Early Endovascular Treatment in Intravenous Tissue Plasminogen Activator–Ineligible Patients

Letícia C. Rebello, MD; Diogo C. Haussen, MD; Jonathan A. Grossberg, MD; Samir Belagaje, MD; Andrey Lima, MD; Aaron Anderson, MD; Michael R. Frankel, MD; Raul G. Nogueira, MD

Background and Purpose—Intravenous tissue-type plasminogen activator (tPA) treatment in acute stroke has many exclusion criteria. We aimed to assess the safety and efficacy of endovascular therapy (ET) in intravenous (IV) tPA–ineligible patients.

Methods—Retrospective analysis of a prospectively collected database of consecutive patients treated with ET within 6 hours of stroke onset between September 2010 and April 2015. Patients treated with IV-tPA followed by ET were compared with those treated with ET alone because of IV-tPA ineligibility. Efficacy and safety end points included the rates of good outcome (90-day modified Rankin scale score ≤2), successful reperfusion (modified Treatment in Cerebral Ischemia 2b-3), parenchymal hematoma (PH-1 and PH-2), and 90-day mortality. Univariate and logistic regression were performed to identify the predictors of outcomes.

Results—A total of 422 patients were included. Two hundred and fifty-three (59%) patients received IV-tPA+ET, and 169 (41%) ET alone. Combined IV-tPA+ET patients were slightly younger (64.9±15.2 versus 67.9±14.9 years; P=0.05), more often males (56% versus 44%; P=0.01), and had less hypertension (70% versus 81%; P=0.02) and vertebrobasilar occlusions (3% versus 8%; P=0.02). The remaining baseline characteristics, including National Institutes of Health Stroke Scale score (20 [15–23] versus 19 [15–24]; P=0.85), Alberta Stroke Program Early CT Score (ASPECTS; 8 [7–9] versus 8 [7–9]; P=0.24), and stroke onset to puncture times (235±70 versus 240±81 minutes; P=0.27), were similar across both groups. There were no significant differences in the rates of modified Treatment in Cerebral Ischemia 2b-3 (83% versus 80%; P=0.52), 90-day modified Rankin scale score ≤2 (45% versus 38%; P=0.21), or any PH (3% versus 5%; P=0.21). Unadjusted 90-day mortality was higher with ET alone (21% versus 34%; P<0.01); however, IV-tPA ineligibility was not associated with modified Treatment in Cerebral Ischemia 2b-3, any PH, good outcome, or 90-day mortality on logistic regression.

Conclusions—IV-tPA-eligible and -ineligible patients seem to have similar outcomes after early ET. (Stroke. 2016;47:1131-1134. DOI: 10.1161/STROKEAHA.115.012586.)

Key Words: endovascular treatment ■ reperfusion ■ stroke ■ tissue-type plasminogen activator

Reperfusion therapy remains the only proven treatment for acute ischemic stroke. Intravenous tissue-type plasminogen activator (IV-tPA) has faster, easier, and broader application as compared with endovascular therapy (ET). However, its use is limited because of a ≤4.5 hour time window and other nontime based contraindications. The effects of ET in IV-tPA–ineligible patients remain poorly studied. Indeed, the recent guidelines provide limited endorsement for ET in the setting of IV-tPA ineligibility. We aimed to compare the results of ET within 6 hours of symptom onset in a large cohort of IV-tPA–ineligible patients to those patients receiving IV-tPA+ET.

Methods

Patient Selection and Group Comparisons
We performed a retrospective analysis of prospectively collected consecutive cases of thrombectomy for persistent intracranial occlusion within 6 hours of stroke onset between September 2010 and April 2015. Two patient groups were identified: IV+ET versus ET-alone because of IV-tPA ineligibility. Subjects were analyzed according to the different time epochs: (1) 0 to 6 hours, (2) 0 to 4.5 hours, and (3) 0 to 3 hours from symptom onset.

Measures of Outcome
The primary outcome measure was the rate of good outcome (modified Rankin scale score ≤2) at 90 days (±2 weeks, obtaining on follow-up visit or structured phone interview). Secondary efficacy end point was the rate of successful reperfusion (modified Treatment in Cerebral Ischemia 2b-3). The safety end points included the rate of any parenchymal hematoma (ECASS PH-1 or PH-2) and 90-day mortality. A stroke/interventional neurologist interpreted all imaging and procedural data. This study was approved by the local Institutional Review Boards.

