Significant excess of early deaths after prehospital ticagrelor: The ATLANTIC trial challenge

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Summary

The recently published Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial concluded that prehospital administration of ticagrelor in patients with acute STEMI appeared to be safe but did not improve pre-PCI coronary reperfusion. The ATLANTIC data fully support the PLATO Angiographic Substudy denying early benefit of ticagrelor, and correspond well with lack of immediate clinical benefit including the early PCI “death paradox” in PLATO-USA patients. Finally, there were significantly (p=0.043) more deaths in early ticagrelor ATLANTIC arm (odds ratio 3.18 (1.02–9.90) challenging stent thrombosis reduction. Indeed, ATLANTIC represents an important step for our better understanding of ticagrelor, although the confirmation of the PLATO mortality wonder in an adequately powered PEGASUS (TIMI-54) to be reported in 2015 will be vital for ticagrelor future.

Table 1: Overall and early all-cause mortality in ATLANTIC trial.

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Prehospital/ In-hospital</th>
<th>Odds Ratio (95 % CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 30 days</td>
<td>30/19</td>
<td>1.68 (0.94–3.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>First 24 hours</td>
<td>12/4</td>
<td>3.18 (1.02–9.90)</td>
<td>0.043</td>
</tr>
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</table>

* – by Fisher’s exact test.

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pulmonary oedema – all well-known complications after ticagrelor already observed in PLATO (5, 6). In light of significant three-fold increase of early ticagrelor deaths, the claim of definite stent thrombosis benefit (secondary endpoint) (1) is especially challenging. The ATLATIC was a simple two arms straight-forward trial, with one drug, and with the same daily dose tested. In fact, the only difference between the treatment regimens was the earlier loading with ticagrelor in the prehospital arm. Therefore, advantage of early ticagrelor in preventing stent thrombosis is most likely attributable to the very early intraprocedural occlusions which are not associated with reduced mortality, as reported in the CHAMPION-PHOENIX cangrelor trial (8). Importantly, if ATLANTIC investigators focus on early 24 hours stent thrombosis, they should mandatory report early mortality comparison, which has been lacking in the ESC presentation of trial results. Moreover, in ATLANTIC the stent thrombosis benefit was not supported by the platelet activity indices, showing no significant difference in platelet inhibition between groups (Suppl. Figures S2 and S3 in [7]). Unfortunately, stent thrombosis “benefits” lately represent a universal tool to please the sponsor, especially obvious when not accompanied by even small trends in mortality advantage, or reverse trends as have happened in ATLANTIC. Such a mismatch between claimed stent thrombosis advantage and identical deaths has been previously observed in clopidogrel CURRENT trial (9), and more profoundly striking in cangrelor CHAMPION-PHOENIX trial (8) when stent thrombosis “reduction” was observed on top of worsened 30-days mortality. Another unpleasant surprise has been finally reported by the ClinTrials.gov but not yet published for the long awaiting PHILO ticagrelor study (NCT01294462) conducted in Asia, in predominantly Japanese patients. Applying the identical to PLATO efficacy endpoint (2), in PHILO preventing of vascular events after ticagrelor (34 events, or 10.3 %) was numerically inferior to clopidogrel (24 events or 8.5 %) with a hazard ratio of 1.44; a 95% confidence interval of 0.85–2.43, and no p-value, or mortality numbers reported. Finally, ATLANTIC unquestionably represents an important step for our better understanding of ticagrelor, although the confirmation of the PLATO mortality wonder in an adequately powered PEGASUS (TIMI-54) (10) to be reported in 2015 will be vital for ticagrelor future.

Conflicts of interest
Dr. Serebruany is listed as an inventor in a pending US patent application: “Treating cardiac arrhythmias, heart failure, peripheral vascular disease and stroke with cyclopentyl-triazolo-pyrimidine or derivative thereof (USN 61/253,829) assigned to HeartDrug”. He received consultant fees from ticagrelor manufacturer.

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References
8 Serebruany et al. Early deaths after ticagrelor