ATLANTIC: another reason to investigate the disconnect between stent thrombosis and mortality?

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Administration of a $P2Y_{12}$-inhibitor is recommended by current guidelines in patients with acute coronary syndromes (ACS) (1). In clinical routine, this recommendation often results in pre-treatment with the respective $P2Y_{12}$-inhibitor before the coronary anatomy is known. Two randomised trials from the clopidogrel era suggested that a significant reduction may be achieved with clopidogrel pre-treatment regarding the risk of major adverse cardiac events, also reflecting the circumstance that clopidogrel is a pro-drug with a delayed onset of action (2, 3). However, these studies were often criticised due to their inappropriate designs, long pre-treatment intervals before PCI and lower than recently recommended dosage of clopidogrel loading (4). Observational studies also suggested that ST-segment elevation patients without clopidogrel pre-treatment had an elevated risk for mortality (5) and therefore, pre-treatment with clopidogrel became a widely applied strategy in Europe.

However, an important limitation of clopidogrel is the high variability of its antiplatelet efficacy with the consequent result of high on-treatment platelet reactivity that is associated with an elevated risk for stent thrombosis and mortality (6). Indeed, high on-treatment platelet reactivity has been much discussed and debated, with regards to its definition, measurement and usefulness to clinical practice (7–9).

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The novel oral $P2Y_{12}$-inhibitors prasugrel and ticagrelor provide faster and more predictable platelet inhibition as compared to clopidogrel, and according to the results of two pivotal, large randomised trials, these properties resulted in significant reductions in the composite endpoint of cardiovascular mortality, myocardial infarction or stroke in patients with ACS (10, 11). Since the time needed to achieve peak level of $P2Y_{12}$-inihibition with prasugrel and ticagrelor is substantially shorter than it is the case for clopidogrel, it is a relevant clinical question whether these novel agents should also be used at first medical contact or can be postponed until coronary anatomy is known and the decision of PCI is established (4).

The Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pre-treatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) trial was the first randomized trial to assess the safety and efficacy of prasugrel pretreatment in non-ST elevation acute coronary syndrome (NSTE-ACS) patients (12). According to the results, no benefit was seen in the composite ischaemic endpoint of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularisation, or glycoprotein IIb/IIIa inhibitor rescue therapy; however, the pre-treatment arm using a halved loading dose of 30 mg prasugrel showed a significant excess in major bleeding events (hazard ratio [HR]: 1.90, 95% confidence interval [CI]: 1.19–3.02, p=0.006). (12) These results made current guidelines prohibit the use of prasugrel before coronary angiography in patients with NSTE-ACS. (1)

Following this, the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST-Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) trial aimed at comparing pre- vs intrahospital ticagrelor administration in patients with ST-segment elevation myocardial infarction (13). As a result, no difference was observed in the co-primary surrogate endpoints between the two study arms, and the combined ischaemic secondary endpoint showed no difference, either. Notably, the investigators observed a significant reduction in acute and early definite stent thrombosis with pre-hospital ticagrelor administration; on the contrary, this benefit did not come along with a reduction in all-cause mortality. Interestingly, an even numerically higher risk for mortality was found in the group of patients with pre-hospital ticagrelor administration (3.3% vs 2.0%, p=0.08) (13).

These debatable results prompted Dr. Serebruany and colleagues to write a critical viewpoint on the interpretation of the results and the implications of the ATLANTIC trial (14). This follows other similar provocative critiques of the novel oral $P2Y_{12}$-inhibitors, their trials and the recommendations for their use in guidelines by Serebruany (15, 16).

First, the authors highlight that lack of benefit in the surrogate co-primary endpoints of ATLANTIC trial "corresponds well" with the PLATO angiographic substudy and with lack of early benefit of ticagrelor compared to clopidogrel in the PLATO study (10, 13). It should be clearly emphasised, however, that any comparisons in outcome measures between ATLANTIC and PLATO or its substudies are of limited value, since PLATO evaluated the impact of ticagrelor as reference to clopidogrel, while ATLANTIC was a timing trial, with the single investigational agent of ticagrelor (10, 13). Similarly, regional differences in the observed benefit

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with ticagrelor in contrast to clopidogrel, also known as the "North-American paradox", cannot be supported by the results of the ATLANTIC trial, because the reference arms were completely different. Any unresolved issues from the PLATO study regarding the relative efficacy and safety of ticagrelor in contrast to clopidogrel may potentially be answered and evaluated in context to the upcoming trials of the huge PARTHENON clinical trial program, involving nearly 80,000 patients at high risk of cardiovascular events due to their underlying disease. Since PLATO, PHILO is the only completed randomised, clopidogrel-controlled trial with ticagrelor. Although the results were not yet published, they are presented at www.clinicaltrials.gov., also cited by Dr. Serebruany. Although PHILO enrolled a substantially lower number of patients (n=800) that may result in lack of power to compare hard clinical outcomes such as mortality, results presented at the www.clinicaltrials.gov website suggest no benefit of ticagrelor over clopidogrel in East-Asians with ACS. (NCT01294462) However, we should wait for the peer-reviewed publication to draw any meaningful conclusions regarding the concerns raised by Dr. Serebruany and colleagues, currently being not more than suspicions (14).

Finally, one important aspect needs to be highlighted from ATLANTIC trial that is also stressed in the Viewpoint article: despite the observed reductions in acute and early stent thrombosis, all-cause mortality with pre-hospital ticagrelor was going in the opposite direction, with a trend towards a worse outcome in the pre-treatment arm at 30 days (odds ratio [OR]: 1.68 95% CI: 0.94–3.01, p=0.08), and even showing a post-hoc calculated significant p value (OR: 3.18 95% CI: 1.02–9.90, p=0.04) for events within 24 hours (h) (13, 14). Importantly, ATLANTIC was not powered for 30-day mortality or ST, even not for events within 24 h, so there is a reasonable probability that any differences for ST and mortality may be chanceful findings rather than true clinical observations. However, when putting the study in context, ATLANTIC is not the only recent trial that leaves us surprised with a complete disconnect between stent thrombosis and mortality. Although the explanations of Dr. Serebruany i.e. stent thrombosis would be a universal tool in recent clinical trials "to please the sponsor", is far too provocative and should be rejected, our long-lasted paradigm associating stent thrombosis reductions with mortality benefit may truly be challenged in recent $P2Y_{12}$-inhibitor studies (14). For example, the recently published large Dual Antiplatelet Therapy (DAPT) trial also showed that a prolonged exposure to $P2Y_{12}$-inhibitors effectively reduced stent thrombosis and myocardial infarction; however, despite this clear finding, a trend towards an excess risk for all-cause mortality was found (HR: 1.36, 95% CI: 1.00–1.85, p=0.05). (18)

These lines of evidence may suggest that in contrast to our prior knowledge, the road to an improved survival in modern interventional cardiology using new-generation drug-eluting stents and detailed intracoronary imaging modalities is not simply paved with reductions in stent thrombosis: as a potential consequence of the large reductions in the absolute risk of stent thrombosis, stent thrombosis may not be the dominant mechanism behind overall mortality any more, and other factors such as bleeding, arrhythmias and non-cardiac events might have an enlarged impact in overall patient survival.

Conflicts of interests

DA has received consulting fees from Verum Diagnostica; Lecture fees from DSI/Lilly, AstraZeneca, Verum Diagnostica, Roche, Krka. DS has received speaker fees and honoraria for consulting from Eli Lilly, Daiichi Sankyo, Bayer Vital, Astra Zeneca, Verum Diagnostica and Roche Diagnostics and research grants from Roche Diagnostics.

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