Risk of Intracranial Hemorrhage With Protease-Activated Receptor-1 Antagonists

Meng Lee, MD; Jeffrey L. Saver, MD; Keun-Sik Hong, MD, PhD; Hsiu-Chuan Wu, MD; Bruce Ovbiagele, MD, MSc

Background—Recent clinical trial data suggest that protease-activated receptor-1 (PAR-1) antagonists may increase the risk of intracranial hemorrhage. Our objective was to investigate the qualitative and quantitative risks of intracranial hemorrhage in patients receiving PAR-1 antagonist therapy.

Methods—Pubmed, EMBASE, Cochrane Central Register of Controlled Trials, and Clinicaltrials.gov from 1966 to May 2012, were searched to identify relevant studies. We included randomized controlled trials that included a comparison of PAR-1 antagonist with placebo and in which the total number of patients and intracranial hemorrhage events were reported separately for active treatment and control groups. Summary incidence rates, relative risks, and 95% confidence intervals (CIs) were calculated using random-effects models. Between-study heterogeneity was assessed using the I² statistic.

Results—In 9 PAR-1 antagonist trials with 42,000 patients with a history of thrombotic vascular disease or acute coronary syndrome, PAR-1 antagonist treatment was associated with increased risk of intracranial hemorrhage (0.59% vs 0.30%; relative risk, 1.98; 95% CI, 1.46–2.68; P<0.0001; number needed to harm, 345). There was no heterogeneity across trials (P²=0.84; I²=0%), PAR-1 antagonist agent (P=0.52), treatment duration (P²=0.38), or trial-qualifying event (P=0.59). Risk of death from any cause or a cardiovascular cause did not differ between active treatment and control groups.

Conclusion—In a pooled analysis of data from 9 trials, PAR-1 antagonist therapy was associated with an increased risk for intracranial hemorrhage. (Stroke. 2012;43:XXX-XXX.)

Key Words: acute coronary syndrome ■ antiplatelet ■ intracranial hemorrhage ■ protease-activated receptor-1 antagonists ■ thrombin antagonists

Thrombin is the key factor of the coagulation cascade and the most potent activator of platelets. Platelet responses to thrombin are mediated by surface G-protein-coupled receptors known as protease-activated receptors (PARs) or thrombin receptors. Thrombin-mediated platelet activation in humans occurs through PAR-1 and PAR-4 receptors, with PAR-1 acting as the major thrombin receptor on human platelets. Inhibition of PAR-1 function therefore is a rational strategy for optimizing treatment of atherothrombotic disorders in humans, but even though enhanced antithrombosis may reduce the risk of symptomatic ischemic events, it also could boost the risk of intracranial hemorrhage (ICH). Recent clinical trial evidence suggests that PAR-1 antagonist treatment may lessen the risk of recurrent ischemic events at the expense of greater ICH risk. However, the nature and extent of the association of PAR-1 antagonist therapy with ICH risk has not been clearly established. The objective of this study was to conduct a meta-analysis of randomized controlled trials to qualitatively and quantitatively evaluate the risk of ICH in patients receiving PAR-1 antagonist therapy.

Materials and Methods

This study was performed in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (the PRISMA Statement). We searched PubMed (1966–May 2012), EMBASE (1980–May 2012), the Cochrane Central Register of Controlled Trials (CENTRAL), and the clinical trial registry maintained at clinicaltrials.gov with the following terms: thrombin receptor antagonist or protease-activated receptor-1 antagonist or atopaxar or vorapaxar or SCH530348 or E5555 AND intracranial hemorrhage or intracerebral hemorrhage or intraparenchymal hemorrhage or subdural hemorrhage or epidural hemorrhage or subarachnoid hemorrhage or brain hemorrhage or epidural hemorrhage or subarachnoid hemorrhage or brain hemorrhage or epidural hemorrhage or subarachnoid hemorrhage or brain hemorrhage.

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hemorrhage or brain bleeding or hemorrhagic stroke or ICH or major bleeding or adverse effect or side effect or safety. We restricted our search to humans.

Criteria for inclusion of a study were as follows: (1) the study design was a randomized controlled trial; (2) the study included a comparison of PAR-1 antagonist with placebo; and (3) total participants and the number of ICH events were reported separately for active treatment and control groups. Studies were excluded when either the control group or the active therapy group received additional treatment that the other group did not receive. All data from eligible studies were abstracted by 2 investigators (M.L. and K.-S.H.) according to a standard protocol. Discrepancies were resolved by discussion with a third investigator (B.O.) and by referencing the original report.

