Comparing Ticagrelor Versus Clopidogrel in Patients With a History of Cerebrovascular Disease
A Net Clinical Harm?

James J. DiNicolantonio, PharmD; Victor L. Serebruany, MD, PhD

The PLATO trial was a phase 3, randomized, double-blind, parallel-group, multinational, clinical study comparing the efficacy of ticagrelor (formerly known as AZD6140, marketed as Brilinta) versus standard care treatment with clopidogrel. Patients (n=18,624) with moderate- to high-risk acute coronary syndrome undergoing coronary intervention or medically managed were randomized to ticagrelor 180 mg loading dose followed by 90 mg twice daily thereafter, or clopidogrel 300 to 600 mg loading dose followed by 75 mg once daily for 6 to 12 months.1 The primary end point was the time of the first event of death from vascular causes, myocardial infarction or stroke, and occurred in 11.7% of patients treated with clopidogrel, versus 9.8% of patients randomized to ticagrelor, representing a highly significant benefit (hazard ratio [HR]=0.84; CI=0.77–0.92; P<0.001) for ticagrelor.1 Importantly, the benefit of ticagrelor was driven equally by the reduction of vascular death (P<0.001), and myocardial infarction (P<0.005) with 89 events favoring ticagrelor each, but not stroke (P=0.22) with 19 less events in the clopidogrel arm.1 Moreover, the original PLATO data indicated a 17% increase in stroke (19 extra events; number needed to harm 491) with ticagrelor versus clopidogrel (125/9333 [1.3%] versus 106/9291 [1.1%]; HR=1.17 [0.91–1.52]; P=0.22) (Table 1).1 However, the Food and Drug Administration complete response review indicates an even greater risk of stroke (24% increase) with ticagrelor versus clopidogrel (27 extra strokes; 138/9333 versus 111/9291; HR=1.24 [0.97–1.59]; number needed to harm=352) just missing statistical significance (P=0.09).2 In summary, the original PLATO results may underestimate the risk of stroke on ticagrelor compared with clopidogrel.

The Food and Drug Administration complete response review indicates that patients having a history of cerebrovascular disease (cerebrovascular, carotid artery disease, vertebrobasilar artery disease) had a >2-fold increase in the risk of a cerebrovascular event (stroke or transient ischemic attack [TIA]) on ticagrelor compared with clopidogrel (8.1% versus 4.0%; P=0.24) in the PLATO trial (Table 2).1 Patients who had a history of cerebrovascular disease on ticagrelor had a >5-fold increase in the risk of a stroke or TIA compared with all patients treated with clopidogrel (4.0% versus 1.49%; relative risk=2.5), albeit half the increased risk that was associated with ticagrelor.3 Moreover, compared with clopidogrel, patients on ticagrelor had a 2-fold increase in major or life-threatening intracranial hemorrhage (n=27 [0.3%] versus n=14 [0.15%]; relative risk=2.0; P=0.05, respectively), a 10-fold increase in fatal intracranial hemorrhage (n=11 [0.12%] versus n=1 [0.0%; P=0.02), and a 73% increase in out of hospital intracranial hemorrhage (n=17 [0.19%] versus n=10 [0.11%]; relative risk=1.73; P=0.19, respectively) (Table 2).2

These complete response review data are in direct contrast to a recent editorial that indicated an equal amount of intracranial hemorrhagic events among patients with a history of stroke or TIA on ticagrelor and clopidogrel (4 versus 4, respectively).3 Moreover, authors state that among patients with a history of stroke or TIA, the primary composite outcome was not significantly reduced at 1 year with ticagrelor versus clopidogrel (HR=0.87; 95% CI=0.66–1.13; P=0.84), yet there was a significant reduction in mortality (HR=0.62; 95% CI=0.42–0.91). Additionally, overall PLATO defined bleeding rates were similar between ticagrelor and clopidogrel (14.6% versus 14.9%; HR=0.99; 95% CI=0.71–1.37, respectively). Thus, the Editorial concludes that acute coronary syndrome patients with a prior history of ischemic stroke or TIA had a favorable net benefit because of ticagrelor’s reduction on mortality.3 However, an editorial by Verheugt indicates that an interaction between ticagrelor and intracranial hemorrhage in patients with previous stroke cannot be ruled out.4 The low

