Younger Stroke Patients With Large Pretreatment Diffusion-Weighted Imaging Lesions May Benefit From Endovascular Treatment

Marc D. Gilgen, MSc*; Dariusz Klimek*; Kai T. Liesirova, MD; Julia Meisterernst; Pascal P. Klinger-Gratz, MD; Gerhard Schroth, MD; Pasquale Mordasini, MD; Kety Hsieh, MD; Johannes Slotboom, PhD; Mirjam R. Heldner, MD; Anne Broeg-Morvay; Marie-Luise Mono, MD; Urs Fischer, MD; Heinrich P. Mattle, MD; Marcel Arnold, MD; Jan Gralla, MD; Marwan El-Koussy, MD*; Simon Jung, MD*

**Background and Purpose**—Lesion volume on diffusion-weighted magnetic resonance imaging (DWI) before acute stroke therapy is a predictor of outcome. Therefore, patients with large volumes are often excluded from therapy. The aim of this study was to analyze the impact of endovascular treatment in patients with large DWI lesion volumes (>70 mL).

**Methods**—Three hundred seventy-two patients with middle cerebral or internal carotid artery occlusions examined with magnetic resonance imaging before treatment since 2004 were included. Baseline data and 3 months outcome were recorded prospectively. DWI lesion volumes were measured semiautomatically.

**Results**—One hundred five patients had lesions >70 mL. Overall, the volume of DWI lesions was an independent predictor of unfavorable outcome, survival, and symptomatic intracerebral hemorrhage (P<0.001 each). In patients with DWI lesions >70 mL, 11 of 31 (35.5%) reached favorable outcome (modified Rankin scale score, 0–2) after thrombolysis in cerebral infarction 2b-3 reperfusion in contrast to 3 of 35 (8.6%) after thrombolysis in cerebral infarction 0-2a reperfusion (P=0.014). Reperfusion success, patient age, and DWI lesion volume were independent predictors of outcome in patients with DWI lesions >70 mL. Thirteen of 66 (19.7%) patients with lesions >70 mL had symptomatic intracerebral hemorrhage with a trend for reduced risk with avoidance of thrombolytic agents.

**Conclusions**—There was a growing risk for poor outcome and symptomatic intracerebral hemorrhage with increasing pretreatment DWI lesion volumes. Nevertheless, favorable outcome was achieved in every third patient with DWI lesions >70 mL after successful endovascular reperfusion, whereas after poor or failed reperfusion, outcome was favorable in only every 12th patient. Therefore, endovascular treatment might be considered in patients with large DWI lesions, especially in younger patients. (Stroke. 2015;46:2510-2516. DOI: 10.1161/STROKEAHA.115.010250.)

Key Words: carotid artery internal ■ cerebral hemorrhage ■ diffusion ■ endovascular therapy ■ magnetic resonance imaging ■ reperfusion ■ stroke

The aim of acute stroke treatment is to rescue hypoperfused but still viable brain tissue using intravenous thrombolysis (IVT), endovascular treatment, or bridging IVT and endovascular treatment. Nonviable tissue, that is, the infarct core of acute stroke can be determined approximately with diffusion-weighted magnetic resonance (MR) imaging (DWI). Several studies in conservatively treated stroke patients found large initial DWI lesion volumes as an independent predictor of poor outcome,1–9 whereas others did not find such an association.10–12 In patients treated with IVT or endovascular treatment, large initial DWI lesions also predicted poor outcome13–22 except in 1 study.23

Few endovascular treatment studies analyzed the outcome after treatment of stroke with large (>70 mL) DWI lesions. They all observed low rates of favorable outcome ranging from 0% to 17%.23–25

Although the reported number of treated patients with large DWI lesions is low, large DWI lesion volumes have become a reason to exclude such patients from acute stroke therapy in both clinical routine and studies. In the Diffusion
Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2 (DEFUSE-2) and Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA) trial, DWI lesion volumes >70 mL and in SWIFT PRIME trial >50 mL were an exclusion criterion. The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial excluded patients with Alberta Stroke Program Early CT (ASPECT) scores ≤6 on computed tomography, and the Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours (REVASCAT) trial patients with ASPECT scores <7 on computed tomography or ≤6 on magnetic resonance imaging (MRI).

