Beware of Novel Antiplatelet Therapy in ACS Patients with Previous Stroke

Running title: Verheugt; Novel antiplatelet therapy in ACS

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Journal Subject Codes: [122] Secondary prevention; [44] Acute Cerebral Infarction

Key words: acute coronary syndrome; antiplatelet; Editorials; stroke
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 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 to aspirin alone. This has been established in the large trials with clopidogrel in acute coronary syndromes and thereafter, as well as in atrial fibrillation. Especially in the latter dual antiplatelet therapy has shown to be as hazardous as oral anticoagulation. The novel platelet P2Y12 receptor antagonists prasugrel and ticagrelor are more effective than clopidogrel in patients, but show more non-CABG related TIMI major bleeding than clopidogrel. 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 megatrials with patients with acute coronary syndromes and thereafter also more associated with this dreadful complication compared to 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 TIA.

The finding of excess intracranial bleeding with dual antiplatelet therapy over single therapy in prior stroke patients was not new (Table 1). In the 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. The same was observed in the much larger PROFESS study with similar patients, in which the combination of aspirin and dipyridamole increased significantly the risk of intracranial bleeding compared to clopidogrel.
alone\textsuperscript{12}. Finally, in the 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 to aspirin alone\textsuperscript{13}.

In this issue of \textit{Circulation} the results are published of the prespecified subgroup analysis of patients with a previous stroke or TIA from the well-known PLATO trial on ticagrelor versus clopidogrel in acute coronary syndromes\textsuperscript{14}. These patients faced higher rates of death, stroke and myocardial infarction than those without a previous cerebrovascular event. Also non-CABG TIMI major bleed was seen more often. Although statistically non-significant the reduction of ischemic endpoints with ticagrelor, however, was of the same magnitude as in patients without a prior stroke. This finding is at odds with results of the TRITON trial\textsuperscript{8}, where patients with prior 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 1) that current studies on novel dual antiplatelet therapy in ACS and thereafter exclude patients with previous stroke. The TRILOGY ACS-2 trial (NCT00699998) comparing prasugrel to clopidogrel in 10,000 ACS patients without ST-segment elevation initially treated conservatively excluded prior stroke patients\textsuperscript{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...
PEGASUS trial (NCT01225562), in which 21,000 high risk patients with a remote (1 to 3 years) myocardial infarction are randomized between ticagrelor or placebo on top of aspirin, patients with prior 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 prior 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 prior stroke in the ACS trials mentioned is low (4 to 6%) and the number of excess intracranial bleedings by novel dual antiplatelet therapy even much lower (1 to 2% of that subpopulation). Therefore, in 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.

Conflict of Interest 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:


Table 1. Intracranial Bleeding with Dual Versus Single Antiplatelet Therapy in Large RCTs with Previous Stroke/TIA Patients

<table>
<thead>
<tr>
<th>trial</th>
<th>indication</th>
<th>number 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>TRA-2P**</td>
<td>post stroke/TIA</td>
<td>5,746</td>
<td>100</td>
<td>20/2,876 (0.9%)</td>
<td>2.55 (1.52-4.28)</td>
<td>0.001</td>
</tr>
<tr>
<td>MATCH†</td>
<td>post stroke/TIA</td>
<td>7,540</td>
<td>100</td>
<td>17/3,781 (0.5%)</td>
<td>1.31 (1.02-3.59)</td>
<td>0.03</td>
</tr>
<tr>
<td>PROFESS‡</td>
<td>post stroke/TIA</td>
<td>21,332</td>
<td>100</td>
<td>103/10,151 (1.0%)</td>
<td>1.42 (1.11-1.83)</td>
<td>0.006</td>
</tr>
<tr>
<td>ACTIVE-A††</td>
<td>SPAF**</td>
<td>7,554</td>
<td>13</td>
<td>29/3,782 (0.2%)</td>
<td>1.87 (1.19-2.94)</td>
<td>0.006</td>
</tr>
</tbody>
</table>

*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>number 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>TRITON§</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>PLATO¶</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>

*present study
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Circulation. published online May 9, 2012;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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