Statistical Analysis
Between-group comparisons were made with Student t test, Mann–Whitney U test, or analysis of variance, χ², or Fisher test as appropriate. Univariate analyses for the primary and secondary outcomes...
### Table. Baseline Characteristics and Outcomes in Patients Treated With tPA+ET Versus ET in Different Time Ranges

<table>
<thead>
<tr>
<th></th>
<th>TPA+ET (n=253)</th>
<th>ET (n=169)</th>
<th>TPA+ET (n=177)</th>
<th>ET (n=102)</th>
<th>TPA+ET (n=60)</th>
<th>ET (n=40)</th>
</tr>
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<tbody>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td></td>
<td>66 (53–78)</td>
<td>72 (57–79)</td>
<td>65 (52–78)</td>
<td>68 (55–79)</td>
<td>63 (51–78)</td>
<td>64 (53–75)</td>
</tr>
<tr>
<td><strong>Sex (male)</strong></td>
<td>144 (56%)</td>
<td>76 (44%)</td>
<td>103 (58%)</td>
<td>48 (47%)</td>
<td>30 (50%)</td>
<td>23 (57%)</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>179 (70%)</td>
<td>137 (81%)</td>
<td>133 (75%)</td>
<td>85 (83%)</td>
<td>48 (80%)</td>
<td>35 (87%)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>92 (36%)</td>
<td>66 (39%)</td>
<td>68 (38%)</td>
<td>42 (41%)</td>
<td>25 (41%)</td>
<td>18 (45%)</td>
</tr>
<tr>
<td><strong>Atrial fibrillation</strong></td>
<td>100 (39%)</td>
<td>75 (44%)</td>
<td>66 (37%)</td>
<td>38 (37%)</td>
<td>23 (38%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>61 (24%)</td>
<td>45 (26%)</td>
<td>42 (23%)</td>
<td>29 (28%)</td>
<td>13 (21%)</td>
<td>15 (37%)</td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>48 (18%)</td>
<td>23 (13%)</td>
<td>33 (18%)</td>
<td>13 (12%)</td>
<td>7 (11%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>135±50</td>
<td>143±60</td>
<td>134±53</td>
<td>145±54</td>
<td>124±44</td>
<td>147±60</td>
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<tr>
<td><strong>Creatinine</strong></td>
<td>1.05±0.6</td>
<td>1.09±0.7</td>
<td>1.1±0.7</td>
<td>1.1±0.8</td>
<td>1.2±1.2</td>
<td>1.0±0.3</td>
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<tr>
<td><strong>Platelets</strong></td>
<td>213±85</td>
<td>223±94</td>
<td>218±85</td>
<td>220±89</td>
<td>227±96</td>
<td>227±91</td>
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<tr>
<td><strong>INR</strong></td>
<td>1.00±0.0</td>
<td>1.07±0.25</td>
<td>1.0±0.0</td>
<td>1.0±0.2</td>
<td>1.0±0.0</td>
<td>1.0±0.2</td>
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<tr>
<td><strong>SBP</strong></td>
<td>141±29</td>
<td>146±31</td>
<td>144±31</td>
<td>142±28</td>
<td>142±33</td>
<td>145±19</td>
</tr>
<tr>
<td><strong>Transfer OSH</strong></td>
<td>147 (58%)</td>
<td>109 (64%)</td>
<td>81 (45%)</td>
<td>58 (56%)</td>
<td>12 (20%)</td>
<td>13 (32%)</td>
</tr>
<tr>
<td><strong>bNIHSS</strong></td>
<td>20 (15–23)</td>
<td>19 (15–24)</td>
<td>20 (16–23)</td>
<td>19 (15–24)</td>
<td>21 (17–24)</td>
<td>19 (15–21)</td>
</tr>
<tr>
<td><strong>Mean time IV-tPA, min</strong></td>
<td>119 (90–160)</td>
<td>NA</td>
<td>108 (81–135)</td>
<td>NA</td>
<td>92 (69–105)</td>
<td>NA</td>
</tr>
<tr>
<td><strong>ASPECTS</strong></td>
<td>8 (7–9)</td>
<td>8 (7–9)</td>
<td>8 (7–9)</td>
<td>9 (6–9)</td>
<td>7 (7–10)</td>
<td></td>
</tr>
<tr>
<td><strong>CPT</strong></td>
<td>99 (39%)</td>
<td>73 (43%)</td>
<td>67 (37%)</td>
<td>40 (39%)</td>
<td>17 (28%)</td>
<td>16 (40%)</td>
</tr>
<tr>
<td><strong>Last normal to puncture</strong></td>
<td>235 (181–289)</td>
<td>250 (181–304)</td>
<td>207 (165–240)</td>
<td>202 (160–246)</td>
<td>150 (125–165)</td>
<td>135 (101–167)</td>
</tr>
<tr>
<td><strong>Procedure length</strong></td>
<td>66 (48–98)</td>
<td>70 (48–111)</td>
<td>64 (45–93)</td>
<td>70 (44–105)</td>
<td>61 (41–83)</td>
<td>58 (36–97)</td>
</tr>
</tbody>
</table>

