There’s life in the old dog yet: Clopidogrel competing with prasugrel and ticagrelor for treatment of ACS patients

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In acute coronary syndromes (ACS), blood platelets are highly activated and this generates the need for achieving reliable, consistent and potent platelet inhibition in affected patients. Achieving adequate platelet inhibition is of utmost importance in particular for those ACS patients undergoing percutaneous coronary intervention (PCI) with stent implantation, the preferred treatment strategy for these patients. Clopidogrel, as part of a dual antiplatelet treatment (DAPT) consisting of aspirin and a P2Y₁₂ receptor inhibitor, has been the standard of care for ACS patients in the past. Due to its pharmacological characteristics including a delayed onset of action, a large response variability and an insufficient antiplatelet action in some patients (1), there was a need to develop, to study and to introduce new agents that may overcome these limitations. With the thienopyridine prasugrel (2) and the cyclo-pentyl-triazolo-pyrimidine ticagrelor (3) two potent agents for treatment of ACS patients are now available. Both agents have demonstrated their superiority over clopidogrel in terms of thrombotic risk reduction in large-scale randomised trials (2–4). However, despite their clear superiority over clopidogrel with regard to reducing ischaemic events, only a fraction of ACS patients are currently receiving either of the potent antiplatelet drugs, suggesting a substantial underutilisation.

In a Viewpoint article published in this issue of Thrombosis and Haemostasis, Serebruany and Fortmann (5) provide their personal views and give possible explanations for the limited use of prasugrel and ticagrelor in clinical practice and specifically in the treatment of ACS patients. According to the authors, a substantial gap exists between the growing totality of published scientific data supporting use of novel antiplatelet drugs in ACS patients, deriving mostly from the dedicated phase III trials (2, 3) TRITON-TIMI 38 (for prasugrel) and PLATO (for ticagrelor), and their use and sales numbers in clinical practice, that have not met expectations so far. As a major reason for underutilisation of the potent antiplatelet agents the authors allege a considerable mistrust with regard to published trial data resulting in resistance of interventional cardiologists and physicians to implement prasugrel and ticagrelor as a first-line strategy in the pharmacological treatment of ACS patients. According to the authors, skepticism of physicians is also caused by other factors, including doubtful event adjudication, unrealistic cost-effectiveness analyses, confusion caused by negative results of prasugrel in conservatively managed patients (6) and a lack of specific data reporting on the sub-group of PCI-treated patients in the case of ticagrelor. Serebruany has challenged the data on prasugrel and ticagrelor (and their respective clinical trials) numerous times, even in this journal (7–9), firing up much debate and discussion (10).

Indeed, published data do not support the use of prasugrel in ACS patients without invasive vascularisation (6), while data are clearly positive for ticagrelor in this regard (11). However, the development of both prasugrel and ticagrelor was originally driven by the idea of having more potent drugs available for the treatment of ACS patients undergoing PCI, the recommended treatment strategy in ACS (12, 13). While the trial design of TRITON-TIMI 38 reflected this circumstance (2), the design of the PLATO trial (3), in which approximately 30% of the patients were managed non-invasively, makes it difficult to draw meaningful conclusions on benefits and shortcomings of ticagrelor in the PCI sub-group. The published PLATO invasive sub-study (14) combined PCI-treated patients and patients scheduled to undergo CABG. Despite their importance, such data reporting cannot substitute for detailed and in-depth analyses on the PCI sub-cohort.

Interestingly, non-peer-reviewed raw data on the PCI subgroup was made available during the approval process of the drug in France by the French National Authority for Health showing no mortality benefit and a modest benefit for ticagrelor vs. clopidogrel with regard to the primary ischaemic study end point (15). Certainly, these data reporting require further confirmation by the PLATO investigators in the form of a peer-reviewed publication focusing specifically on the invasive PLATO PCI-cohort. With regard to CABG-treated patients, which were also included into the published PLATO invasive sub-study (14), the ongoing Study Comparing Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG (TiCAB) (ClinicalTrials.gov Identifier: NCT01755520) will provide important results on the use of ticagrelor vs aspirin as monotherapy for patients undergoing surgical revascularisation.

While the present Viewpoint paper surely raises some valid points, it also includes some debatable hypotheses that require further investigation. In particular, caution is advised on drawing too early conclusions on critical aspects of randomised trials like end point reporting and event adjudication. Specifically for PLATO, this issue is under investigation by the US Department of Justice and we should wait for the results of this investigation. The
Viewpoint paper also emphasises the need for further independent and comparative assessments of the two newer antiplatelet agents.

While a direct comparison of prasugrel vs. ticagrelor is still lacking, the ongoing Prospective, Randomized Trial of Ticagrelor Versus Prasugrel in Patients With Acute Coronary Syndrome (ISAR-REACT 5) (16) aims at closing this gap of knowledge (ClinicalTrials.gov Identifier: NCT01994800).

Bleeding complications, having a huge impact on patients’ mortality (17), are a major down-side of novel anti-platelet agents and it is likely that the higher risk for non-CABG related bleeding observed for both prasugrel (2) and ticagrelor (3) constitutes the key reason for their underutilisation nowadays. Bleeding events and especially the differential bleeding risk at different time points during DAPT treatment receive little attention in the current viewpoint manuscript (5). In this context, it is worth mentioning that current NSTEMI and STEMI guidelines recommend a 12-month treatment duration for both prasugrel and ticagrelor as part of a DAPT regimen (12, 13). These recommendations, however, are challenged by a dedicated landmark analysis of the TRITON-TIMI 38 trial (18), showing that most of the benefit of prasugrel with regard to thrombotic risk reduction is gained during the early phase of treatment, while bleeding risk is not an issue of the acute but of the sub-acute and chronic phase of treatment. Consequently, strategies to optimise P2Y12 receptor directed antiplatelet treatment beyond the acute phase and during the maintenance phase of treatment might significantly improve the outcome of ACS patients undergoing PCI. Such strategies also appear reasonable considering that the physiological life-time of platelets in the peripheral blood stream amounts to about 7-10 days with a daily renewal rate of about 20% of the total platelet count. Thus, randomised and well-controlled trials are urgently needed that aim at investigating ways of antiplatelet treatment de-escalation during the different phases (acute, sub-acute, chronic) of an ACS. The HORIZONS-AMI II trial, already announced (19) and scheduled to start in autumn 2014, and the already ongoing Testing Responsiveness to Platelet Inhibition on Chronic Antiplatelet Treatment For Acute Coronary Syndromes (TROPICAL-ACS) trial (ClinicalTrials.gov Identifier: NCT01959451) are focusing on such a treatment de-escalation consisting of prasugrel treatment in the acute phase and a switch to clopidogrel during the sub-acute and chronic phase of treatment. This type of treatment de-escalation may also lead to increased utilisation of potent antiplatelet agents in the acute phase of an ACS and a more selective use during the sub-acute and chronic treatment phase. It may well be that these and other upcoming studies will keep the old dog of clopidogrel alive, much longer than originally expected.

Conflicts of interest
Dirk Sibbing reports receiving speaker fees from Daiichi Sankyo, Verum Diagnostica, Astra Zeneca, Eli Lilly and Roche Diagnostics and consultancy fees from Verum Diagnostica, Haemonetics and Eli Lilly. Steffen Massberg reports no conflicts of interest

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References