Severe Renal Impairment Is Associated With Symptomatic Intracerebral Hemorrhage After Thrombolysis for Ischemic Stroke

Serdar Tütüncü, MD*; Annerose M. Ziegler, MD*; Jan F. Scheitz, MD; Torsten Slowinski, MD; Andrea Rocco, MD; Matthias Endres, MD; Christian H. Nolte, MD

Background and Purpose—Patients with renal impairment (RI) have an increased risk of both thrombotic and hemorrhagic events. We aimed to clarify whether RI increases the risk of intracerebral hemorrhage (ICH) after intravenous thrombolysis with recombinant tissue plasminogen activator.

Methods—Patients who received intravenous thrombolysis with recombinant tissue plasminogen activator within 4.5 hours of symptom onset were retrospectively analyzed. Creatinine levels on admission served to calculate glomerular filtration rate (GFR) to estimate RI according to International Classification of Diseases criteria. Effect of RI on symptomatic ICH (sICH) was assessed using dichotomized (GFR <90 and <30 mL/min) and continuous GFR (centered data to test for linear and centered and squared data to test for curvilinear association).

Results—Of the 740 patients included, 83% had any RI (GFR <90 mL/min) and 5% had severe RI (GFR <30 mL/mL); 4.6% experienced sICH. Univariate comparisons revealed higher prevalence of sICH in patients with severe RI (P<0.01) but not with any RI. GFR as a continuous variable (centered and squared) was also associated with sICH (P=0.02), but GFR on its own was not. Severe RI and GFR (centered and squared) remained independently associated with sICH in multiple regression analyses.

Conclusions—Severe RI (GFR <30 mL/min) is associated with sICH after intravenous thrombolysis with recombinant tissue plasminogen activator. The association is curvilinear. Severe RI must be taken into account when balancing the risk–benefit ratio of intravenous thrombolysis with recombinant tissue plasminogen activator. (Stroke. 2013;44:3217-3219.)

Key Words: acute renal failure ■ cerebral hemorrhage ■ stroke ■ thrombolytic therapy

Intravenous thrombolysis with recombinant tissue plasminogen activator (iv-tPA) is the only approved treatment for acute ischemic stroke. However, iv-tPA increases the risk of symptomatic intracranial hemorrhage (sICH). Recently, several risk scores have been proposed to assess the risk of sICH. These scores included age, sex, stroke severity quantified by the National Institutes of Health Stroke Scale (NIHSS), baseline blood sugar, early infarct signs, systolic blood pressure, history of hypertension, body weight, onset-to-treatment time (OTT), and pretreatment with antiplatelet drugs.

Although renal impairment (RI) is common in patients with stroke, only a few studies investigated whether RI influences the risk of sICH. Patients with low glomerular filtration rate (GFR) are known to have endothelial and platelet dysfunction and are at risk for both thrombotic and hemorrhagic events. In this study, we investigated the association between RI and prevalence of sICH in patients with stroke receiving iv-tPA.

Study Population

All patients with stroke who received iv-tPA within 4.5 hours of symptom onset at our institution between January 2005 and August 2012 were included. Iv-tPA was administered according to European license. The register has been described in detail elsewhere. Serum creatinine levels (mmol/L) were measured for each patient on admission. Renal function was assessed by estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Patients on dialysis were excluded. GFR values were dealt with as (1) centered data (cGFR) to test for linear association, (2) centered and squared data (csGFR) to test for curvilinear association, and (3) dichotomized data. Categorization was according to International Classification of Diseases for RI: no RI (GFR ≥90 mL/min), mild RI (GFR=60–89 mL/min), moderate RI (GFR=50–59 mL/min), and severe RI (GFR <30 mL/min). For univariate comparisons, GFR was dichotomized at 90 mL/min (any RI) and 30 mL/min (severe RI).

Sociodemographic data, vascular risk factors, laboratory data, medication, OTT, and NIHSS were collected from the medical records. Outcome measures were sICH defined according to the European Cooperative Acute Stroke Study (ECASS) criteria (any

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ICH ≤36 hours and NIHSS worsening by ≥4)1 and radiologically detected type 1 and type 2 parenchymal hemorrhage (anyPH) within 36 hours after thrombolysis.

Statistical Analysis
For univariate analyses, 2-sided Pearson $\chi^2$ test was used. Continuous data were demonstrated as median and interquartile range, and Mann–Whitney $U$ test was applied for univariate analyses. Multivariable logistic stepwise regression analyses were used to test for independent associations with sICH and anyPH. Adjustment was made for variables associated with sICH or anyPH with $P<0.1$ in univariate comparisons, including cGFR, csGFR, and dichotomized GFR (severe RI). Sensitivity analyses included adjustment for variables suggested by the literature (history of hypertension, pretreatment with antiplatelet drugs, NIHSS, OTT, age, baseline blood sugar, and systolic blood pressure). Statistical analyses were performed using SPSS 19.

