Beware of Novel Antiplatelet Therapy in Acute Coronary Syndrome Patients With Previous Stroke

Freek W.A. Verheugt, MD, FACC, FESC

Dual antiplatelet therapy with aspirin and the platelet P2Y12 receptor antagonist clopidogrel has become the cornerstone of the treatment of patients undergoing coronary stenting and of those with acute coronary syndromes (ACS) with or without stent implantation. Consequently, many patients in the cardiology practice in 2012 are on dual antiplatelet therapy, mainly aspirin and clopidogrel. The only important side effect of dual antiplatelet therapy is increased bleeding in comparison with aspirin alone. This has been established in the large trials with clopidogrel in acute coronary syndromes2–3 and thereafter,4 as well as in atrial fibrillation.5 Especially in the latter, dual antiplatelet therapy has been shown to be as hazardous as oral anticoagulation.6 The novel platelet P2Y12 receptor antagonists prasugrel and ticagrelor are more effective than clopidogrel in patients but show more noncoronary artery bypass graft–related thrombolysis in myocardial infarction major bleeding than clopidogrel.7,8 In the latter trial it became clear that patients with a previous stroke had significantly more bleeding with prasugrel, especially intracranial bleeding, than those without a history of stroke. Triple antiplatelet therapy with aspirin, clopidogrel, and the oral platelet thrombin receptor antagonist vorapaxar was in 2 megatrails with patients with acute coronary syndromes9 and thereafter10 also more associated with this dreadful complication compared with aspirin and clopidogrel alone. The former study had to be stopped prematurely by the data monitoring committee because of this, and in the latter the same had to be done for the patients with a previous stroke or transient ischemic attack (TIA).

The finding of excess intracranial bleeding with dual antiplatelet therapy over single therapy in previous stroke patients was not new (Table 1). In the Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) trial, where patients with a recent stroke or TIA were randomized to aspirin plus clopidogrel or to clopidogrel alone, dual therapy significantly doubled the risk of intracranial bleeding.11 The same was observed in the much larger PROFESS study for Effectively avoiding Second Strokes (PROFESS) study with similar patients, in which the combination of aspirin and dipyridamole increased significantly the risk of intracranial bleeding compared with clopidogrel alone.12 Finally, in the Atrial fibrillation Clopidogrel Trial21 with Irbesartan for prevention of Vascular Events A (ACTIVE-A) trial for stroke prevention in patients with atrial fibrillation unsuitable for warfarin, the combination of aspirin and clopidogrel doubled the rate of intracranial bleeding compared with aspirin alone.13

In this issue of Circulation the results are published of the prespecified subgroup analysis of patients with a previous stroke or TIA from the well-known PLATElet inhibition and patient Outcomes (PLATO) trial on ticagrelor versus clopidogrel in acute coronary syndromes.14 These patients faced higher rates of death, stroke, and myocardial infarction than those without a previous cerebrovascular event. As well, noncoronary artery bypass graft thrombolysis in myocardial infarction major bleeding was seen more often. Although statistically nonsignificant, the reduction of ischemic end points with ticagrelor, however, was of the same magnitude as in patients without a previous stroke. This finding is at odds with results of the Trial to assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel (TRITON) trial,8 where patients with previous stroke did not benefit from prasugrel and tended to be harmed with prasugrel. Interestingly, excess intracranial bleeding was not seen with ticagrelor in the current analysis, whereas it was with prasugrel in the TRITON study (Table 2).

Are the data presented today reassuring enough to treat ACS patients with a history of stroke routinely with ticagrelor rather than with clopidogrel? The total number of intracranial bleedings in this subset was very low (0.8%) and lower than in the TRITON subpopulation with previous stroke (1.2%), but every excess intracranial bleeding is a catastrophe. This hazard in the studies specifically aiming for the reduction of ischemic stroke is so striking (Table 2) that current studies on novel dual antiplatelet therapy in ACS and thereafter exclude patients with previous stroke. The Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS-2) trial (NCT00699998) comparing prasugrel with clopidogrel in 10,000 ACS patients without ST-segment elevation initially treated conservatively–excluded previous stroke patients,15 probably because of the untoward effects seen in the earlier TRITON trial. But the strongest signal comes from ticagrelor trialists themselves: in the currently running Perioperative Genetics and Safety Outcomes (PEGASUS) trial (NCT01225562), in which 21,000 high-risk patients with a remote (1–3 years) myocardial infarction are randomized between ticagrelor or placebo.
on top of aspirin, patients with previous stroke are also excluded. How will the results of the current analysis concur with the future outcome of PEGASUS? Or in other words, if ACS patients with a previous stroke will be routinely treated with ticagrelor, what will be the value of the PEGASUS results for such patients?