The aim of this study was to analyze the efficacy and safety of endovascular treatment patients with lesion volumes >70 mL.

Patients and Methods

Patients and Treatment

This study includes patients of the Bernese stroke registry, a prospectively collected database. Some of its aspects have been reported previously.31–34 Patients were included in this analysis if (1) diagnosis of ischemic stroke was established with MRI before treatment, (2) they underwent endovascular treatment or bridging IVT and endovascular treatment, (3) they had an occlusion of the internal carotid artery or middle cerebral artery, and (4) MR was recorded into the picture archiving and communication system (as performed since 2004).

The treating neurologist and neuroradiologist decided whether to perform endovascular treatment on a case-to-case basis in view of the patient’s age, past medical history, severity of stroke, and radiological findings. In particular, endovascular treatment was usually withheld if there was no relevant diffusion–perfusion mismatch on MRI or if the T2-weighted spin-echo images revealed large areas of hyperintense T2 signal. All patients underwent 4-vessel diagnostic digital subtraction angiography. Reperfusion was graded by thrombolysis in cerebral infarction (TICI) perfusion scale scores retrospectively by 2 neuroradiologists blinded for clinical data (K.H., P.M.). Disagreements in scoring were resolved by discussion.

Age, sex, medication, National Institutes of Health Stroke Scale (NIHSS), time from symptom onset to treatment, atrial fibrillation, diabetes mellitus, hypertension, hypercholesterolemia, previous stroke, smoking, occlusion type, treatment type, reperfusion after endovascular treatment, and sICH, was used to determine the predictors of clinical outcome, survival, and bleeding complications. Subgroup analysis was performed for patients with lesions >70 mL. A P value <0.05 was considered significant. Logistic regression analysis with age and DWI lesion volume as factors was used to calculate the predicted probability of favorable outcome for each patient.

MRI Methods and Image Analysis

Pretreatment MRI was performed using a 1.5T or 3T MR imaging system (Magnetom, Siemens). The MRI protocol included whole brain DWI (b=1000, 24 slices, thickness=5 mm, repetition time=3200 ms, echo time=87 ms, number of averages=2, matrix size=256x256) yielding isotropic b0 and b1000, as well as apparent diffusion coefficient (ADC) maps that were calculated automatically. Apparent diffusion coefficient maps were calculated according to the exponential relation S(b)=S(0) exp(–b·ADC), where S(b) is the signal intensity using diffusion weighting with the value b, and S(0) is the signal intensity with b=0. Segmentation of the DWI lesion volumes was performed with the java software SCANalyze Version 5.1.r668.35 DWI lesion volumes were calculated using semiautomated thresholding with adjustable SD of pixel values to identify hyperintense regions of interest.

A computed tomography or MRI scan was obtained 24 to 72 hours after treatment or in any case of clinical deterioration. Symptomatic (sICH) and asymptomatic intracerebral hemorrhage were graded according to the definition of the Intra-arterial Prourokinase for Acute Ischemic Stroke (PROACT II) Study.36

The study was performed with approval of the local ethic committee.

Statistical Analysis

Statistical analysis was performed using SPSS 21 (SPSS Inc., Chicago, IL). Bivariate analysis of categorical variables was performed with χ2 and Fisher exact test as appropriate and continuous variables with Mann–Whitney test. Outcome was dichotomized into favorable (mRS score, 0–2) or poor clinical outcome (mRS score, 3–6) and reperfusion as seen on digital subtraction angiography into good/successful (TICI grades 2b–3) or poor reperfusion (TICI grades 0–2a). Forward stepwise logistic regression, including all variables with P<0.2 in bivariate analysis (age, sex, time to thrombolysis, NIHSS score on admission, DWI lesion volume [square root transformed to achieve normal distribution], atrial fibrillation, diabetes mellitus, hypertension, hypercholesterolemia, previous stroke, smoking, occlusion type, treatment type, reperfusion after endovascular treatment, and sICH), was used to determine the predictors of clinical outcome, survival, and bleeding complications. Subgroup analysis was performed for patients with lesions >70 mL. A P value <0.05 was considered significant. Logistic regression analysis with age and DWI lesion volume as factors was used to calculate the predicted probability of favorable outcome for each patient.

