Editorial

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

Guido J. Falcone, MD, MPH; H. Bart Brouwers, MD; Jonathan Rosand, MD, MSc

See related article, p 3189.

Acutely clinical syndromes caused by atherosclerotic disease of the arterial wall are among the world’s leading causes of death and disability.1 These conditions include acute coronary syndromes, ischemic stroke/transient ischemic attack, and symptomatic peripheral arterial disease. As average life expectancy continues to rise, the burden posed by these diseases is expected to increase.2 Antiplatelet therapy plays a pivotal role in primary and secondary prevention of acute atherothrombotic events by targeting platelet activation, a mechanism that mediates both the beneficial (hemostatic) and detrimental (thrombotic) effect of platelets. This activation process occurs through several pathways, each targeted by different classes of drugs.3 Platelet activation can be triggered by three main extracellular agonists: thromboxane A₂, adenosine diphosphate, and thrombin. These agonists activate the platelet integrin glycoprotein Ib/IIa, a main receptor for both adhesion and aggregation. Endothelial-derived factors limit platelet aggregation by increasing intracellular levels of cyclic nucleotides (cyclic guanosine monophosphate and cyclic adenosine monophosphate).4 The most commonly used oral antiplatelet medications are inhibitors of the thromboxane A₂ (aspirin) and adenosine diphosphate (P₂Y₁₂ inhibitors: clopidogrel, ticlopidine, and prasugrel) pathways. A third group of drugs acts on the cyclic nucleotide-dependent regulation step by inhibiting the phosphodiesterase responsible for the degradation of cyclic nucleotides (dipyridamole and cilostazol), and a fourth group directly inhibits the glycoprotein Ib/IIa (abciximab, eptifibatide, and tirofiban).5 In isolation, any of these agents reduces the risk of acute atherothrombotic events.6 In combination, by concomitantly blocking 2 activation pathways, their therapeutic effect is potentiated, at the expense of a higher rate of serious bleeding events.7

Recently, a new group of drugs targeting the thrombin pathway was introduced: the protease-activated-receptor 1 (PAR-1) antagonists (apaxar and vorapaxar). Preclinical studies have shown that selective PAR-1 blockade results in a potent reduction of platelet aggregation mediated by thrombin, but with preservation of hemostatic function.8 In addition, phase 2 clinical trials involving patients receiving dual antiaggregation therapy in the setting of acute coronary syndromes without ST elevation or percutaneous angioplasty found no significant increase in major bleeding events when compared to placebo.9,10 Unfortunately, the 2 largest phase 3 clinical trials completed to date, aimed at testing the efficacy of vorapaxar in the context of either acute coronary syndromes without ST elevation11 or as a secondary prevention strategy for atherothrombotic events,12 were stopped prematurely because of increased risk of major bleeding events, particularly intracranial hemorrhage, in the intervention group.

In the current issue of Stroke, Lee et al report the results of a meta-analysis specifically aimed at generating a pooled estimate of the effect of PAR-1 antagonists on risk of intracranial hemorrhage. This focus on intracranial hemorrhage constitutes an important next step in understanding the implications of treatment with PAR-1 antagonists, as 2 recently published meta-analyses13,14 addressing safety and efficacy of these drugs did not specifically tackle this issue. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines,15 the authors analyzed data on 42,000 subjects enrolled in 9 studies (4 involving atopaxar and 5 vorapaxar). Only data from placebo-controlled, randomized clinical trials were considered, and the overall quality of each study was assessed by means of the Jadad score.16 Of particular interest to the readers of Stroke, stratified analyses were undertaken to consider different types of intracranial hemorrhage: intraparenchymal, subarachnoid, subdural, and epidural hemorrhages. This represents a noteworthy strength of the study, in light of the known differences in the underlying biological pathways that lead to each of these subtypes of intracranial hemorrhage. In addition to pooled relative risk of intracranial hemorrhage (and its subtypes), other relevant outcomes were considered, including death from any cause and death attributable to cardiovascular causes.