**Occlusion site**

- **MCA M1**
  - TPA+ET: 141 (55%)
  - ET: 87 (51%)
  - TPA+ET: 99 (56%)
  - ET: 47 (46%)
  - TPA+ET: 35 (58%)
  - ET: 15 (37%)
- **MCA M2**
  - TPA+ET: 45 (17%)
  - ET: 25 (14%)
  - TPA+ET: 30 (17%)
  - ET: 17 (16%)
  - TPA+ET: 11 (18%)
  - ET: 9 (22%)
- **ICA-T**
  - TPA+ET: 47 (18%)
  - ET: 36 (21%)
  - TPA+ET: 34 (19%)
  - ET: 24 (23%)
  - TPA+ET: 9 (15%)
  - ET: 6 (15%)
- **Vertebrobasilar**
  - TPA+ET: 8 (3%)
  - ET: 14 (8%)
  - TPA+ET: 6 (3%)
  - ET: 11 (10%)
  - TPA+ET: 1 (1%)
  - ET: 7 (17%)
- **Tandem**
  - TPA+ET: 25 (9%)
  - ET: 20 (11%)
  - TPA+ET: 15 (8%)
  - ET: 6 (5%)
  - TPA+ET: 4 (6%)
  - ET: 2 (5%)
- **Stentriever**
  - TPA+ET: 145 (57%)
  - ET: 112 (66%)
  - TPA+ET: 109 (62%)
  - ET: 69 (67%)
  - TPA+ET: 35 (58%)
  - ET: 25 (62%)

**Reperfusion**

- **mTICI 2b-3**
  - TPA+ET: 210 (83%)
  - ET: 136 (80%)
  - TPA+ET: 147 (83%)
  - ET: 81 (79%)
  - TPA+ET: 51 (85%)
  - ET: 33 (82%)
- **mTICI 3**
  - TPA+ET: 103 (40%)
  - ET: 61 (36%)
  - TPA+ET: 77 (43%)
  - ET: 39 (38%)
  - TPA+ET: 24 (41%)
  - ET: 18 (45%)

**Hemorrhage**

- **Any PH**
  - TPA+ET: 8 (3%)
  - ET: 10 (5%)
  - TPA+ET: 6 (3%)
  - ET: 6 (5%)
  - TPA+ET: 2 (3%)
  - ET: 0
- **SAH**
  - TPA+ET: 13 (5%)
  - ET: 10 (5%)
  - TPA+ET: 8 (4%)
  - ET: 6 (5%)
  - TPA+ET: 3 (5%)
  - ET: 0
- **mRS0-2 at 3 mo**
  - TPA+ET: 110 (45%)
  - ET: 62 (38%)
  - TPA+ET: 78 (45%)
  - ET: 33 (35%)
  - TPA+ET: 29 (50%)
  - ET: 16 (40%)
- **Mortality 90 days**
  - TPA+ET: 52 (21%)
  - ET: 55 (34%)
  - TPA+ET: 79 (45%)
  - ET: 34 (36%)
  - TPA+ET: 9 (15%)
  - ET: 15 (37%)

The values are given as median/IQR and mean/standard deviation. ASPECTS indicates Alberta Stroke Program Early CT Score; bNIHSS, baseline National Institutes of Health Stroke Scale; CTP, computed tomographic perfusion ET, endovascular therapy; ICA, internal carotid artery; INR, international normalized ratio; IQR, interquartile range; MCA, middle cerebral artery; mRS, modified Rankin scale; mTICI, modified Treatment in Cerebral Ischemia; OSH, outside hospital; PH, parenchymal hematoma; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; and tPA, tissue-type plasminogen activator.