Results
The definition of the study population is shown in Figure 1. Among the 740 patients analyzed, 391 (53%) were men, median [interquartile range] age was 75 [66–83] years, median NIHSS on admission was 9 [5–16], median OTT was 120 [95–162.5] minutes, and median GFR was 66.95 [49.73–84.68] mL/min. sICH occurred in 34 (4.6%) and anyPH in 48 (6.5%) patients. RI based on GFR was absent in 124 (17%), mild in 336 (45%), moderate in 241 (33%), and severe in 39 (5%) patients.

Prevalence of both sICH and anyPH showed a steep increase in patients with severe RI compared with patients with no, mild, and moderate RI (Figure 2). Univariate comparison did not suggest higher sICH rates in patients with any RI. For baseline parameters see the online-only Data Supplement.

There was no significant linear association between cGFR and sICH or anyPH. But csGFR was indeed associated with sICH ($P=0.02$), suggesting a curvilinear association with an increase of sICH/anyPH in patients with low GFR. Additional variables suggesting association with sICH because of univariate comparisons with $P<0.1$ were older age, history of hypertension, and pretreatment with antiplatelet drugs.

Severe RI and csGFR remained independently associated with sICH after adjustment for these 3 variables (odds ratio$\text{severe RI}=3.75$, 95% confidence interval [1.44–9.80]; odds ratio$\text{csGFR}=1.56$, 95% confidence interval [1.13–2.15]; $P<0.01$ for both). Furthermore, severe RI and csGFR both remained independently associated with sICH after additionally adjusting for further variables suggested by the literature: NIHSS, baseline blood glucose, OTT, and systolic blood pressure (odds ratio$\text{severe RI}=3.80$, 95% confidence interval [1.45–9.96]; odds ratio$\text{csGFR}=1.61$, 95% confidence interval [1.16–2.23]; $P<0.01$ for both).

Discussion
This retrospective cohort study did not find an increased risk for sICH after iv-tPA in acute stroke patients with any RI. Nevertheless, our findings did suggest an increased risk for sICH in patients with severe RI (<30 mL/min). This finding was robust in 2 alternative multivariable regression analyses adjusted for various confounding factors and was supported by a third using continuous GFR, suggesting a curvilinear association with low GFR.

Patients with severe RI are indeed at an increased risk of any bleeding, including spontaneous sICH. This increased risk may partly be mediated by endothelial and platelet dysfunction.9 Patients with RI may have more severe white matter disease, which may facilitate sICH after iv-tPA as well.10

Severe RI is not included in current risk scores to assess rt-PA–associated sICH.4,6 Previous data from observational studies are scarce and conflicting. Most of these studies did not show a significant association of RI with sICH. However, the studies lacked appropriate sample size and used different cutoffs for dichotomization.11–13 The largest previous study (N=578) originates from Japan, where rt-PA is administered at a lower dose (0.6 mg/kg BW). It demonstrated an increased risk for sICH in patients with moderate RI (GFR <60 mL/min). But Japanese patients might be more prone to sICH.

Figure 1. Derivation of study population.

Figure 2. Frequency of symptomatic intracerebral hemorrhage (sICH) and radiologically detected type 1 and type 2 parenchymal hemorrhage (anyPH) according to the severity of renal impairment.
per se. It is questionable to transfer the results directly to a white population. Our findings suggest a lower cutoff (GFR <30 mL/min) here.

Certain limitations of the study have to be considered. First, although all other variables identified to show an association with a higher risk of sICH are consistent with the current literature, we could not adjust for imaging criteria such as severity of white matter disease. Second, this is a single-center study restricting generalization. Third, GFR was calculated on the basis of one serum creatinine taken on admission only. Equations for estimating GFR do not account for potential dynamics in ongoing acute kidney injury. Thus, it was not possible to differentiate chronic renal disease from acute kidney injury. Finally, applying iv-tPA in patients with severe RI may still be better than withholding it.

Summary
Severe RI (GFR <30 mL/min) is associated with sICH after iv-tPA. The association is curvilinear. Severe RI must be taken into account when balancing the risk–benefit ratio of iv-tPA. Severe RI should be considered for future risk scores.

