Hungerbühler and G. Schweger. Universitätsklinik Basel (283, 9 years): S.T. Engelter, F. Fluri, F. Hatz, and P.A. Lyrer. Inselspital Bern (37, 8 years): M. Arnold, H.P. Mattle, and K. Nedeltchev. CHUV Lausanne (217, 8 years): P. Michel, M. Reichhart, and M.P. Rutgers. HUG Geneva (75, 8 years): L. Sekoranja and R. Sztajzel. Kantonsspital Muensterlingen (85, 8 years): F. Müller. Kantonsspital St Gallen (24, 5 years): R. Lüthy. All centers have organized stroke services and are networked in the task force “Stroke Unit & Thrombolysis” of the Cerebrovascular Working Group of Switzerland.

### Acknowledgments

We thank Susanna Papa for language assistance and Andreas Schötzau for statistical advice.

### Disclosures

None.

### References


Intravenous Thrombolysis in Stroke Attributable to Cervical Artery Dissection

Stroke. 2009;40:3772-3776; originally published online October 15, 2009;
doi: 10.1161/STROKEAHA.109.555953
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/40/12/3772

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/