*\(n=244\).*

†\(n=160\).*

‡\(n=170\).*

§\(n=94\).*

¶\(n=58\).*

||\(n=58\).*
were performed. This was followed by multivariable logistic regression analyses for factors associated with each outcome (dependent variable). The multivariable analyses included variables with <0.1 level of significance in the univariate analyses and used the Enter method (IBM SPSS Statistics 21Armonk, NY).

Results
Out of 699 patients who underwent ET over the study period, 422 met our inclusion criteria. A total of 253 patients (60%) received IV-tPA+ET, and 169 (40%), ET alone. ET-alone patients were IV-tPA-ineligible either because of presentation >4.5 hours (n=66, 39%) or because of nontime-based reasons (n=103, 61%). Baseline characteristics, efficacy, and safety end points are shown in Table. Combined IV-tPA+ET patients were slightly younger (64.9±15.2 versus 67.9±14.9 years; P=0.05), more often males (56% versus 44%; P=0.01), and had less hypertension (70% versus 81%; P=0.02) and vertebrobasilar occlusions (3% versus 8%; P=0.02) as compared with ET-alone/IV-tPA-ineligible patients.

There were no statistical difference in the rates of 90-day modified Rankin scale score ≤2 (45% versus 38%; P=0.21), successful reperfusion (83% versus 80%; P=0.52), or any PH (3% versus 5%; P=0.21) across the 2 groups. Unadjusted 90-day mortality was higher with ET-alone (21% versus 34%; P<0.01); however, IV-tPA-ineligibility was not associated with 90-day mortality on multivariable analyses. Overall, these results were consistent across the different time epochs (Table).

Table I in the online-only Data Supplement contains the results of logistic regression for each specific end point. Current smoking status (odds ratio [OR] 3.08, 95% confidence interval [CI] 1.14–8.29) and stent-retriever use (OR 2.25, 95% CI 1.09–7.09) were independently associated with successful reperfusion. Younger age (OR 0.97, 95% CI 0.95–0.99), lower baseline National Institutes of Health Stroke Scale (OR 0.92, 95% CI 0.87–0.97), higher baseline Alberta Stroke Program Early CT Score (ASPECTS; OR 1.46, 95% CI 1.21–1.76), shorter procedure length (OR 0.99, 95% CI 0.98–0.99), and successful reperfusion (OR 2.78, 95% CI 1.09–7.09) were independently associated with 90-day good outcome.

There were no identified predictors of any PH in the current analysis likely because of its overall low frequency and the cohort size. Older age (OR 1.05, 95% CI 1.03–1.08), higher glucose levels on admission (OR 1.00, 95% CI 1.00–1.01), higher baseline National Institutes of Health Stroke Scale (OR 1.01, 95% CI 1.03–1.16), lower baseline ASPECTS (OR 0.75, 95% CI 0.62–0.90), failure to achieve modified Treatment in Cerebral Ischemia 2b-3 reperfusion (OR 0.38, 95% CI 0.19–0.74), and any PH (OR 4.39, 95% CI 1.32–14.57) were independently associated with 90-day mortality. Notably, there was no association between the use of IV-tPA and 90-day mortality on logistic regression (OR 0.62, 95% CI 0.34–1.12). Sensitivity analyses were performed forcing the use of IV-tPA into the models and failed to demonstrate its association with any of the study outcomes.

Discussion
Intravenous tPA was administered in 73% to 100% of the patients enrolled in the recent randomized trials demonstrating the superiority of ET over medical therapy. Moreover, patients who did not qualify for IV-tPA for reasons other than time to presentation, such as anticoagulation use, bleeding diathesis, recent surgery, intracranial or systemic bleeding, trauma, or recent stroke, were for the most part excluded from these trials. Consequently, Level 1a data to support ET in IV-tPA-ineligible patients is still lacking, and these patients have received more limited attention in the recently published guidelines. The current study revealed that the benefit of ET in IV-tPA-ineligible patients seems to be comparable to those treated with IV-tPA+ET, despite similar times to ET. These results are consistent with a recent multicenter study of 130 IV-tPA-ineligible patients with anterior circulation strokes treated with stent retriever within 4.5 hours of symptom onset.

