Endovascular Stroke Therapy

Tirofiban Is Associated With Risk of Fatal Intracerebral Hemorrhage and Poor Outcome

Lars Kellert, MD; Christian Hametner, MD; Stefan Rohde, MD; Martin Bendszus, MD; Werner Hacke, PhD; Peter Ringleb, MD; Sibylle Stampfl, MD

Background and Purpose—To investigate the relationship between severe bleeding complications and outcome after mechanical thrombectomy with or without glycoprotein-IIb/IIIa inhibitor tirofiban treatment.

Methods—The study included prospectively collected data of consecutive patients with acute ischemic stroke in whom mechanical thrombectomy was performed in the years 2006 to 2011.

Results—Of 162 patients, 128 patients had anterior circulation stroke, and 34 patients had posterior circulation stroke. Additional treatment with tirofiban was given to 30 of 128 patients with anterior circulation stroke and to 20 of 34 patients with posterior circulation stroke. Treatment with tirofiban did not influence recanalization rates. Fatal intracerebral hemorrhage occurred more frequently in tirofiban-treated patients in the entire cohort (12.0% vs 2.7%; P=0.03) and in tirofiban-treated patients with anterior circulation stroke (13.3% vs 3.1%; P=0.05). Logistic regression found age (odds ratio, 1.17; 95% confidence interval, 1.00–1.37; P=0.05) and tirofiban treatment (odds ratio, 3.03; 95% confidence interval, 1.50–4.05; P=0.04) to be independent predictors for fatal intracerebral hemorrhage. Tirofiban treatment was also an independent predictor for poor outcome (odds ratio, 6.60; 95% confidence interval, 1.06–41.52; P=0.04) in addition to National Institute of Health Stroke Scale (odds ratio, 1.08; 95% confidence interval, 1.00–1.17; P=0.05).

Conclusions—In endovascular stroke therapy, additional treatment with the glycoprotein-IIb/IIIa inhibitor tirofiban is associated with increased risk of fatal intracerebral hemorrhage and poor outcome. (Stroke. 2013;44:00-00.)

Key Words: acute stroke • endovascular stroke therapy • GP-IIb/IIIa inhibitor • intracerebral hemorrhage • mechanical recanalization • thrombolysis • tirofiban

Although intravenous thrombolysis is still first-line treatment in acute ischemic stroke up to a 4.5 hour time window, endovascular treatment might be superior to intravenous thrombolysis alone to achieve large-vessel recanalization.1–3 Endovascular recanalization approaches are heterogeneous in nature, including mechanical extraction of the thrombus, angioplasty, and stenting, which all can cause endothelial damage. The glycoprotein-IIb/IIIa inhibitor tirofiban is often used in endovascular treatment to prevent thromboembolic complications and early recoclusion because of endothelial damage. Here, we aimed to identify a role of tirofiban in bleeding complications and outcome in those patients.

Methods

From our local prospective stroke database, we analyzed clinical and imaging data for all consecutive patients (n=191) who received endovascular therapy from 2006 to 2011. We excluded 8 patients in whom recombinant tissue plasminogen activator was administered intraarterially without additional mechanical intervention, 20 patients because of missing outcome or imaging data, and 1 patient who died before follow-up imaging. None of the excluded patients had a fatal intracerebral hemorrhage (ICH). Time to treatment was defined as the time from onset of stroke symptoms to start of either intravenous thrombolysis or angiography. Time to recanalization was defined as time to Thrombolysis In Cerebral Infarction score ≥2a.4 Thrombolysis In Cerebral Infarction scores 0 and 1 were presumed as unsuccessful recanalization. Early infarct signs were calculated using the Alberta Stroke Program Early CT score.5 The number of thrombectomy attempts by the recanalization device was counted as possible surrogate marker correlating to endothelial damage. Three-month outcome was assessed by the modified Rankin scale. Good outcome was defined as modified Rankin scale 0 to 2 and excellent outcome as modified Rankin scale 0 to 1. Symptomatic ICH was defined according to European Cooperative Acute Stroke Study II (ECASS 2) definition.6 Local standard operating procedures recommend delivering tirofiban, if stenting is performed or relevant endothelial damage is feared, for example, because of multiple thrombectomy passages during the recanalization procedure (additional information regarding methods are available in the Appendix in the online-only Data Supplement).

Groups were compared with the Mann–Whitney U test, the Student t test, or the Fisher exact test, where appropriate. Multivariate logistic regression model was performed to test the influence of tirofiban on fatal ICH and outcome. A P value of 0.05 was considered significant.
For all statistical testing, we used the Statistical Package for Social Science (SPSS Inc., 16.0 for Windows).

