The elusive disconnection between mortality and early stent thrombosis: Observations from the CHAMPION-PHOENIX trial

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Ever since coronary stenting became the standard of care for the treatment of acute ST-elevation myocardial infarction (STEMI), the flip side of this approach became evident. Stent thrombosis annihilates the effect of early and complete reperfusion of the culprit lesion, and leads to considerable mortality (1). Failure to inhibit platelets contributes to stent thrombosis, and therefore after acute coronary syndromes (ACS) optimal antiplatelet therapy is considered the best weapon against it (2, 3).

So far, the oral platelet P2Y12 blockers on top of aspirin are the standard of care in patients undergoing percutaneous coronary intervention (PCI) for ACS (4, 5). In the previous century the intravenous platelet glycoprotein IIb/IIIa receptors were introduced. They inhibit the final common pathway of platelet aggregation immediately and are still often used for bail-out in patients undergoing PCI for ACS, especially STEMI, who have a large thrombus load on angiography. Recently, it was shown that oral anticoagulation also reduces stent thrombosis after ACS (6). Finally, modern stent design makes stent thrombosis less likely in the first place.

The problem with the new P2Y12 antiplatelet agents is that they block platelet reactivity only after several hours in STEMI (7, 8). Indeed, various aspects of the novel P2Y12 antplatelet agents have stimulated healthy debate and discussion (9-14). The novel intravenous P2Y12 blocker cangrelor blocks platelet aggregation immediately and, thus, has theoretical advantages. In a recent meta-analysis it was shown that cangrelor is more effective than clopidogrel in PCI including STEMI in three major trials (15). Therefore, cangrelor seems the ideal antiplatelet agent for the invasive treatment of ACS.

In this issue of *Thrombosis and Haemostasis* an interesting viewpoint (16) focuses on the differences between the reduction in stent thrombosis with cangrelor and the lack of a mortality benefit in the recent large CHAMPION-PHOENIX trial (17). The authors are right in that intra-procedural stent thrombosis is included in the definition of stent thrombosis, and that is the reason that the rate of stent thrombosis is much larger than in the two previous trials with cangrelor for PCI (18, 19). Early stent thrombosis can be taken care of in hospital and, therefore, has little early prognostic impact. This is very likely the reason for the disconnection between the rates of early stent thrombosis and mortality. In CHAMPION-PLATFORM, however, there was a relation between the two, but that disappeared within 30 days (18). Early stent thrombosis though carries a risk of repeat out-of-hospital stent thrombosis, probably of stent position or specific patient features. Here stronger antiplatelet agents may have a role, but were not given in CHAMPION-PHOENIX.

The second point in the viewpoint on the lack of 30-day data is correct. This should be given not only because they were presented earlier on a large cardiology convention, but they were also included in the very recent meta-analysis of the three trials of cangrelor for PCI (9). One can only guess, why these data were not published in the main paper. Possibly, the 9% excess mortality with cangrelor in CHAMPION-PHOENIX is the reason, but in the meta-analysis mortality was neutral between cangrelor and clopidogrel.

Here we come to the Achilles heel of cangrelor in PCI: there is a reduction in myocardial infarction and stent thrombosis, but without a mortality reduction in nearly 25,000 patients when compared to clopidogrel (15). Very similar results were seen in the 25,000 patients CURRENT-OASIS-7 study. In comparison to standard of care a higher loading of clopidogrel and a one month run with a higher maintenance dose in PCI for ACS was associated with less stent thrombosis and numerically less myocardial infarction, but without a mortality-benefit (20). Likely the increased bleeding seen with cangrelor and with a higher dose of clopidogrel is responsible for neutralisation of a potential mortality benefit. Bleeding may lead to discontinuation by the physician or patient of lifesaving antithrombotic agents (21) or, even worse, of other lifesaving medication.

Thus, for use in PCI cangrelor seems a promising agent, but is certainly not a breakthrough. If registered, it will be a costly drug. Worldwide many patients in the need of PCI are pretreated with dual antiplatelet agents because of unstable coronary syndromes or, in elective cases, just by physicians’ preference in the view of optimal protection during PCI. Clopidogrel has a slow onset of action and should be started several days ahead of PCI for optimal protection during the procedure. Possibly in STEMI, where the novel antiplatelet agents show also a slow platelet inhibition, it may work better, but this should be tested in a new prospective trial with liberal use of...
glycoprotein receptor blockers, that were hardly used in the three trials with cangrelor. But such a STEMI trial is unlikely to be carried out in the future.

Conflicts of interest
F. Verheugt is advisor for Astra-Zeneca, the Medicines Company and Daiichi-Sankyo.

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References