Table 1. Baseline Characteristics and Outcome of 372 Patients After Endovascular Treatment

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (SD)</td>
<td>66.3 (14.3)</td>
</tr>
<tr>
<td>Women</td>
<td>173 (46.5%)</td>
</tr>
<tr>
<td>Vascular risk factors (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>222/369 (60.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>57/370 (15.4)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>138/325 (42.5)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>84/362 (23.2)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>198/365 (54.2)</td>
</tr>
<tr>
<td>Baseline NIHSS score, median (range)</td>
<td>14 (0–36)</td>
</tr>
<tr>
<td>Occlusion localization (%)</td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>106 (28.5)</td>
</tr>
<tr>
<td>MCA</td>
<td>266 (71.5)</td>
</tr>
<tr>
<td>Intra-arterial thrombolysis type (%)</td>
<td></td>
</tr>
<tr>
<td>Urokinase with or without mechanical procedures</td>
<td>204 (54.8)</td>
</tr>
<tr>
<td>Mechanical only</td>
<td>103 (27.7)</td>
</tr>
<tr>
<td>Any mechanical procedure</td>
<td>271 (73.0)</td>
</tr>
<tr>
<td>Solitaire stent retriever</td>
<td>135/271 (49.8)</td>
</tr>
<tr>
<td>Bridging therapy (intravenous thrombolysis and EVT)</td>
<td>65 (17.5)</td>
</tr>
<tr>
<td>Minutes from symptom onset to treatment, median (range)</td>
<td>270 (45–943)</td>
</tr>
<tr>
<td>Reperfusion and outcome (%)</td>
<td></td>
</tr>
<tr>
<td>Reperfusion TICI 2b-3</td>
<td>186 (50)</td>
</tr>
<tr>
<td>mRS score 0–2</td>
<td>173/358 (48.3)</td>
</tr>
<tr>
<td>Survival</td>
<td>286/358 (79.9)</td>
</tr>
<tr>
<td>Complications (%)</td>
<td></td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>22/370 (5.9)</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>83/370 (22.4)</td>
</tr>
</tbody>
</table>

n (%): 372 patients if not stated otherwise. EVT indicates endovascular treatment; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; and TICI, thrombolysis in cerebral infarction perfusion scale.
Figure 1. A, Percentage of favorable outcome (modified Rankin Scale [mRS] score, 0–2) in dependence of diffusion-weighted imaging (DWI) lesion volume and reperfusion success. B, Functional outcome at 3 months according to the mRS in dependence of reperfusion success in patients with DWI lesions <70 or >70 mL.
In patients with lesions <70 mL, 157 of 280 (56.1%) patients without and 1 of 9 (11.1%) patients with sICH reached favorable outcome. In patients with lesions >70 mL, 14 of 53 (26.4%) patients without but none of 13 patients with sICH reached favorable outcome.

The percentages of successful reperfusion, sICH, and favorable outcome in dependence of the treatment type in patients with DWI lesions >70 mL are illustrated in Figure 2. More patients with bridging therapy had sICH compared with patients with only mechanical procedures ($P=0.047$) in univariate analysis, and there was a trend for more sICH in patients treated with urokinase compared with patients with only mechanical procedures ($P=0.141$), but treatment type was not an independent predictor of sICH or favorable outcome in multivariable regression analysis.

In multivariable regression analysis, reperfusion success, age, and smaller DWI lesion volumes were independent predictors for favorable outcome in patients with DWI lesions >70 mL (Table 2).

One hundred sixty-six of 319 (52%) patients with DWI lesion volumes <100 mL reached favorable outcome and 265 survived (83.1%), whereas 7 of 39 patients with volumes >100 mL ($P<0.001$) had a favorable outcome and 21 survived (53.8%). There was a trend for better outcomes in patients with DWI volumes >100 mL after TICI 2b-3 reperfusion (5/15, 33.3%) compared with TICI 0-2a reperfusion (2/24, 8.3%; $P=0.085$). Survival rates were similar among TICI 2b-3 and TICI 0-2a reperfusion groups.