Results
Of 162 patients who received mechanical thrombectomy, 128 patients suffered from anterior circulation stroke and 34 from posterior circulation stroke. Additional treatment with tirofiban was given to 50 patients. Mean age of our patients was 66.4 (13.8) years, and median National Institute of Health Stroke Scale was 19 (15, 23). Median time to treatment was 145 minutes (94, 271; 16 unknown), median time to recanalization was 243 minutes (162, 367; 16 unknown), and 114 patients (70.4%) received bridging therapy. Complete recanalization rate (Thrombolysis In Cerebral Infarction $\geq 2b$) was 61.1%, without any differences between patients treated with or without tirofiban (Table 1). With regard to other baseline characteristics and risk factors, there were no differences between patients with anterior circulation stroke or posterior circulation stroke, and between patients treated with or without tirofiban (data available in the online-only Data Supplement Appendix).

Fatal ICH was seen more often in tirofiban-treated patients in the entire cohort (12.0% vs 2.7%; $P=0.03$) and in tirofiban-treated patients with anterior circulation stroke (13.3% vs 3.1%; $P=0.05$). Median modified Rankin scale after 3 months was 5 (3, 6) in patients treated with tirofiban and 4 (2, 6; $P=0.04$) in patients treated without tirofiban (Table 2).

Final stepwise logistic regression model found age (odds ratio, 1.17; 95% confidence interval, 1.00–1.37; $P=0.05$) and tirofiban treatment (odds ratio, 3.03; 95% confidence interval, 1.50–4.05; $P=0.04$) as independent predictors for fatal ICH. Poor outcome was independently predicted by tirofiban treatment (odds ratio, 6.60; 95% confidence interval, 1.06–41.52; $P<0.04$) and National Institute of Health Stroke Scale (odds ratio, 1.08; 95% confidence interval, 1.00–1.17; $P<0.05$; Table 3).

Discussion
The glycoprotein-IIb/IIIa inhibitor tirofiban is administered in acute stroke patients undergoing mechanical thrombectomy...
and stenting to avert the risks of thromboembolic complications caused by endothelial damage. Here, we demonstrate for the first time a significant increase of fatal ICH in stroke patients who received mechanical thrombectomy under the administration of tirofiban. Although the absolute number of patients who suffered fatal ICH is small (9 of 162) and statistical power thus limited, tirofiban treatment persists in multivariable analysis to predict fatal ICH. In addition, tirofiban treatment was independently associated with poor outcome. These observations are even more notable when considering that patients with anterior circulation stroke who received tirofiban had a lower National Institute of Health Stroke Scale and a shorter time window—both factors should favor a good outcome and lower rates of ICH. The higher rate of stenting in tirofiban-treated patients might be a confounder regarding bleeding complications, but did not reach significant prediction in our study population. Future studies may evaluate oral antiplatelet agents or lower doses of tirofiban for reduction of bleeding complications.

Given that a randomised controlled trial is unlikely to be performed on this topic, single centers should publish their data so that a meta-analysis can be conducted in the future to clarify the role of glycoprotein-IIb/IIIa inhibitors in stroke patients undergoing endovascular treatment.

**Disclosures**

Drs Bendszus and Rohde received lecture fees from Micrus/Codman Neurovascular. Drs Hacke and Ringleb received honoraria and compensations from Boehringer Ingelheim.

**References**


### Table 3. Logistic Regression to Predict Fatal ICH and Poor Outcome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Fatal ICH</th>
<th>Poor Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.17</td>
<td>0.08</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.66</td>
<td>0.05</td>
</tr>
<tr>
<td>TTT</td>
<td>0.37</td>
<td>0.85</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>3.03</td>
<td>0.04</td>
</tr>
<tr>
<td>TICI ≥ 2</td>
<td>0.99</td>
<td>0.14</td>
</tr>
<tr>
<td>Stenting</td>
<td>0.41</td>
<td>0.79</td>
</tr>
<tr>
<td>Number of passages</td>
<td>0.07</td>
<td>0.31</td>
</tr>
<tr>
<td>Anterior circulation</td>
<td>0.99</td>
<td>0.51</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; TICI, Thrombolysis In Cerebral Infarction score; and TTT, time to treatment.
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Supplemental Methods:
Our local standard operating procedures (SOP) recommend selecting patients for the endovascular recanalization approach as an individual decision and in every case as an off-label treatment following current guidelines\(^1\)\(^,\)\(^2\). The decision is mainly influenced by evidence of proximal vessel occlusion detected by computed tomography angiography (CTA) or magnet resonance angiography (MRA) plus severe acute stroke symptoms in a time window of <4.5 hours since onset of stroke symptoms (e.g. NIHSS > 10). Usually a CTA or MRA is performed when stroke severity suggests proximal vessel occlusion\(^3\). In case of severe stroke and an unknown or prolonged (e.g., >4.5h) time window, the decision for performing interventional recanalization is based on MRI according to the DWI/PWI mismatch concept and proof of vessel occlusion\(^4\). Endovascular treatment alone was performed if IVT was contraindicated. Otherwise we routinely start with IVT with a reduced dose of 0.6mg/kg while the interventional procedure is simultaneously being prepared (bridging therapy). Local SOPs recommend delivering tirofiban if stenting is performed or relevant endothelial damage is feared, e.g. because of multiple thrombectomy passages during the recanalization procedure. Continuous intravenous administration of tirofiban adapted for weight and creatinine clearance should proceed for at least 12 hours after intervention following our local SOPs. Our in-house standard favors tirofiban because it is highly selective for inhibiting GPIIb/IIIa receptors and it is rapidly eliminated after cessation of infusion due to its half-life of about 2 hours\(^5\).