Because all included studies were randomized controlled trials, the Jadad score was used to assess study quality.1 This 5-point scoring system evaluates the randomization process (2 questions), blinding (2 questions), and the description of withdrawals and dropouts (1 question).

The leading outcome of interest was the association of PAR-1 antagonist and ICH risk. We further categorized intracranial hemorrhages based on type as intracerebral, subdural, epidural, subarachnoid, and unknown, and then explored the association of PAR-1 antagonist therapy with each hemorrhage type. Traumatic brain hemorrhages were not excluded. Additional outcomes of interest were risk of a major adverse cardiovascular event, myocardial infarction, any stroke, ischemic stroke, myocardial infarction, death from any cause, death from cardiovascular causes, and major bleeding.

Subgroup analyses for the primary end point, ICH, were conducted for different trial characteristics as follows: subjects with acute coronary syndrome vs subjects with a history of coronary artery disease or other vascular disease, active treatment drug (atopaxar vs vorapaxar), and study quality (Jadad score ≥3 vs <3). Further analyses for ICH, major adverse cardiovascular events, myocardial infarction, ischemic stroke, and major bleeding stratified by active treatment duration (<12 months vs ≥12 months) were conducted to better characterize the association of PAR-1 antagonist therapy with the various prespecified end points.

Relative risk (RR) with 95% confidence interval (CI) was used as a measure of the association between an active treatment group with PAR-1 antagonist vs a control group and risk of ICH. Heterogeneity was assessed by $I^2$ statistic and $P$, which describes the percentage of variability in the event estimates that is attributable to heterogeneity rather than chance. Heterogeneity was considered significant if the $P$ value of $I^2$ statistics was <0.05. We regarded $I^2$ of <40% as minimal and >74% as considerable.46 We pooled data across trials using the random-effects model based on Mantel-Haenszel methods and compared the results with those obtained from a fixed-effects model.46 Publication bias was visually assessed by funnel plots displaying SE as the measure of sample size and RR as the measure of treatment effect.60 Data were analyzed according to the intention-to-treat principle. For all analyses, $P<0.05$ was considered statistically significant. The Review Manager was used for this meta-analysis.

## Results

The literature review identified 11 articles for detailed assessment, among which 3 were excluded for review content only. Our final analysis included 8 articles comprising 9 randomized controlled trials that enrolled 42,000 individuals (Figure 1).8,9,17–22 The study design, quality, and baseline characteristics of these randomized controlled trials are shown in Table 1. Four trials used atopaxar9,17,18 as an active treatment drug and 5 trials used vorapaxar8,19–22 as an active treatment drug. Four trials included individuals with acute coronary syndrome,9,17,19,21 whereas 5 trials included individuals with coronary artery disease or other vascular diseases.8,17,18,20,22 Six trials showed good scores (≥3),8,9,18,20,22 and 3 trials showed a lower score on a quality scale evaluated by Jadad score.7,19

Pooling the results from the random-effects model showed that PAR-1 antagonists were associated with increased risk of ICH (RR, 1.98; 95% CI, 1.46–2.68; $P<0.00001$; Figure 2). There was no heterogeneity across trials ($P=0.84; F=0%$). The estimates from the fixed-effects model (RR, 1.99; 95% CI, 1.47–2.69; $P<0.00001$) were similar to those of the random-effects model. The funnel plots showed asymmetry with small trials showing low ICH risk (Supplementary Figure I).

When we analyzed the effect of PAR-1 antagonists based on the ICH type, only risk of intracerebral hemorrhage increased significantly (RR, 2.20; 95% CI, 1.58–3.08; $P<0.00001$; Figure 3).

Additional end points are provided in Table 2. All 9 trials reported data for major vascular events. Pooling the results showed that PAR-1 antagonists were associated with lower risk of major vascular events (RR, 0.86; 95% CI, 0.77–0.95; $P=0.004$). All 9 trials reported data on myocardial infarction end points. Pooling the results showed that PAR-1 antagonists were associated with lower risk of myocardial infarctions (RR, 0.79; 95% CI, 0.67–0.93; $P=0.005$). All 9 trials reported data for stroke end points. Pooling the results showed that PAR-1 antagonists were not significantly associated with lower risk of stroke (RR, 0.96; 95% CI, 0.84–1.10; $P=0.57$). All 9 trials reported data for ischemic stroke end points. Pooling the results showed that PAR-1 antagonists were associated with lower risk of ischemic stroke (RR, 0.84; 95% CI, 0.72–0.97; $P=0.02$). Five trials reported data for all-cause death rates. Pooling the results showed that PAR-1 antagonists were not significantly associated with lower risk of death from any cause (RR, 0.99; 95% CI, 0.90–1.08; $P=0.83$). All 9 trials reported data for deaths attributable to cardiovascular causes. Pooling the results showed that PAR-1 antagonists were not significantly associated with lower risk of death from cardiovascular causes (RR, 0.94; 95% CI, 0.83–1.06; $P=0.29$). All 9 trials reported data on major bleeding events. Pooling the results showed that PAR-1 antagonists were associated with increased risk of major bleeding (RR, 1.48; 95% CI, 1.29–1.70; $P<0.00001$).

