The hazards of approximations and extrapolations: Insights from the ATLANTIC study

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The ATLANTIC study demonstrated that administration of the potent P2Y₁₂ antagonist ticagrelor shortly before primary percutaneous coronary intervention (PCI) of STEMI did not improve reperfusion of the culprit artery before the procedure (primary objective) but was safe (1). The pre-specified secondary endpoint of post-procedural definite stent thrombosis was reduced significantly with the prehospital administration of ticagrelor, these results being timely consistent with the pharmacodynamic and electrocardiographic findings suggesting that maximal effect of the pre-hospital administration of ticagrelor occurred shortly after the end of the procedure. All the other pre-specified clinical endpoints were not significantly affected by the pre-hospital administration of ticagrelor.

In this issue of Thrombosis and Haemostasis, Serebruany and colleagues’ Viewpoint focuses on one of these non-significant endpoints. Consistent with his prior critiques, Dr. Serebruany relies on several approximations and extrapolations on non-significant endpoints from grossly underpowered subgroups (2–4).

We answer point by point to each critique addressed to the ATLANTIC study and investigators.

“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.”

This critique is a shortcut of three ideas jumping to a wrong conclusion. First, the authors refer to an exploratory analysis which examined the subset of patients with planned invasive management who actually received PCI within 24 hours (h) of randomisation, defining a subgroup in timing for the PCI subset of PLATO (“early PCI”). They do not report the primary endpoint for this subgroup of subgroup, which was actually similar to the overall PLATO results, hazard ratio (HR)=0.85, 95% confidence interval (CI) (0.74, 0.99) (5). There was no significant difference in cardiovascular death for this subgroup of subgroup but a numerical trend in the wrong direction for ticagrelor: thus, there was no death paradox in the “early PCI subgroup” exploratory analysis.

Second, they extend this speculations to the USA patients who represented 7.6% of the total PLATO population. In the redefined USA subset (different from the initial North America subset), the primary endpoint was not significantly different between ticagrelor and clopidogrel (HR 1.27 (0.92–1.75), p=0.15) but the trend was not favorable to ticagrelor, going in the opposite direction than for the remaining 92.4% of patients (p for interaction=0.009) (2).

However, considering CV death in the US cohort, 24 US patients died on ticagrelor (3.4%) vs 19 (2.7%) on clopidogrel, p=0.45 (p value for interaction was not significant, p=0.12): thus again, there was no death paradox in the US sub-population. Interestingly, in this analysis the numerical difference in death occurred late, beyond four months, unlike in the ATLANTIC study where the numerical difference occurred very early, within the first 24 h. In PLATO, the US subpopulation was different from the rest-of-the-world population by many characteristics including more NSTEMI and more early PCI. Whether ticagrelor treatment before rapid coronary angiography/PCI in NSTEMI (like in the US population) is appropriate is another question which has not been evaluated with ticagrelor but with prasugrel in another study (6–8).

Third, the lack of early ticagrelor benefit in the overall invasive PLATO cohort is well recognised with potential explanations (role of clopidogrel pre-treatment and of the selected population) (9).

Thus, we believe that the significant reductions in death with ticagrelor observed in the main PLATO trial (n=18,758) and in its pre-specified PCI cohort (n=13,408) are real. There was also no effect one way or the other on early mortality in PCI patients in both PLATO and ATLANTIC. Multiplying the subgroups and analysing small subgroups expose rapidly to the risk of false positive. The next remark relates to another subgroup with a new extrapolation to mortality.

“early ticagrelor may have some interaction with morphine use that resulted in excess of deaths due to shock, oedema, or cardiac arrest”

The authors use the results of a subgroup to draw an inadequate conclusion. The interaction we reported in ATLANTIC with morphine was on the primary endpoint of ST segment resolution before angiography, not on clinical endpoints and certainly not on death (1). Other studies have suggested delayed absorption of ticagrelor when mor...
phine is administered, neutralising its biological effect (10). The authors suggest that this may cause death but they contradict themselves as ticagrelor cause death in their 1st point and when neutralised cause death also in their 2nd point. The clinical relevance of this interaction still remains to be proven and registry reports published on this question are not consistent. A secondary ATLANTIC paper on this interaction will be published and, until then, we recommend not to accept the idea that morphine led to more deaths in our study.

“The rates of major adverse cardiovascular events differed between the two study groups”

As shown in Table 3 of our paper, except for stent thrombosis, none of the clinical endpoints differed at 30 days (1). It is interesting that the authors dismiss the only significant finding (stent thrombosis) but speculate on the non-significant finding of mortality. Indeed the deaths occurred very early, when there was no detectable biological effect of ticagrelor according to the platelet function substudy; some of these deaths occurred before PCI was started. In contrast with the significant stent thrombosis effect of early ticagrelor which occurred when there was the largest difference in platelet function between the two groups, the numerical difference in deaths occurred before the antplatelet effect of ticagrelor was detectable in both groups. Thus, the hypothesis of an immediate mortality effect of ticagrelor, observed only in the prehospital group and not in the in-hospital group, when the difference in timing of administration is 31 minutes between the two groups, is not very plausible. A more likely explanation is the imbalance between the two groups in terms of severity of patients, as suggested by a higher TIMI score in the pre-hospital group, leading to more early cardiogenic shock, cardiac arrest, or cardiac rupture in the pre-hospital group. We would suggest that these complications are well known complications of serious acute myocardial infarction rather than well known complications of ticagrelor as stated by the authors.

“The advantage of early ticagrelor in preventing stent thrombosis is most likely attributable to the very early intra-procedural occlusions”

This is another erroneous statement from the authors to dismiss the reduction of definite stent thrombosis with early ticagrelor. Our definition of stent thrombosis did not include low-flow or no-flow complications occurring during the procedure. The stent thrombosis events occurred after PCI, they were angiographically proven, declared by the investigators and confirmed by the adjudication committee.

“the stent thrombosis benefit was not supported by the platelet activity indices”

The small number of patients (n=37) recruited in the platelet function substudy, limited the statistics which were adjusted for the multiple time points. There were obvious differences in platelet reactivity and there was consistency of these results with the findings on the ECG and on stent thrombosis at the same time points and with previous reports on platelet reactivity after oral ticagrelor in STEMI patients (1). The ATLANTIC platelet function substudy with all the pharmacokinetic and pharmacodynamic measurements will be soon published, showing the differential effect between the two strategies after the end of the procedure.

“if ATLANTIC investigators focus on early 24 h stent thrombosis, they should mandatory report early mortality comparison, which has been lacking in the ESC presentation of trial results”

The ATLANTIC results have been reported at the European Society of Cardiology and in the New England Journal of Medicine as indicated in the study protocol and statistical analysis plan, at 30-day follow-up. We understand, however, the interest of the authors for the first 24 h and we will report the results of the study for this period, as we have indeed interesting findings on efficacy for the pre-hospital administration of ticagrelor.

Finally we agree with the authors on the fact that PEGASUS will bring important new information on clinical outcomes of coronary patients treated with ticagrelor.

Conflicts of interest


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References


