Influence of Arterial Occlusion on Outcome After Intravenous Thrombolysis for Acute Ischemic Stroke

Friedrich Medlin, MD; Michael Amiguet, PhD; Peter Vanacker, MD; Patrik Michel, MD

Background and Purpose—We aimed to assess the interaction between intravenous thrombolysis (IVT) and arterial occlusion on acute cervicocerebral computed tomographic angiography on the outcome of patients with acute ischemic stroke.

Methods—Patients from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL) registry with onset-to-door-time ≤4 hours, acute cervicocerebral computed tomographic angiography, a premorbid modified Rankin Scale ≤2, and a National Institute of Health Stroke Scale (NIHSS) >4 were selected. Patients with significant intracranial arterial obstruction (≥50%–99%) and undergoing acute endovascular treatment were excluded. An interaction analysis of IVT and initial arterial occlusion for favorable 3 months outcome (modified Rankin Scale <3) were performed with adjustment for potential confounders.

Results—Among 654 included patients, 382 (58%) showed arterial occlusion, of whom 263 (69%) received IVT. Two hundred seventy-two showed no/minimal obstruction of whom 139 (51%) received IVT. In the adjusted interaction analysis, there was a trend in favor of the arterial occlusion group (odds ratio [OR]=3.97; 95% confidence interval [CI], 0.83–18.97; P=0.08). IVT (versus no IVT) was associated with better outcome in patients with occlusion (adjusted OR for favorable outcome, 3.01; 95% CI, 1.10–8.28) but not in patients with no/minimal obstruction (OR, 0.76; 95% CI, 0.21–2.74). Conversely, patients with occlusion had a similar rate of favorable outcome as no/minimal obstruction when thrombolysed (OR, 0.5; 95% CI, 0.17–1.47) but had a less favorable outcome without thrombolysis (OR, 0.13; 95% CI, 0.04–0.44).

Conclusions—In this retrospective analysis of consecutive patients with acute ischemic stroke, there was a trend for more favorable outcomes with IVT in the setting of initial arterial occlusion than in the setting of no/minimal obstruction.

Before confirmation in randomized controlled studies, this information should not influence thrombolysis decisions, however. (Stroke. 2015;46:126-131. DOI: 10.1161/STROKEAHA.114.006408.)

Key Words: patient outcome assessment ■ stroke ■ thrombolytic therapy ■ tissue-type plasminogen activator

Intravenous thrombolysis (IVT) with recombinant tissue-type plasminogen activator (r-tPA) improves outcomes in acute ischemic strokes when administered within 4.5 hours of symptom onset,1,2 likely through increasing the chance of recanalization and reperfusion of at-risk ischemic tissue. Its use is associated with a reperfusion rate of ≈50%, depending on the location of the occlusion,3,4 clot size,3 and other factors.

Up to 50% of patients with acute ischemic stroke have no significant occlusion or stenosis on acute arterial imaging, however.6 Little is known whether such patients also benefit from thrombolysis. Post hoc analysis from randomized trials and large case series suggest such a benefit in lacunar stroke, where arterial occlusion typically cannot be demonstrated.1,7,8 For nonlacunar strokes, the few studies examining the effect of thrombolysis found no significant radiological9 or clinical10,11 benefit in the absence of prethrombolysis occlusion. The presence of occlusion of major cervicocerebral arteries is associated with poorer prognosis,12 especially in the presence of large volumes of clot and concomitant cervical artery occlusion.13 In retrospective analyses, patients with normal findings on acute computed tomographic angiography (CTA) had a better prognosis,14 independent of the use or not of IVT15 or did not seem to benefit from it.16 Contrarily, randomized trials have shown a benefit of late recanalization in the subgroup of patients with initial arterial occlusion but not in others,11 a result that was confirmed in a subgroup of a combined intravenous endovascular randomized trial.16 The aim of this study was to investigate the interaction of initial arterial occlusion and acute intravenous r-tPA use on 3 months functional outcome.