In subgroup analyses, PAR-1 antagonists increased risk of ICH in subjects with acute coronary syndrome (RR, 2.40; 95% CI, 1.12–5.14; $P=0.02$) and subjects with a history of coronary artery disease or other vascular disease (RR, 1.91; 95% CI, 1.37–2.66; $P=0.0001$), and there was no heterogeneity between these 2 groups ($P=0.59, F=0%$). Also, there was no heterogeneity for treatment with atopaxar vs vorapaxar for study quality.

Duration of PAR-1 antagonist treatment, <12 months vs >12 months, did not influence the risk of ICH, ischemic stroke, or major bleeding. However, the benefits for reducing major adverse cardiovascular events (<12 months vs >12 months: RR, 0.45 and 95% CI, 0.28–0.74 vs RR, 0.89 and 95% CI, 0.83–0.94; $P$ for heterogeneity among groups=0.008) and myocardial infarction (RR, 0.44 and 95% CI, 0.28–0.68 vs RR, 0.86 and 95% CI, 0.80–0.93; $P$ for heterogeneity among groups=0.003) were smaller with prolonged PAR-1 antagonist treatment (Figure 4).
Figure 1. Flow of study selection.

Table 1. Characteristics of Included Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Active Treatment Drug</th>
<th>No. of Participants (Women, %)</th>
<th>Mean Age</th>
<th>History of Stroke, %</th>
<th>Active Treatment Duration/Total Study Duration</th>
<th>Percent of Aspirin Use, %</th>
<th>Percent of Clopidogrel or Other Thienopyridine Use, %</th>
<th>Study Quality (Jadad Score), 5-Point Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>J-Lancelot ACS¹⁷</td>
<td>ACS within 24 h</td>
<td>Atopaxar</td>
<td>241 (20)</td>
<td>65</td>
<td>8.3</td>
<td>12 wk/16 wk</td>
<td>98</td>
<td>93</td>
<td>2</td>
</tr>
<tr>
<td>J-Lancelot CAD¹⁷</td>
<td>CAD with a history of 1 of the following conditions: DM, PAD, atherothrombotic TIA or stroke for &gt;1 y before inclusion</td>
<td>Atopaxar</td>
<td>263 (13)</td>
<td>66.5</td>
<td>16</td>
<td>24 wk/28 wk</td>
<td>100</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Lancelot ACS³⁹</td>
<td>ACS within 72 h</td>
<td>Atopaxar</td>
<td>603 (32)</td>
<td>62</td>
<td>0</td>
<td>12 wk/16 wk</td>
<td>96</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>Lancelot CAD³¹</td>
<td>CAD with at least 1 high-risk indicator (hsCRP &gt;3.0 mg/L, DM, PAD, stroke (1 y earlier), or carotid arterial disease at the time of enrollment</td>
<td>Atopaxar</td>
<td>720 (24)</td>
<td>64</td>
<td>11</td>
<td>24 wk/28 wk</td>
<td>93</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>NSTE ACS¹⁰</td>
<td>ACS within 24 h and with planned PCI</td>
<td>Vorapaxar</td>
<td>117 (21)</td>
<td>64</td>
<td>NA</td>
<td>60 d/60 d</td>
<td>100</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>Shinohara et al²⁰</td>
<td>Ischemic stroke occurring ≥14 d and &lt;1 y</td>
<td>Vorapaxar</td>
<td>90 (23)</td>
<td>65</td>
<td>100</td>
<td>60 d/120 d</td>
<td>100</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>TRA2P TIMI 50³⁸</td>
<td>History of MI and ischemic stroke within previous 2 wk and 2 y or PAD</td>
<td>Vorapaxar</td>
<td>26449 (24)</td>
<td>61</td>
<td>24</td>
<td>24 mo/24 mo</td>
<td>98</td>
<td>62</td>
<td>4</td>
</tr>
<tr>
<td>TRACER²¹</td>
<td>ACS within 24 h</td>
<td>Vorapaxar</td>
<td>12944 (28)</td>
<td>64</td>
<td>4.3</td>
<td>386 d/502 d</td>
<td>99</td>
<td>92</td>
<td>4</td>
</tr>
<tr>
<td>TRAPCI²²</td>
<td>CAD with nonurgent PCI</td>
<td>Vorapaxar</td>
<td>573 (23)</td>
<td>64</td>
<td>0</td>
<td>60 d/120 d</td>
<td>99</td>
<td>97</td>
<td>5</td>
</tr>
</tbody>
</table>