Results of Multivariable Regression Analysis

Table 2. Results of Multivariable Regression Analysis

<table>
<thead>
<tr>
<th>Predicting Factor</th>
<th>$P$ Value</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS score 0–2</td>
<td>&lt;0.001</td>
<td>0.807</td>
<td>0.726–0.897</td>
</tr>
<tr>
<td>DWI lesion volume</td>
<td>&lt;0.001</td>
<td>0.933</td>
<td>0.911–0.955</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>0.057</td>
<td>0.007–0.493</td>
</tr>
<tr>
<td>sICH</td>
<td>&lt;0.001</td>
<td>2.914</td>
<td>1.666–5.037</td>
</tr>
<tr>
<td>Reperfusion TICI 2b-3</td>
<td>&lt;0.001</td>
<td>0.858</td>
<td>1.080–9.010</td>
</tr>
<tr>
<td>NIHSS</td>
<td>&lt;0.001</td>
<td>0.022</td>
<td>1.284–1.590</td>
</tr>
<tr>
<td>Occlusion location</td>
<td>0.008</td>
<td>0.997</td>
<td>0.995–0.999</td>
</tr>
<tr>
<td>Age</td>
<td>0.009</td>
<td>1.284</td>
<td>1.036–1.590</td>
</tr>
</tbody>
</table>

Results

Baseline characteristics, treatment details, and outcome of the 372 included patients are listed in Table 1. Internal carotid artery was occluded in 106 patients and middle cerebral artery in 266 patients. The frequency of favorable outcome in dependence of DWI lesion volumes (50 mL groups) and reperfusion success is demonstrated in Figure 1A. In multivariable logistic regression analysis, the increasing DWI lesion volume was a negative predictor of favorable outcome ($P<0.001$; odds ratio, 0.807; 95% confidence interval, 0.726–0.897), survival ($P<0.001$; odds ratio, 0.795; 95% confidence interval, 0.714–0.866), and positive predictor of sICH ($P<0.001$; odds ratio, 1.310; 95% confidence interval, 1.162–1.476; Table 2).

Reperfusion success, outcome, and bleeding complications for patients with DWI lesion volumes >70 or <70 mL and >100 or <100 mL are listed separately in Tables 3 and 4 and in Figure 1B. Favorable outcome was reached in 159 of 292 (54.5%) patients with lesions <70 mL and in 14 of 66 (21.2%) patients with lesions >70 mL ($P<0.001$), and 251 of 663 (38.4%) patients with lesions >100 mL ($P<0.001$) had a favorable outcome and 205 survived (63.3%). There was a trend for more sICH in patients treated with urokinase compared with patients with only mechanical procedures ($P=0.141$), but treatment type was not an independent predictor of sICH or favorable outcome in multivariable regression analysis.

Discussion

The main finding of this study is that, despite growing risk for poor outcome and sICH with increasing pretreatment DWI lesion volume, >70 mL >70 mL

Table 3. Bleeding Complications, 3-Month Outcome, and Effect of Reperfusion of 372 Patients With Diffusion-Weighted Imaging Lesion Volumes of <70 and >70 mL