Subjects and Methods

Study Population and Clinical Assessment

We used data from the Acute Stroke Registry and Analysis of Lausanne (ASTRAL), which is the prospective registry of all acute ischemic stroke admitted to the stroke unit and intensive care unit of the Centre Hospitalier Universitaire Vaudois (CHUV) within 24 hours of symptom onset.17 Patients with acute ischemic stroke were eligible for inclusion if they were 18 to 90 years old and able to give informed consent. Exclusion criteria were recent intracranial hemorrhage, untreated untreated hyperperfusion, and known contraindications to IVT.18 All patients were scanned within 6 hours of symptom onset with a 64-slice computed tomographic device. Stroke treatment was decided by the neurologist in charge of the patient at the stroke unit and was administered by a licensed nurse under the supervision of the neurologist.

Study Variables

The study outcomes were dichotomized as favorable (modified Rankin Scale <3) or unfavorable (modified Rankin Scale ≥3). Initially, all patients were prospectively followed for 3 months at the hospital and then annually until death or loss to follow-up. In the present study, 3 months was the primary outcome. We used the following study variables:

- Symptom onset time—The time of symptom onset was determined with medical history, witness statements, and the time patients or caregivers arrived at hospital, using the time they thought the stroke symptoms were at their peak.
- Onset to treatment time—This was the time from symptom onset to the start of IVT when given, or to system start in other endovascular procedures.
- National Institute of Health Stroke Scale (NIHSS) score—The NIHSS score was performed within 24 hours of symptom onset.
- Anterior circulation occlusion—Arterial occlusion was classified as anterior or posterior circulation based on the location of the occlusion.

Analysis

Data were analyzed with SPSS software (version 22.0; IBM). Descriptive statistics were calculated using medians and ranges for continuous variables and proportions for categorical variables. The χ² test was used to compare proportions, and the Kruskal-Wallis test to compare medians. Logistic regression was used to quantify the independent association of clinical and imaging factors with outcomes. Odds ratios (or) were calculated with 95% confidence intervals (CIs). In the interaction analysis, arterial occlusion was dichotomized as occlusion or no/minimal obstruction to separate the 2 groups. The online-only Data Supplement is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STROKEAHA.114.006408/-/DC1.

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hours after last-well time, as published previously. Patients between January 2003 and January 2012 were included in the current analysis if they fulfilled IVT criteria, ie, they presented to our institution within 4 hours since last proof of good health, baseline National Institute of Health Stroke Scale score ≥4 (no upper limit), and had a premorbid modified Rankin Scale (mRS) score ≤2. Only patients with a good quality acute cervicocerebral CTA were selected. We excluded patients undergoing acute endovascular treatment and with ≥50% intracranial artery obstruction supplying the ischemic area from our analysis to avoid including patients with spontaneous recanalizing emboli into the no/minimal obstruction group because we intended to compare specifically patients with occlusion and no/minimal obstruction (Figure 1). Stroke mimics were excluded from the analysis when recognized as such based on further clinical, radiological, and laboratory data.

In ASTRAL, demographic data, vascular risk factors, comorbidities, and previous cerebrovascular events were recorded. We collected prestroke mRS and medications. The National Institute of Health Stroke Scale was performed or supervised by National Institute of Health Stroke Scale–certified personnel on admission to the emergency department, and metabolic variables and vital signs were recorded. Thrombolysis decisions were taken immediately after noncontrast CT had ruled out contraindications for thrombolysis. Although CTA was performed, the r-tPA bolus was prepared and given immediately after CTA, and just before CT perfusion, while the patient was still on the CT table. Stroke mechanism was classified according to Trial of Org 10172 in Acute Stroke Treatment (TOAST) with dissection and multiple mechanism added (modified TOAST). IVT was given according to the European Stroke Organisation recommendations,17 which are based on clinical data and noncontrast CT. The rest of the acute stroke management and secondary prevention in our center follows current European Stroke Organisation guidelines.17 The ethics commission for research on humans of the Canton of Vaud (ECCV), subcommission III, has approved the scientific use of ASTRAL data without need of individual patient consent.