ACS indicates acute coronary syndrome; CAD, coronary artery disease, NSTE, non-ST elevation; TRA2P TIMI, TRACER, TRAPCI, DM, diabetes mellitus; PAD, peripheral artery disease; TIA, transient ischemic attack; hsCRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention; MI, myocardial infarction; NA.
Discussion

In this meta-analysis comprising 9 randomized controlled trials of generally good quality among 42,000 people, we found that adding PAR-1 antagonist to standard therapy was associated with a 98% relative increase in the risk of ICH compared with standard therapy in subjects with a history of thrombotic vascular disease or acute coronary syndrome. PAR-1 antagonist therapy also was associated with higher risk of major bleeding. However, PAR-1 antagonist therapy was associated with lower risk of major adverse cardiovascular events, myocardial infarction, and ischemic stroke. The risk of all strokes (ischemic plus hemorrhagic), death from any cause, or a cardiovascular cause did not differ between active treatment and control groups.

The overall clinical risk–benefit profile of PAR-1 antagonist therapy appears to be favorable and largely driven by an impressive reduction in the occurrence of myocardial infarction. Among 1000 patients with a history of thrombotic vascular disease or acute coronary syndrome, PAR-1 antagonist

Figure 2. Relative risk with 95% confidence interval (CI) of intracranial hemorrhage (protease-activated receptor-1 [PAR-1] antagonist vs control) by trials and pooled.

Figure 3. Relative risk with 95% confidence interval (CI) of different types of intracranial hemorrhage (intracerebral hemorrhage vs subdural or epidural or subarachnoid hemorrhage vs unknown) in protease-activated receptor-1 [PPAR-1] antagonist vs control by trials and pooled.
treatment over a period of up to 2 years will avert 12 myocardial infarctions and 4 ischemic strokes at the same time as causing 3 additional ICH events and 7 episodes of major bleeding. Despite the apparent favorable risk–benefit profile for PAR-1 antagonists observed in this meta-analysis, it is important to consider that the impact of the various end points evaluated may not necessarily be equal. Previous studies have suggested that stroke may have a greater adverse effect on a broad range of health status domains than myocardial infarction,23,24 and ICH is generally associated with a much higher risk of mortality than ischemic stroke.25 We are unaware of studies that have specifically evaluated disability-adjusted life-years in ICH compared with ischemic stroke, but studies comparing quality-adjusted life-years for these types of stroke suggest that patients with ICH incur greater loss of health over a lifetime than people with ischemic stroke.26,27 Furthermore, although the link between major bleeding events and disability-adjusted life-years is not well-established, the occurrence of major bleeding with PAR-1 antagonist therapy is likely to interrupt any type of treatment with antithrombotic drugs including single antiplatelet therapy, thereby exposing the patient with a history of symptomatic vascular disease to an extended period of heightened risk of recurrent ischemic events.28–30

Given the differential effects of PAR-1 antagonists on risk of myocardial infarction and ischemic stroke vs ICH, identifying patients for whom the risk–benefit profile of these drugs could be enhanced should be a clinical and research priority. For patients with vascular disease at high risk for ICH, treatment with PAR-1 antagonists may need to be avoided or possibly pursued at lower doses. A combination of age, hypertension, excess alcohol use, history of any stroke, leukoaraiosis, cerebral microbleeds on MRI, genetic carriers of APOE ε2 and ε4,31–33 and additional clinical features may identify a subset of patients with greater hemorrhagic propensity in whom PAR-1 antagonist therapy should be used judiciously, if at all. Furthermore, to reduce the risk of ICH in patients who are using PAR-1 antagonist therapy, it may be prudent to ensure optimal treatment of elevated blood pressure, the premier modifiable risk factor for ICH.34 It is not clear how being enrolled in clinical trials with regular close monitoring by vascular disease experts may have mitigated even worse ICH outcomes from occurring among the patients included in this meta-analysis.