Table 1. Ticagrelor Versus Clopidogrel on the Outcome of Stroke in PLATO1,2

<table>
<thead>
<tr>
<th>Evidence</th>
<th>Ticagrelor (n=9333)</th>
<th>Clopidogrel (n=9291)</th>
<th>RR, NNH, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO*</td>
<td>125 (1.30%)</td>
<td>106 (1.14%)</td>
<td>1.17 NNH=491 (P=0.22)</td>
</tr>
<tr>
<td>FDA CRR</td>
<td>138 (1.48%)</td>
<td>111 (1.19%)</td>
<td>1.24 NNH=352 (P=0.09)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; NNH, number needed to harm; FDA, Food and Drug Administration; CRR, complete response review.
*Data from reference 1.
number of patients with previous stroke having an intracranial hemorrhage in the PLATO trial prevents the exclusion of an interaction, and because of this, we do not have enough data to confirm that ticagrelor is safe in acute coronary syndrome patients with a previous stroke or TIA (Table 2). Importantly, in the ongoing Prevention of Cardiovascular Events (ie, death from heart or vascular disease, heart attack, or stroke) in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial, testing ticagrelor in patients with stable coronary disease, patients with a background of ischemic stroke are specifically excluded. Moreover, the PLATO mortality data has recently been questioned, with results varying by geographical location. In the United States, the primary end point was increased bleeding events to intracranial bleeds, or just heterogeneity of patient data might benefit future trial designs. Finally, the PLATO sponsor, in contrast to the United States, where regional differences, were not analyzed by the Food and Drug Administration complete response review documents. Indeed, regional differences in blood pressure control, concomitant medications, length of hospital stay, ratio of other types of bleeding events to intracranial bleeds, or just heterogeneity of patient data might benefit future trial designs. Finally, the concept of net clinical benefit has been somewhat challenged. In fact, compared with clopidogrel, ticagrelor seems to carry a net clinical harm, especially because the primary end point was not reduced in these individuals.5

Sources of Funding
None.

Disclosures
Dr Serebruany is listed as an inventor for the US patent application: Treating Cardiac Arrhythmias, Heart Failure, Peripheral Artery Disease and Stroke With Cyclopentyl-Triazolo-Pyrimidine or Derivative Thereof (USN 61/253,829) assigned to HeartDrug Manufacturers.

References
1. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrok J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Feijl A, Thorsén M; PLATO Investigators. Ticagrelor versus clopidogrel in patients with a history of cerebrovascular disease, the net clinical benefit with ticagrelor compared with clopidogrel is heavily challenged. In fact, compared with clopidogrel, ticagrelor seems to carry a net clinical harm, especially because the primary end point was not reduced in these individuals.5

Table 2. Ticagrelor Versus Clopidogrel in Patients With a History of Cerebrovascular Disease in PLATO2,4

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>RR, P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA</td>
<td>8.1%</td>
<td>4.0%</td>
<td>&gt;2 (P=0.24)</td>
</tr>
<tr>
<td>Major or life-threatening intracranial hemorrhage</td>
<td>27 (0.3%)</td>
<td>14 (0.15%)</td>
<td>2 (P=0.05)</td>
</tr>
<tr>
<td>Fatal intracranial hemorrhage</td>
<td>11 (0.12%)</td>
<td>1 (0.0%)</td>
<td>10 (P=0.02)</td>
</tr>
<tr>
<td>Outpatient intracranial hemorrhagic events</td>
<td>17 (0.19%)</td>
<td>10 (0.11%)</td>
<td>1.73 (P=0.19)</td>
</tr>
<tr>
<td>Intracranial hemorrhagic events*</td>
<td>4/564 (0.9%)</td>
<td>4/588 (0.7%)</td>
<td>1.00 (0.25–3.99; P=0.96)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; TIA, transient ischemic attack.

*Data from reference 4.

Key Words: carotid disease ■ cerebrovascular disease ■ clopidogrel ■ intracranial hemorrhage ■ stroke ■ ticagrelor ■ transient ischemic attack ■ vertebrobasilar disease
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