Imaging Evaluation, Definition of Arterial Occlusion, and No/Minimal Obstruction

Cervical and cerebral arteries were assessed routinely by acute CTA in patients without contraindications to contrast, as described previously. Occlusion was defined as the absence of contrast in the artery and no/minimal obstruction as a <50% diameter reduction of contrast filling of the artery on continuous axial and reformatted maximum intensity projection CTA pictures after consensus between a stroke neuroradiologist and an institutional neuroradiologist. Early ischemic changes were considered present on acute CT if Alberta Stroke Program Early CT Score (ASPECTS)18 or posterior circulation (pc)-ASPECTS19 was ≤9. Most patients also underwent acute CT perfusion in our center; given that thresholds for this method are still being debated and that we only have a limited number of CT perfusion reconstructions validated for scientific use, we have chosen not to include this parameter in the current analysis.

Outcome Measures

The main outcome of the study was favorable clinical outcome defined as mRS <3 at 3 months that was recorded either at the outpatient stroke clinic visit in an unblinded manner or by a structured telephone interview by mRS-certified medical personnel in a manner blinded to treatment type and recanalisation. The main focus of the study was the influence of an interaction between initial arterial status and IVT with regards to the 3 months clinical outcome as measured by the mRS.

Statistical Analysis

We first analyzed demographic, clinical, biological, and radiological variables from the acute phase of stroke, performing comparisons between the 4 study groups based on intracranial arterial vascular status (occlusion versus no/minimal obstruction) and acute treatment modality (intravenous thrombolysis versus no thrombolysis). Comparisons were made using the χ² test for categorical variable and the F-test (ANOVA) for continuous variables. Then, logistic regression models with interaction between the variables occlusion and IVT were constructed to assess the importance of this effect, the response variable being favorable outcome at 3 months (mRS <3), and the parameters of interest being 4 different odds ratios (ORs) comparing 4 different groups plus the OR for the interaction term (equal to a ratio of ORs). First, unadjusted ORs were calculated, and then a multivariate analysis (Table I in the online-only Data Supplement) was performed, in which a list of variables was used to adjust the parameters of interest. The decision to use a variable for adjustment was made either because the variable had been shown in our previous20-22 and other studies8,23 to influence outcome or because it induced >10% change in one of the parameters of interest, without causing their variance inflation factors to exceed 5.24

The final adjustment model included the following variables: age, National Institute of Health Stroke Scale, prestroke handicap, insurance status, stroke onset-to-door time, known/newly diagnosed diabetes mellitus, current smoking, sleep apnea, history of previous cerebrovascular events, migraine, cancer, visual field deficits and level of consciousness on initial neurological examination, admission

Figure 1. Study flow diagram (patients may had multiple reasons for not being eligible for the analysis). CTA indicates computed tomographic angiography; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NMO-NT, nonthrombolysed patients with no/minimal arterial obstruction; NMO-T, thrombolysed patients with no/minimal arterial obstruction; O-NT, nonthrombolysed patients with arterial occlusion; and O-T, thrombolysed patients with arterial occlusion.
blood glucose, creatinine, total cholesterol levels and white cell count, admission temperature, heart rate and diastolic blood pressure, body mass index, ASPECTS on acute CT, chronic or subacute ischemic lesions on CT scan unrelated to the current stroke, leukoariosis on admission CT and silent strokes on any imaging, significant extracranial pathology in the ischemic territory including 50%–99% stenosis and occlusion, and stroke mechanism (modified TOAST).

To assess the importance of interaction between thrombolysis and initial occlusion, we computed an adjusted model with the same adjusting variables but without the interaction term. Significance of ORs was assessed with Wald tests. General significance level was 0.05. Statistical analysis was performed with R statistical software (R Core Team 2012, R Foundation for Statistical Computing, Vienna, Austria).