As shown in Table 2, the number of patients with previous stroke in the ACS trials mentioned is low (4%–6%), and the number of excess intracranial bleedings by novel dual antiplatelet therapy even lower (1%–2% of that subpopulation). Therefore, in the case of ticagrelor the test for interaction is not statistically significant, but given the insufficient data an interaction cannot be excluded either. Given the above, there is no safe ground to treat ACS patients with a previous stroke or TIA routinely with the novel platelet P2Y12 receptor antagonists prasugrel or ticagrelor rather than with clopidogrel.

**Table 1. Intracranial Bleeding With Dual Versus Single Antiplatelet Therapy in Large Randomized Controlled Trials With Previous Stroke/TIA Patients**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Indication</th>
<th>No. of Patients</th>
<th>% of Patients With Prior Stroke or TIA</th>
<th>Intracranial Bleeding</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events (TRA-2P)† 10*</td>
<td>Post stroke/TIA</td>
<td>5746</td>
<td>100</td>
<td>51/2870 (2.4%)</td>
<td>20/2876 (0.9%)</td>
<td>2.55 (1.52–4.28)</td>
</tr>
<tr>
<td>Management of Atherothrombosis with Clopidogrel in High-Risk Patients With Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH)11</td>
<td>Post stroke/TIA</td>
<td>7540</td>
<td>100</td>
<td>32/3759 (0.9%)</td>
<td>17/3781 (0.5%)</td>
<td>1.31 (1.07–1.61)</td>
</tr>
<tr>
<td>Prevention Regimen For Effectively Avoiding Second Strokes (PROFESS)12</td>
<td>Post stroke/TIA</td>
<td>21 332</td>
<td>100</td>
<td>147/10 181 (1.4%)</td>
<td>103/10 151 (1.0%)</td>
<td>1.42 (1.11–1.83)</td>
</tr>
<tr>
<td>Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events a (ACTIVE-A)13</td>
<td>SPAF†</td>
<td>7554</td>
<td>13</td>
<td>54/3772 (0.4%)</td>
<td>29/3782 (0.2%)</td>
<td>1.87 (1.19–2.94)</td>
</tr>
</tbody>
</table>

RR indicates risk ratio; CI, confidence interval.
*8% of patients of patients were also on clopidogrel.
†Stroke prevention in atrial fibrillation.

**Table 2. Intracranial Bleeding With Novel Versus Conventional Dual Antiplatelet Therapy in ACS Patients With Previous Stroke/TIA**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Intervention</th>
<th>No. of Patients</th>
<th>% of Patients With Prior Stroke or TIA</th>
<th>Intracranial Bleeding</th>
<th>RR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With prasugrel (TRITON)8</td>
<td>Prasugrel vs clopidogrel</td>
<td>13 608</td>
<td>3.8</td>
<td>6/262 (2.3%)</td>
<td>0/256 (0.0%)</td>
<td>...</td>
</tr>
<tr>
<td>PLATElet Inhibition and Patient Outcomes (PLATO)14*</td>
<td>Ticagrelor vs clopidogrel</td>
<td>18 624</td>
<td>6.2</td>
<td>4/564 (0.9%)</td>
<td>4/588 (0.7%)</td>
<td>1.00 (0.25–3.99)</td>
</tr>
</tbody>
</table>

RR indicates risk ratio; CI, confidence interval.
*Present study.

Disclosures

Dr Verheugt has received educational and research grants from Bayer Healthcare, Roche, Eli Lilly, and Boehringer Ingelheim and honoraria for consultancies/speaker fees from Daiichi-Sankyo, Eli Lilly, Merck, The Medicines Company, and Bayer Healthcare.

References


**Key Words:** Editorials ■ acute coronary syndrome ■ antiplatelet agents ■ stroke
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_Circulation._ 2012;125:2821-2823; originally published online May 9, 2012;
doi: 10.1161/CIRCULATIONAHA.112.111930

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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