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.

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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” (1).

A few issues merit brief discussion and/or clarification. First, it was a long five years after PLATO trial publication in 2009 (2) to provide the next set of randomised evidence on a novel reversible antiplatelet agent, ticagrelor (1). The ATLANTIC investigators should be acknowledged for fast enrollment, efficient trial management, speedy data analyses and quality publication (1). Considering the controversy surrounding the PLATO trial (3), new independent randomised data on ticagrelor is of utmost importance for prescribing physicians, current and potentially future patients. Second, the primary outcome measure (TIMI-grade 3 flow) in ATLANTIC trial (1) is in agreement with the PLATO angiographic substudy (PLATO-AS) (4). Indeed, large (n=2,616) PLATO-AS revealed that coronary flow, and myocardial perfusion were almost identical after ticagrelor versus clopidogrel (4), while slightly smaller (n=1,852) ATLANTIC denied angiographic benefit of early prehospital (ambulance) versus in-hospital (in the catheterization laboratory) ticagrelor initiation (1). Similarly to PLATO-AS, ATLANTIC corresponds well with the immediate clinical outcomes including the early PCI “death paradox” in PLATO-USA patients, and lack of early ticagrelor benefit in the overall invasive PLATO cohort reported in details by the FDA (5, 6). Interestingly, early ticagrelor may have some interaction with morphine use that resulted in excess of deaths due to shock, oedema, or cardiac arrest. This phenomenon was reported in the ATLANTIC paper abstract stated that “the rates of major adverse cardiovascular events did not differ significantly between the two study groups” (1). Not exactly. In fact, per Table 3 in that publication, there were 11 more deaths in the early prehospital ticagrelor arm (30 vs 19 fatalities) (1). Most importantly, considering the deaths distribution reported in the ATLANTIC Suppl. Table 4S (7) this difference was significant for the first 24 hours (see Table 1 for details).

These extra immediate deaths after ticagrelor were mostly attributed to cardiogenic shock, cardiac arrests, and important, is that ATLANTIC was predominantly done in Western Europe, with no USA patients enrolled, eliminating another controversy of presumably regional differences in ticagrelor outcomes. Third, the ATLANTIC paper abstract stated that “the rates of major adverse cardiovascular events did not differ significantly between the two study groups” (1). Not exactly. In fact, per Table 3 in that publication, there were 11 more deaths in the early prehospital ticagrelor arm (30 vs 19 fatalities) (1). Most importantly, considering the deaths distribution reported in the ATLANTIC Suppl. Table 4S (7) this difference was significant for the first 24 hours (see Table 1 for details).

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>
</tbody>
</table>

* – by Fisher’s exact test.
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 ATLATIC 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 ATLATIC 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 ATLATIC. 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, ATLATIC 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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