<table>
<thead>
<tr>
<th>Value</th>
<th>&lt;70 mL</th>
<th>&gt;70 mL</th>
<th>$P$ Value Univariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>306</td>
<td>66</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>67 (14.2)</td>
<td>63.3 (14.7)</td>
<td>...</td>
</tr>
<tr>
<td>ICA/MCA</td>
<td>87/219</td>
<td>19/47</td>
<td>...</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>155 (50.7%)</td>
<td>31 (47%)</td>
<td>0.684</td>
</tr>
<tr>
<td>mRS score 0–2 (%)</td>
<td>0.013</td>
<td>0.094</td>
<td>0.973</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>63/149 (42.3)</td>
<td>3/35 (8.6)</td>
<td>&lt;0.001 for &lt;70 mL</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>96/143 (67.1)</td>
<td>11/31 (35.5)</td>
<td>0.014 for &gt;70 mL</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>251/292 (86)</td>
<td>35/66 (53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>118/149 (79.2)</td>
<td>15/35 (42.9)</td>
<td>0.001 for &lt;70 mL</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>133/143 (93)</td>
<td>20/31 (64.5)</td>
<td>0.090 for &gt;70 mL</td>
</tr>
<tr>
<td>sICH (%)</td>
<td>9/304 (3)</td>
<td>13/66 (19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>4/149 (2.7)</td>
<td>8/35 (22.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>5/154 (3.2)</td>
<td>5/31 (16.1)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; mRS, modified Rankin Scale; MCA, middle cerebral artery; sICH, symptomatic intracerebral hemorrhage; and TICI, thrombolysis in cerebral infarction perfusion scale.
lesion volumes on MRI, favorable outcome was observed in every third patient with DWI lesions >70 mL when endovascular reperfusion was successful. However, when reperfusion was poor or failed, outcome was favorable in only every 12th patient. In patients with DWI lesion volumes >100 mL, outcome rates after reperfusion were similar to patients with lesion volumes >70 mL. We found successful reperfusion, younger patient age, and smaller DWI lesion volume as independent predictors of favorable outcome in patients with DWI lesions >70 mL. Therefore, endovascular treatment might be considered in patients with large DWI lesions, especially in younger patients.

Several studies found larger initial DWI lesions in acute stroke to be associated with higher risk for poor outcome after IVT or endovascular treatment. In accordance with these results, we found the initial DWI lesion volume as an independent predictor of unfavorable outcome and survival in our 372 patients at 3 months after endovascular treatment (Table 2). In addition, larger DWI lesions heralded a higher risk of developing sICH, which is also in accordance with previous studies.

Only few studies reported on the outcome after treatment of patients with large initial DWI lesions: the DEFUSE study empirically defined an infarct core of >100 mL DWI lesion as malignant profile and only 1 of 6 patients in this group reached a favorable outcome. A more recent study found even poor outcome in all 6 patients treated with endovascular treatment who had an initial DWI lesion volume of >70 mL, despite reperfusion had been reached in 3 of them. The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) trial reported favorable outcome in 5 of 30 treated patients of the nonpenumbral group who had a mean predicted core infarct volume of 122.8 mL (inversion recovery, 96.9–171.4 mL). In concordance with the 17% favorable outcome rate in the DEFUSE study and MR-RESCUE trial, we observed favorable outcome in 18% of our 39 patients with lesions >100 mL and 21% of 66 patients with lesions >70 mL. However, when reperfusion is taken into account, favorable outcome was achieved in every third patient with DWI lesions >70 mL after successful endovascular reperfusion (TICI 2b-3), whereas only every 12th patient reached favorable outcome after poor or failed reperfusion (Tables 3 and 4; Figure 1B). Outcome after successful reperfusion was even similar in patients with DWI lesion volumes >100 mL. Reperfusion success, younger patient age, and smaller DWI lesion volume were independent predictors for favorable outcome in patients with large DWI lesions.

### Table 4. Bleeding Complications, 3-Month Outcome, and Effect of Reperfusion of 372 Patients With Diffusion-Weighted Imaging Lesion Volumes of <100 and >100 mL