**Results**

A total of 654 patients met the eligibility criteria. Three hundred eighty-two patients (58%) had CTA evidence of arterial occlusion, of whom 263 (69%) received r-tPA (occlusion-intravenous thrombolysis group) and 119 (31%) no r-tPA (occlusion-no thrombolysis group). Of the 272 patients with no/minimal obstruction, 138 (51%) received r-tPA (no/minimal obstruction-intravenous thrombolysis group) and 134 (49%) no r-tPA (no/minimal obstruction-no thrombolysis group; Figure 1). Out of the 253 nonthrombolysed patients who arrived within 4 hours of stroke onset, 16% were on oral anticoagulants and 84% were assessed after the time window for r-tPA treatment of 3 hours (limit applied in our center till August 2008 before publication of European Cooperative Acute Stroke Study [ECASS]-III) or after 4.5 hours (limit applied after August 2008). In the overall sample, 52% had a favorable outcome at 3 months. Within the excluded 182 patients with ≥50% intracranial artery obstruction, 7 had endovascular treatment and 3 had missing 3 months follow-up. Of the remaining 172 patients, 109 (63%) had a favorable 3 months outcome: 59% of the IVT treated patients versus 64% of the non-IVT treated patients.

The baseline characteristics of the sample and of the 4 subgroups (Table 1) showed several differences between groups. In the thrombolysed patients, there was no significant difference of onset-to-needle time between occluded and patients with no/minimal obstruction.

Before (Table II in the online-only Data Supplement) and after adjustment (Table 2; Figure 2), patients with initial occlusion showed a higher likelihood of favorable outcome with IVT than without (adjusted OR=3.01; 95% confidence interval [CI], 1.10–8.28). Patients with no/minimal obstruction did not show a similar increased benefit.

Table 1. Characteristics of the Overall Population Included in the Study and the 4 Comparison Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>NMO-T n=138</th>
<th>NMO-NT n=134</th>
<th>O-T n=263</th>
<th>O-NT n=119</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.6 (17.3)</td>
<td>72.2 (18.9)</td>
<td>70.1 (18.3)</td>
<td>73.6 (21.3)</td>
<td>0.91</td>
</tr>
<tr>
<td>Male sex</td>
<td>90 (64)</td>
<td>85 (63)</td>
<td>146 (56)</td>
<td>62 (52)</td>
<td>0.1</td>
</tr>
<tr>
<td>Onset-to-door time, h</td>
<td>1.4 (1.2)</td>
<td>1.9 (1.8)</td>
<td>1.4 (1.2)</td>
<td>1.9 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Onset-to-needle time, min</td>
<td>148 (65)</td>
<td>...</td>
<td>140 (67.2)</td>
<td>...</td>
<td>0.32</td>
</tr>
<tr>
<td>Premorbid mRS</td>
<td>...</td>
<td>...</td>
<td>191 (75)</td>
<td>169 (73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>9 (9)</td>
<td>7 (7)</td>
<td>7 (6)</td>
<td>7 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>110 (82)</td>
<td>92 (78)</td>
<td>238 (93)</td>
<td>93 (78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Posterior circulation stroke</td>
<td>23 (17)</td>
<td>25 (21)</td>
<td>17 (7)</td>
<td>24 (20)</td>
<td>0.17</td>
</tr>
<tr>
<td>Nonlacunar stroke</td>
<td>116 (84)</td>
<td>114 (85)</td>
<td>255 (97)</td>
<td>119 (99)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>101 (74)</td>
<td>85 (64)</td>
<td>162 (62)</td>
<td>75 (63)</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>31 (23)</td>
<td>25 (19)</td>
<td>43 (16)</td>
<td>19 (16)</td>
<td>0.39</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>106 (77)</td>
<td>87 (66)</td>
<td>175 (67)</td>
<td>67 (57)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>BMI, kg/m2</td>
<td>25 (5)</td>
<td>24 (5.2)</td>
<td>26 (6)</td>
<td>25 (5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Currently smoking</td>
<td>41 (31)</td>
<td>32 (25)</td>
<td>58 (23)</td>
<td>23 (19)</td>
<td>0.19</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>29 (21)</td>
<td>41 (31)</td>
<td>99 (38)</td>
<td>43 (36)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ASPECTS on acute CT</td>
<td>10 (0)</td>
<td>10 (0)</td>
<td>10 (3)</td>
<td>9 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Proximal intracranial occlusion (MCA first segment, carotid T or BA occlusion)</td>
<td>...</td>
<td>...</td>
<td>172 (65)</td>
<td>69 (58)</td>
<td>0.2</td>
</tr>
<tr>
<td>Symptomatic hemorrhagic* transformation ≤7 d</td>
<td>7 (5)</td>
<td>2 (2)</td>
<td>11 (4)</td>
<td>2 (2)</td>
<td>0.24</td>
</tr>
<tr>
<td>3 mo mRS ≥2</td>
<td>48 (35)</td>
<td>40 (29)</td>
<td>144 (55)</td>
<td>80 (67)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are expressed as absolute counts and percentage for categorical variables, or medians and interquartile range (IQR) for continuous variables, unless stated otherwise. P values are given for difference between the 4 groups. BA indicates basilar artery; BMI, body mass index; carotid T, intracranial carotid bifurcation; CT, computed tomography; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; NMO-NT, nonthrombolysed patients with no/minimal arterial obstruction; NMO-T, thrombolysed patients with no/minimal arterial obstruction; O-NT, nonthrombolysed patients with arterial occlusion; and O-T, thrombolysed patients with arterial occlusion.