Interestingly, smoking status was independently associated with higher rates of successful reperfusion, as previously described. Our study has limitations, mostly inherent to its retrospective design and limited sample size. It is possible that the 7% difference across the groups could reach statistical significance with a larger sample size. There were mild imbalances in terms of age, sex, and the prevalence of hypertension and vertebrobasilar occlusions. The higher 90-day mortality rate in the IV-tPA-ineligible patients is likely explained by the older age and higher frequency of vertebrobasilar occlusion in the IV-tPA-ineligible group because no association was seen on multivariable analysis.

Our findings suggest that patients who are ineligible for IV-tPA who presented to ET within 6 hours of symptom onset can safely undergo ET and seem to achieve similar rates of reperfusion and good outcome compared with IV-tPA+ET patients within the same time frame. Given the known poor outcomes in large vessel occlusion strokes treated with IV-tPA only and the superiority of IV-tPA over medical treatment alone, it is unlikely that a randomized trial comparing ET with medical treatment will be ever performed for IV-tPA-ineligible patients. As such, we hope that our study will add to the yet scarce literature on this patient population and will further support the pursuit of endovascular reperfusion in IV-tPA-ineligible patients.

Disclosures
Dr Nogueira received support from Stryker Neurovascular (Trevo-2 Trial-PJ/DWI/PWI and CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention [DAWN] Trial-PJ), Cerebral Angiographic Revascularization Grading (CARG) Collaborators; STIR Revascularization working group; Intravenous tPA vs t-PA Alone in Stroke [SWIFT-PRIME] Steering Committee/ Solitaire FR Thrombectomy for Acute Revascularization [STAR]-Trial Core- Lab), and Penumbra (3-D Trial Executive Committee/Solitaire FR Thrombectomy for Acute Revascularization)

References


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**SUPPLEMENTAL MATERIAL**

**SUPPLEMENTAL TABLE I. Multivariate analysis for efficacy and safety outcomes**

<table>
<thead>
<tr>
<th>Successful reperfusion (TICI 2B-3)</th>
<th>OR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.97-1.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.90</td>
<td>0.90-1.01</td>
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<tr>
<td>Smoking</td>
<td>3.08</td>
<td>1.14-8.29</td>
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<td>NIHSS</td>
<td>0.97</td>
<td>0.91-1.02</td>
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<tr>
<td>ASPECTS</td>
<td>1.20</td>
<td>1.01-1.44</td>
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<td>Stentriever</td>
<td>2.25</td>
<td>1.27-3.96</td>
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<td>Procedure length</td>
<td>0.99</td>
<td>0.98-0.99</td>
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<table>
<thead>
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<th>Good outcome (mRS 0-2) 90 days</th>
<th>OR</th>
<th>95% CI</th>
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<tr>
<td>Sex</td>
<td>1.10</td>
<td>0.61-1.98</td>
</tr>
<tr>
<td>Age</td>
<td>0.97</td>
<td>0.94-0.99</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.99</td>
<td>0.99-1.00</td>
</tr>
<tr>
<td>SBP</td>
<td>0.99</td>
<td>0.98-1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.78</td>
<td>0.38-1.58</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>0.87</td>
<td>0.46-1.66</td>
</tr>
<tr>
<td>Current smoking status</td>
<td>0.83</td>
<td>0.40-1.71</td>
</tr>
<tr>
<td>NIHSS</td>
<td>0.92</td>
<td>0.87-0.97</td>
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<tr>
<td>ASPECTS</td>
<td>1.46</td>
<td>1.21-1.76</td>
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<tr>
<td>Procedure length</td>
<td>0.99</td>
<td>0.98-0.99</td>
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<tr>
<td>Reperfusion (mTICI 2b-3)</td>
<td>2.78</td>
<td>1.09-7.08</td>
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<tr>
<td>Hemorrage (any PH)</td>
<td>0.39</td>
<td>0.07-2.03</td>
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<table>
<thead>
<tr>
<th>Mortality 90 days</th>
<th>OR</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age</td>
<td>1.06</td>
<td>1.03-1.08</td>
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<tr>
<td>Glucose</td>
<td>1.00</td>
<td>1.00-1.01</td>
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<tr>
<td>NIHSS</td>
<td>1.10</td>
<td>1.03-1.16</td>
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<td>ASPECTS</td>
<td>0.75</td>
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<td>IV tPA</td>
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<td>0.34-1.12</td>
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<td>Successful reperfusion (mTICI 2b-3)</td>
<td>0.38</td>
<td>0.19-0.74</td>
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<tr>
<td>Hemorrage (any PH)</td>
<td>4.39</td>
<td>1.32-14.57</td>
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