<table>
<thead>
<tr>
<th></th>
<th>&lt;100 mL</th>
<th>&gt;100 mL</th>
<th>P Value Univariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>333</td>
<td>39</td>
<td>...</td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>67.1 (14.2)</td>
<td>60.2 (13.7)</td>
<td>...</td>
</tr>
<tr>
<td>ICA/MCA</td>
<td>92/241</td>
<td>14/25</td>
<td>...</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>171 (51.4%)</td>
<td>15 (38.5%)</td>
<td>0.175</td>
</tr>
<tr>
<td>mRS score 0–2 (%)</td>
<td>166/319 (52)</td>
<td>7/39 (17.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>64/160 (40)</td>
<td>2/24 (8.3)</td>
<td>&lt;0.001 for &lt;100 mL</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>102/159 (64.2)</td>
<td>5/15 (33.3)</td>
<td>0.085 for &gt;100 mL</td>
</tr>
<tr>
<td>Survival (%)</td>
<td>265/319 (83.1)</td>
<td>21/39 (53.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>122/160 (76.3)</td>
<td>11/24 (45.8)</td>
<td>0.002 for &lt;100 mL</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>143/159 (89.9)</td>
<td>10/15 (66.7)</td>
<td>0.323 for &gt;100 mL</td>
</tr>
<tr>
<td>sICH (%)</td>
<td>15/331 (4.5)</td>
<td>7/39 (17.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>TICI 0-2a</td>
<td>7/160 (4.4)</td>
<td>5/24 (20.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>TICI 2b-3</td>
<td>8/169 (4.7)</td>
<td>2/16 (12.5)</td>
<td>0.210</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin Scale; sICH, symptomatic intracerebral hemorrhage; and TICI, thrombolysis in cerebral infarction perfusion scale.

Figure 2. Percentage of successful reperfusion, symptomatic intracerebral hemorrhage (sICH), and favorable outcome in dependence of treatment type in patients with diffusion-weighted imaging lesions >70 mL. mRS indicates modified Rankin Scale.
patients with DWI lesions >70 mL. After successful reperfu-
sion in patients with DWI lesions >70 mL, 7 of 12 (58.3%) pa-
tients <60 years and 4 of 10 (40%) patients aged between
60 and 75 years reached favorable outcome, whereas none of
the nine patients >75 had a favorable outcome. The important
influence of the patient’s age with regard to large DWI lesions
has also been noted by Ribo et al14 who found decreased
target DWI lesion cutoff values for favorable outcome with
increasing age. The influence of reperfusion and age on out-
come in dependence of DWI lesion volume is demonstrated in
Figure I in the online-only Data Supplement.

Beside the patient’s age, another factor limiting the chance
for favorable outcome in patients with large lesions is the
high percentage of sICH. Thirteen of 66 (19.7%) patients
with lesions >70 mL had sICH and none of them reached a
favorable outcome. The risk of sICH might be influenced by
the therapy type as demonstrated in Figure 2, which shows a
trend for more sICH after bridging therapy and urokinase
application in comparison with mechanical procedures only.
Nevertheless, treatment type was not an independent predictor
of sICH or favorable outcome, but this might be explained by
the small number of patients and sICH and therefore a firm
conclusion cannot be drawn.

Although the rates for favorable outcome in patients with
DWI lesions >70 mL are better than expected, we cannot at-
tribute this unequivocally to the treatment effect of endovas-
cular treatment, on one hand because this is a retrospective
comparison of selected patients and on the other hand because
of the lack of an untreated control group. There is only 1 study
in patients treated with IVT that analyzed the treatment effect
compared with placebo in dependence of the initial DWI
lesion volumes.15 In this study, a benefit of IVT over placebo
in regard to excellent outcome (mRS score, 0–1) was seen
only in patients with DWI lesion volumes ≤25 mL. Given the
high frequency of proximal vessel occlusions in patients
with large DWI lesions and the low recanalization rates after
IVT of proximal vessel occlusions41,42 in contrast to endo-
vascular therapy,43 a substantially higher upper DWI lesion
volume limit for a treatment effect of endovascular treat-
ment may be hypothesized. This assumption is supported by
a subgroup analysis of the SWIFT PRIME study that proved
a treatment effect of endovascular therapy over IVT also in
patients with ASPECT scores of 6 to 7 indicating markedly
larger DWI lesion volumes ≥25 mL, although there is no
exact correlation between ASPECT scores and DWI lesion
volumes.28 ASPECT scores 4 to 6 correspond to a mean DWI
volume of 66 mL.44

As demonstrated by our data and the receiver operating
characteristics curve in the Figure II in the online-only Data
Supplement, no reasonable cutoff value of DWI lesion vol-
ume can be identified that would allow accurate prediction
of outcome after treatment. The difficulty to define such a
value is also expressed by the wide range of proposed cut-
off values ranging from 13.7 to 80 mL in previous IVT stud-
ies.16,17 Therefore, we refrain from defining a simple cutoff
value for DWI lesion volumes to select or deselect patients
for treatment. To decide for or against treatment of a patient
with a large DWI lesion volume, additional factors such as the
patient’s age have to be considered.