*Symptomatic intracranial hemorrhage was defined according the European Cooperative Acute Stroke Study (ECASS)-2.
not demonstrate better outcomes with IVT compared with those who did not receive thrombolysis (adjusted OR=0.76; 95% CI, 0.21–2.74). Among patients who were thrombolysed, initial occlusion status was associated with a trend toward less favorable outcome after adjustment. Among patients who were not thrombolysed, patients with arterial occlusion had a lower likelihood of favorable outcome than those with no/minimal obstruction (adjusted OR of 0.13, 95% CI, 0.04–0.44). These results are illustrated on Figure 2.

In the unadjusted analysis, the interaction between the thrombolysis and presence of occlusion was significant (interaction OR=2.10; 95% CI, 1.06–4.15). After adjustment, the interaction OR seemed more pronounced (3.97, 95% CI, 0.83–18.97) but did not reach significance level anymore (P=0.08). However, in the model without interaction (not shown), the OR was 1.83 (P=0.15) for all patients, whereas it was 3.01 (P=0.03) for patients with occlusion and 0.76 (P=0.67) for patients with no/minimal obstruction (Figure I in the online-only Data Supplement). Thus, introduction of interaction into the model produces reversion of the effect direction for patients with no/minimal obstruction and increase in effect size for occluded patients.

The adjusted logistic regression model with interaction performed well, as shown by the Hosmer–Lemeshow test and the area under the curve in the complete data set and the 4 study groups (data not shown).

### Discussion

In this retrospective study of 654 patients with acute ischemic stroke, and after adjustment for multiple prognostic factors, we found that patients with initial arterial occlusion had an ≈3-fold higher odds of favorable outcome if they were thrombolysed than if they were not. Patients with no/minimal arterial obstruction seemed to have less benefit from thrombolysis.

Despite a borderline nonsignificant P value for the interaction between occlusion and thrombolysis, the ORs comparing the different groups clearly suggest an association of occlusion status and the clinical effect of thrombolysis. This study’s findings support the hypothesis that the thrombolysis effect depends on the presence of initial arterial occlusion.