Treatment with PAR-1 antagonists was associated with a significantly increased risk of intracranial hemorrhage. This effect was mainly driven by the effect of these drugs on risk of intraparenchymal hemorrhage (or intracerebral hemorrhage [ICH]), yielding nonsignificant results for other subtypes. In both mixed- and fixed-effect meta-analyses, treatment with PAR-1 antagonists doubled the risk of intracranial bleeding (relative risk 1.98; P<0.001). This effect was even stronger when the analysis was restricted to ICH (relative risk 2.2; P<0.001). These results remained unchanged in stratified analyses aimed to assess potential effect modifiers: type of qualifying event for enrollment (acute coronary syndrome vs chronic coronary artery disease), medication subtype (apaxar

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Center for Human Genetic Research, Massachusetts General Hospital, Boston, MA; Hemorrhagic Stroke Research Group, Massachusetts General Hospital, Boston, MA; Division of Neurocritical Care and Emergency Neurology, Department of Neurology, Massachusetts General Hospital, Boston MA; and Program in Medical and Population Genetics, Broad Institute, Cambridge MA.

Correspondence to Jonathan Rosand, MD, MSc, Center for Human Genetic Research, Massachusetts General Hospital, 185 Cambridge St, CPZN-6818, Boston, MA 02114. E-mail jrosand@partners.org


© 2012 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.112.676932

3158
vs vorapaxar), and duration of treatment (<1 vs >1 year). Interestingly, treatment with PAR-1 antagonists did not substantially modify all-cause (relative risk 0.99;  P=0.83) or cardiovascular-related mortality (relative risk 0.94;  P=0.29).

These results are likely to be robust, as no heterogeneity across meta-analyzed studies was observed. Nonetheless, the disproportionate weight that 2 of the included trials had in the analyses underscores the need to update the current analysis as additional data become available.

The analysis of Lee et al raises important questions that will require future study. First, given the proven beneficial effect of PAR-1 antagonists in achieving greater antithrombotic effect when combined with standard therapy, it could become useful to identify subjects at particularly high risk of bleeding if exposed to these drugs. A prescription strategy based on stratification of patients based on their risk of bleeding would allow clinicians to still take advantage of the beneficial effects of PAR-1 antagonists, while avoiding, at least in part, their deleterious effects. In this regard, 1 important clue emerged from one of the large clinical trials mentioned above: the risk of intracranial hemorrhage was substantially higher in subjects with a history of previous stroke than in those without it (2.4% vs 0.9%;  P<0.001). In addition, known risk factors for ICH represent another appealing option to be tested in prediction models of bleeding risk for subjects receiving PAR-1 antagonist. These risk factors include hypertension, alcohol consumption, cerebral microbleeds, white matter hyperintensities, and a number of common genetic variants.

Second, it may be useful to know whether the mechanism of bleeding in subjects receiving PAR-1 antagonists has a predilection for so-called lobar or nonlobar locations. For patients >55 years of age, the majority of (nontraumatic) ICH cases occurs in the presence of cerebral small vessel disease. Pathological studies have shown that ICH location frequently correlates with different underlying small vessel diseases. Although hypertension-related lipohyalinosis is the corresponding pathology for deep ICH, cerebral amyloid angiopathy is recognized as the leading cause of lobar ICH (with chronic hypertension playing a much more limited role). Consequently, determining whether the effect of PAR-1 antagonists on risk of ICH differs by location could provide further clues to the mechanism of bleeding.

Disclosures

Dr Rosand has received research grants from the National Institutes of Health and from the American Heart Association. The other authors have no conflicts to report.

References


Key Words: antiplatelet agents, antiplatelet drugs, intracranial hemorrhage
Risk of Intracranial Hemorrhage With Protease-Activated Receptor-1 Antagonists
Guido J. Falcone, H. Bart Brouwers and Jonathan Rosand

Stroke. 2012;43:3158-3159; originally published online November 15, 2012;
doi: 10.1161/STROKEAHA.112.676932

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/43/12/3158

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/