The most important limitations of our study are its retro-
spective character and the lack of an untreated control group.
In addition, our study heralds a selection bias. We tended to
select more young patients with large DWI lesions for treat-
ment, which may have contributed to the relatively high rate
of favorable outcome of our successfully reperfused patients
with large DWI lesions.

In conclusion, our data indicate that patients with large
DWI lesion volumes should not be strictly excluded from
devascular treatment, as favorable outcome was achieved in
every third patient with DWI lesion volumes >70 mL after
successful endovascular reperfusion. Especially younger
patients with large initial DWI lesions may benefit from endo-
vascular treatment and the avoidance of thrombolytic agents
might reduce the risk of sICH. Nevertheless, further studies
are needed to validate the treatment effect and to optimize
patient selection.

Acknowledgments
We thank Pietro Ballinari for his statistical advice.

Disclosures
Dr Arnold received honoraria for advisory boards from Boehringer
Ingelheim, Bayer, BMS, and Coviden and speaker’s honoraria from
Boehringer Ingelheim, Bayer, BMS, and Coviden. Dr Gralla re-
ceived honoraria as consultant for Coviden. The other authors report
no conflicts.

References
1. Thijs VN, Landsberg MG, Beaulieu C, Marks MP, Moses ME, Albers
GW. Is early ischemic lesion volume on diffusion-weighted imaging
an independent predictor of stroke outcome? A multivariable analysis.
2. Warach S, Dashe JF, Edelman RR. Clinical outcome in ischemic
stroke predicted by early diffusion-weighted and perfusion magnetic
3. Lövblad KO, Baird AE, Schlaug G, Benfield A, Siewert B, Voetsch B,
et al. Ischemic lesion volumes in acute stroke by diffusion-weighted mag-
netic resonance imaging correlate with clinical outcome. Ann Neurol.
4. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D,
et al. Prediction of stroke outcome with echoplanar perfusion- and dif-
Diffusion-weighted magnetic resonance imaging in acute stroke. Stroke.
et al. A three-item scale for the early prediction of stroke recovery.
7. Schellinger PD, Fiebach JB, Jansen O, Ringleb PA, Mehr A, Steiner T,
et al. Stroke magnetic resonance imaging: a preliminary analysis.
199601000-00006.
volume on apparent diffusion coefficient maps correlates with length of
stay and outcome after middle cerebral artery artery stroke. Cerebrovasc
9. Hand PJ, Wardlaw JM, Rivers CS, Armitage PA, Bastin ME, Lindley
RI, et al. MR diffusion-weighted imaging and outcome prediction after
wnl.0000202524.43850.81.
The clinical significance of diffusion-weighted MR imaging in infratentorial


Younger Stroke Patients With Large Pretreatment Diffusion-Weighted Imaging Lesions May Benefit From Endovascular Treatment
Marc D. Gilgen, Dariusz Klimek, Kai T. Liesirova, Julia Meisterernst, Pascal P. Klinger-Gratz, Gerhard Schroth, Pasquale Mordasini, Kety Hsieh, Johannes Slotboom, Mirjam R. Heldner, Anne Broeg-Morvay, Marie-Luise Mono, Urs Fischer, Heinrich P. Mattle, Marcel Arnold, Jan Gralla, Marwan El-Koussy and Simon Jung

Stroke. 2015;46:2510-2516; originally published online August 6, 2015;
doi: 10.1161/STROKEAHA.115.010250

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 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/46/9/2510

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/08/07/STROKEAHA.115.010250.DC1

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/
SUPPLEMENTAL MATERIAL

Online supplemental Figure I. Predicted probability for favorable outcome after 3 months in dependence of the pretreatment DWI lesion volume and patients age in 174 patients with TICI 2b-3 reperfusion.
Online supplemental Figure II. Receiver operating characteristics curve for predicting favorable outcome at 3 months in 174 patients with TICI 2b-3 reperfusion.