This largest study to date examining this question confirms the results of a smaller retrospective analysis which reported less or no clinical effect of r-tPA in the absence of arterial occlusions on CTA, and of subgroup findings in the Desmoteplase in Acute Ischemic Stroke (DIAS)-2 study, a randomized trial of late thrombolysis. In a similar retrospective analysis of the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET) and Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study (DEFUSE) studies, infarct growth on repeat neuroimaging was attenuated in the thrombolysed group of patients with initial occlusion but was no difference in the absence of initial occlusion. Contrarily to our results, Lahoti et al found in 256 patients without arterial occlusion on initial magnetic resonance angiogram that IVT was associated with more excellent (mRS=0–1) outcome than no IVT. Compared with our analysis, this study did not adjust for onset-to-door time and several other variables that might have affect the primary outcome; furthermore, it did not confirm their finding with an analysis of patients with occlusion that were thrombolysed or not. Although it is true that patients without occlusion have a spontaneously better 3 months prognosis, our analysis should not be used to abstain from IVT.
because of its nonrandomized design with its well-known limitations and because our sample size might be too small to assert an effect of thrombolysis. Therefore, r-tPA should in general not be withheld in patients without arterial occlusion on initial imaging. Again, the response of IVT in moderate/severe arterial obstruction (≥50%) was not investigated in this analysis.

None of the randomized r-TPA trials routinely assessed or controlled for arterial pathology, but some arterial data were collected in the International Stroke Trial (IST)-3 trial26 and await analysis. The advantage of performing IVT without added imaging is the shortening of onset to treatment time. Its drawback may be that patients are receiving thrombolysis with little benefit and little pathophysiological justification. This may increase the rate of futile treatments and the number of patients needed to treat. In this regard, adding imaging of early infarct (core) and salvageable tissue (penumbra) may further help to identify the patients most likely to benefit from acute recanalization.2728 Although this still had to be shown in large clinical trials.2930 Our observations of the contribution of initial imaging of arterial occlusion may be considered when planning future thrombolysis trials.

The strengths of our study are the routine collection of acute arterial information by CTA in the absence of contraindication to iodinated contrast.6 Second, we prospectively collect a large number of variables with potential prognostic importance, including demographic, clinical, metabolic, and radiological factors, thus allowing more appropriate adjustment for clinical outcome. Finally, the single center design decreases the risk of heterogeneity of stroke management and outcome assessment, and drop-out rates can be kept low (2.5% in our sample).

Limitations of our study are its nonrandomized and retrospective nature. Second, a sampling bias for administration of r-TPA because of initial arterial status for IVT patients is possible although IVT in our institution is given immediately after noncontrast CT and before cervicocerebral CTA is available. Third, exclusion of patients because of missing initial CTA (9.5% of eligible patients) or added endovascular therapy (10.1% of thrombolysed patients) could have biased our population with initial occlusion. Given the current absence of evidence showing superiority of bridging therapy, the exclusion of such patient should not have biased the results significantly. Fourth, the limited number of patients available for analysis may lead to type II errors, ie, a minor effect of IVT could also be present in patients without visible occlusion. This will need to be analyzed in larger patient samples, and, if possible, in prospective, randomized trials. Fifth, it is possible that unmeasured variables have influenced our results, in particular variables related to the decision not to perform IVT or the decision to perform endovascular treatment. Again, we have attempted to reduce this potential bias by the large number of the aforementioned parameters that were collected and used for the adjustments. Last, we did not have MRI confirmation of strokes in all patients, making it, therefore, possible that some stroke mimics were included in the study, in particular in the nonocclusion group.

In conclusion, this study suggests that the OR of IVT for favorable outcome is larger in the setting of initial arterial occlusion than in the setting of no/minimal obstruction. Despite a borderline nonsignificant P value for this interaction, these findings are an incentive toward investigation of the effect of thrombolysis in randomized trials, which could demonstrate larger IVT effect in the setting of initial occlusion.

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