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Disclosures
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References
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Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/09/03/STROKEAHA.113.002859.DC1
### Table 1: All baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>sICH yes</th>
<th>sICH no</th>
<th>p</th>
<th>anyPH (PH1+PH2) yes</th>
<th>anyPH (PH1+PH2) no</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male % (n)</td>
<td>50% (17)</td>
<td>53% (374)</td>
<td>0.80</td>
<td>58% (28)</td>
<td>52% (363)</td>
<td>0.41</td>
</tr>
<tr>
<td>Age, Median [IQR]</td>
<td>79 [69-86]</td>
<td>74 [66-83]</td>
<td>0.05</td>
<td>77.5 [69-85]</td>
<td>74 [66-83]</td>
<td>0.14</td>
</tr>
<tr>
<td>NIHSS o.A.* ≥ 10, % (n)</td>
<td>53% (18)</td>
<td>50% (353)</td>
<td>0.72</td>
<td>58% (28)</td>
<td>49% (343)</td>
<td>0.23</td>
</tr>
<tr>
<td>Adm. from a nursing home, % (n)</td>
<td>14% (4)</td>
<td>12% (82)</td>
<td>0.74</td>
<td>10% (4)</td>
<td>12% (82)</td>
<td>0.63</td>
</tr>
<tr>
<td>Arterial Hypertension, % (n)</td>
<td>94% (32)</td>
<td>82% (585)</td>
<td>0.08</td>
<td>94% (45)</td>
<td>82% (572)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes Mellitus, % (n)</td>
<td>27% (9)</td>
<td>25% (180)</td>
<td>0.88</td>
<td>29% (14)</td>
<td>25% (175)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hyperlipoproteinemia, % (n)</td>
<td>48% (15)</td>
<td>48% (331)</td>
<td>0.93</td>
<td>56% (25)</td>
<td>47% (321)</td>
<td>0.27</td>
</tr>
<tr>
<td>Atrial fibrillation, % (n)</td>
<td>47% (16)</td>
<td>40% (284)</td>
<td>0.42</td>
<td>48% (23)</td>
<td>40% (277)</td>
<td>0.27</td>
</tr>
<tr>
<td>Previous Stroke or TIA †, %, (n)</td>
<td>15% (5)</td>
<td>24% (171)</td>
<td>0.21</td>
<td>21% (10)</td>
<td>24% (166)</td>
<td>0.63</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>15% (5)</td>
<td>22% (159)</td>
<td>0.29</td>
<td>15% (7)</td>
<td>23% (157)</td>
<td>0.18</td>
</tr>
<tr>
<td>OTT ‡ ≤ 180 Minutes, % (n)</td>
<td>91% (31)</td>
<td>84% (596)</td>
<td>0.26</td>
<td>88% (42)</td>
<td>84% (585)</td>
<td>0.53</td>
</tr>
<tr>
<td>BP (syst.) o.A. §, mmHg, Median [IQR]</td>
<td>160 [138-172]</td>
<td>150 [134-173]</td>
<td>0.45</td>
<td>158 [135-172]</td>
<td>150 [134-172]</td>
<td>0.57</td>
</tr>
<tr>
<td>Imaging by MRI, % (n)</td>
<td>18% (6)</td>
<td>29% (209)</td>
<td>0.14</td>
<td>23% (11)</td>
<td>29% (204)</td>
<td>0.35</td>
</tr>
<tr>
<td>Glucose mmol/l, Median [IQR]</td>
<td>7 [6-7.9]</td>
<td>6.6 [5.9-7.9]</td>
<td>0.30</td>
<td>7 [5.9-8]</td>
<td>6.6 [5.9-7.9]</td>
<td>0.19</td>
</tr>
<tr>
<td>INR, Median [IQR]</td>
<td>1.06 [1.01-1.12]</td>
<td>1.04 [0.99-1.11]</td>
<td>0.51</td>
<td>1.07 [1.01-1.13]</td>
<td>1.04 [0.99-1.11]</td>
<td>0.12</td>
</tr>
<tr>
<td>Pre-treatment antithrombotic drugs, % (n)</td>
<td>65% (22)</td>
<td>44% (307)</td>
<td>0.02</td>
<td>67% (32)</td>
<td>43% (297)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pre-treatment OA †, % (n)</td>
<td>3% (1)</td>
<td>3% (23)</td>
<td>0.91</td>
<td>6% (3)</td>
<td>3 (21)</td>
<td>0.23</td>
</tr>
<tr>
<td>Severe RI †, % (n)</td>
<td>18% (6)</td>
<td>5% (33)</td>
<td>&lt;0.01</td>
<td>13% (6)</td>
<td>5% (33)</td>
<td>0.02</td>
</tr>
<tr>
<td>Any RI**, % (n)</td>
<td>85% (29)</td>
<td>83% (587)</td>
<td>0.74</td>
<td>88% (42)</td>
<td>83% (574)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

*) National Institutes of Health Stroke Scale - Score on admission, †) Transient ischemic attack, ‡) Onset to treatment time, §) Systolic blood pressure on admission, ||) Oral anticoagulants, #) Severe renal impairment = GFR < 30ml/min, * *) Any renal impairment = GFR < 90ml/min