Following catheters, thrombectomy devices, and stent systems were used (in some cases more than one device was deployed): solitaire® stent (n=58), revive® device (n=54), enterprise® stent (n=9), phenox clot retriever® (n=8), fastracker micro catheter® (n=8), excel micro catheter® (n=6), maverick® balloon catheter (n=6), iriss® stent (n=4), merci® retriever (n=4), carotid wallstent® (n=3), excelsior micro catheter® (n=3), gateway balloon catheter® (n=2), 6 F neuron catheter® (n=2), hyperglide balloon catheter® (n=2), driver RX-stent® (n=1), prowler select plus catheter® (n=1), rebar micro catheter® (n=1), super select micro catheter® (n=1), hyperform balloon catheter® (n=1), and pharos vitesse stent® (n=1).
Supplemental References:


## Supplemental Table: Cardiovascular risk factors according to stroke localization and treatment with Tirofiban

<table>
<thead>
<tr>
<th></th>
<th>All patients, n=162</th>
<th></th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>Tirofiban n=50</td>
<td>No Tirofiban n= 112</td>
<td>P*</td>
<td>Anterior circulation Stroke n=128</td>
<td>P*</td>
<td>Posterior circulation Stroke n=34</td>
<td>P*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tirofiban n=30</td>
<td>No Tirofiban n=98</td>
<td>Tirofiban n=20</td>
<td>No Tirofiban n=14</td>
<td></td>
</tr>
<tr>
<td>Hyper-tension</td>
<td>120 (74.1%)</td>
<td>37 (74.0%)</td>
<td>83 (74.1%)</td>
<td>1.00</td>
<td>26 (86.7%)</td>
<td>73 (74.5%)</td>
<td>11 (55.0%)</td>
<td>10 (71.4%)</td>
<td>0.48</td>
</tr>
<tr>
<td>Diabetes</td>
<td>36 (22.2%)</td>
<td>12 (24.0%)</td>
<td>24 (21.4%)</td>
<td>0.84</td>
<td>7 (23.3%)</td>
<td>21 (21.4%)</td>
<td>5 (25.0%)</td>
<td>3 (21.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hyperlipid-emia</td>
<td>52 (32.1%)</td>
<td>16 (32.0%)</td>
<td>36 (32.1%)</td>
<td>1.00</td>
<td>10 (33.3%)</td>
<td>31 (31.6%)</td>
<td>6 (30.0%)</td>
<td>5 (35.7%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Smoking</td>
<td>26 (16%)</td>
<td>10 (20.0%)</td>
<td>16 (14.3%)</td>
<td>0.36</td>
<td>7 (23.3%)</td>
<td>13 (13.3%)</td>
<td>3 (15.0%)</td>
<td>3 (21.4%)</td>
<td>0.67</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>56 (34.6%)</td>
<td>14 (28.0%)</td>
<td>42 (37.5%)</td>
<td>0.29</td>
<td>10 (33.3%)</td>
<td>38 (38.8%)</td>
<td>4 (20.0%)</td>
<td>4 (28.6%)</td>
<td>0.69</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>28 (17.3%)</td>
<td>7 (14.0%)</td>
<td>21 (18.8%)</td>
<td>0.51</td>
<td>5 (16.7%)</td>
<td>19 (19.4%)</td>
<td>2 (10.0%)</td>
<td>2 (14.3%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>43 (26.5%)</td>
<td>14 (28.0%)</td>
<td>29 (25.9%)</td>
<td>0.72</td>
<td>11 (36.7%)</td>
<td>25 (25.5%)</td>
<td>3 (15.0%)</td>
<td>4 (28.6%)</td>
<td>0.27</td>
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<tr>
<td>Peripheral artery disease</td>
<td>7 (4.3%)</td>
<td>2 (4.0%)</td>
<td>5 (4.5%)</td>
<td>0.75</td>
<td>2 (6.7%)</td>
<td>4 (4.1%)</td>
<td>0 (0%)</td>
<td>1 (7.1%)</td>
<td>0.22</td>
</tr>
</tbody>
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* Fisher’s exact Test