We observed that risk of ICH was not significantly increased in trials with prolonged PAR-1 treatment (>12 months), but that the benefit of fewer major cardiovascular events and myocardial infarction was smaller in prolonged treatment trials. This varied effect on ischemic events by treatment duration could be attributable to smaller trials lasting <12 months exerting a larger beneficial effect35 or could be because the ischemic protective

<p>| Table 2. Effect of Protease-Activated Receptor-1 Antagonists on Clinical End Points |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>End Points</th>
<th>PAR-1 Antagonist, n (%)</th>
<th>Control, n (%)</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hemorrhage</td>
<td>127/21 657 (0.59)</td>
<td>61/20 343 (0.30)</td>
<td>1.98 (1.46–2.68)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Major vascular events</td>
<td>1906/21 657 (8.8)</td>
<td>2119/20 343 (10.4)</td>
<td>0.86 (0.77–0.95)</td>
<td>0.004</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1229/21 657 (5.7)</td>
<td>1401/20 343 (6.9)</td>
<td>0.79 (0.67–0.93)</td>
<td>0.005</td>
</tr>
<tr>
<td>Any stroke</td>
<td>417/21 657 (1.9)</td>
<td>428/20 343 (2.1)</td>
<td>0.96 (0.84–1.10)</td>
<td>0.57</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>328/21 657 (1.5)</td>
<td>388/20 343 (1.9)</td>
<td>0.84 (0.72–0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>875/20 276 (4.3)</td>
<td>883/19 897 (4.4)</td>
<td>0.99 (0.90–1.08)</td>
<td>0.83</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>499/21 657 (2.3)</td>
<td>528/20 343 (2.6)</td>
<td>0.94 (0.83–1.06)</td>
<td>0.29</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>512/21 657 (2.4)</td>
<td>336/20 343 (1.7)</td>
<td>1.48 (1.29–1.70)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

PAR-1 indicates protease-activated receptor-1; RR, relative risk.

Figure 4. Impact of protease-activated receptor-1 (PAR-1) antagonist treatment duration on clinical end points.
benefits associated with an add-on PAR-1 antagonist diminish with long-term treatment. Randomized controlled trials suggest that the use of dual antiplatelet therapy for a period >12 months in patients who have received drug-eluting stents is not more effective than aspirin monotherapy in reducing the rate of major adverse cardiovascular events. Compliance with using multiple medications and higher financial costs also may be real-world concerns with long-term add-on PAR-1 antagonist treatment.\(^1\)

Two meta-analyses of PAR-1 antagonist therapy were published recently, but ICH was neither a primary nor a secondary end point in these 2 studies.\(^3,4\) Both studies focused on the increased risk of major bleeding in PAR-1 antagonist group. Major bleeding is an important adverse clinical event, but unless it leads to mortality, it does not typically cause permanent disability in affected patients. Furthermore, the risk of upper gastrointestinal bleeding, 1 of the most common manifestations of major bleeding, often can be mitigated through the use of proton pump inhibitors.\(^5,6\) However, ICH tends to have a comparatively higher rate of mortality and permanent disability than most other manifestations of major bleeding. The protocol of the largest PAR-1 antagonist trial to date was amended because of concerns about an excessive occurrence of ICH in patients with a previous stroke.\(^8\)

Our study has several limitations. First, meta-analyses may be biased when the literature search fails to identify all relevant trials or when the selection criteria for including a trial are applied in a subjective manner. To minimize these risks, we performed thorough searches across multiple literature and used explicit criteria for study selection and data abstraction. Second, the results were based largely on 2 phase III trials with different populations (acute coronary syndrome and history of thrombotic vascular disease, respectively), and some of the phase II trials included had short study durations (<6 months) and very few ICH events. Accidental or more, long-term, randomized controlled trials of PAR-1 antagonists may be necessary to definitively resolve this issue.

In the meantime, this meta-analysis showed that patients with a history of thrombotic vascular disease or acute coronary syndrome treated with PAR-1 antagonists are at higher risk for experiencing ICH, a dreaded form of stroke, associating with high mortality and greater loss of health over the lifetime of a survivor than ischemic stroke. When combined with an overall higher risk of systemic bleeding, despite a net vascular preventive benefit, clinicians should be keenly aware of the higher hemorrhagic complications of these drugs and consider prudent prescription of these therapies in patients identified to be at high risk for ICH or systemic bleeding.

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