Any room left for new antiplatelet agents in acute coronary syndrome?

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Editorial

This editorial refers to ‘Effect of vorapaxar on myocardial infarction in the thrombin receptor antagonist for clinical event reduction in acute coronary syndrome (TRA-CER) trial’†, by S. Leonardi et al., on page 1723

Over the past two decades, the combination of aspirin and clopidogrel has been the gold standard antiplatelet strategy to prevent recurrent ischaemic events after an acute coronary syndrome (ACS). Several new pharmacological options have been evaluated since then. This includes more potent dual antiplatelet therapy (DAPT) with the new generation of P2Y12 inhibitors, and triple oral antithrombotic therapy (TOAT), a combination of aspirin and clopidogrel with either oral low dose Xa inhibition or oral platelet thrombin receptor blockade. Selecting the most favourable strategy for the post-ACS period warrants a careful evaluation of the risks and benefits for each patient. Although the one size fits all strategy is not ideal, the strategy of selecting drugs and doses according to patient characteristics remains challenging. Indeed, the ischaemic risk decreases over time, and the benefit of a prolonged and stronger antiplatelet treatment is so far unknown, especially in fragile patients who deserve more protection against ischaemic events but are also exposed to more severe bleeding on treatment.

A more aggressive P2Y12 receptor blockade has consistently improved clinical outcome of ACS patients as compared with clopidogrel. Shorter and stronger platelet inhibition has also become an option in percutaneous coronary intervention (PCI) with the superiority of canegrelor over clopidogrel in the CHAMPION PHOENIX trial, although even a treatment limited to the time of PCI was associated with more bleeding complications. The benefit of stronger P2Y12 inhibition is particularly clear in patients with ST elevation myocardial infarction (STEMI) undergoing primary PCI. In these patients, the benefit of stronger P2Y12 inhibition is mainly driven by a reduction of stent thrombosis and recurrent myocardial infarction (MI), with no excess of major bleeding events. The associated mortality benefit and the lack of an indication of excess bleeding accounts for the class I recommendation of this strategy in the current guidelines for STEMI. The trade-off between an increase in bleeding and the reduction of ischaemic events in non-ST-elevation myocardial infarction (NSTEMI) patients highlights the need for a careful risk stratification in this particular subset of patients. The reduction of further cardiovascular events with a striking mortality benefit in patients who survived a first non-fatal event without additional recurrent major bleeds, when compared with clopidogrel, is another demonstration in favour of a more aggressive P2Y12 blockade strategy in the highest risk patients (Figure 1). The approach of personalized P2Y12 inhibition in the high risk/fragile patients in whom the net clinical benefit of prolonged P2Y12 inhibition is uncertain due to higher risk of bleeding (NCT01538446) is an attractive option to solve the trade-off, although such a strategy was unsuccessful in low to moderate risk patients undergoing PCI.

Long-term factor-Xa blockade appears to be a new possibility for secondary prevention after a high risk ACS. The mortality benefit of enoxaparin over unfractionated heparin in patients undergoing PCI has paved the way for more specific investigation of this pharmacological target, especially in the context of primary PCI for STEMI when all patients are on DAPT. However, the benefit of subcutaneous low molecular weight heparin on top of aspirin was mainly restricted to the first week after ACS in medically managed patients, with limited additional reduction in ischaemic events when a full anticoagulation regimen was continued for a prolonged period of weeks to months. The new oral factor-Xa inhibitors have the potential to improve secondary prevention of ACS. Four phase II and phase III trials evaluated dosing strategies and long-term clinical benefit of TOAT using rivaroxaban or apixaban in addition to DAPT after an ACS. High baseline risk of the patients, previous stroke or transient ischaemic attack, and excess dosing of apixaban led to excessive bleeding and no ischaemic benefit of TOAT in APPRAISE-2. The ATLAS ACS 2-TIMI 51 (NCT00809965) was a phase III trial that randomized 15 526 patients with recent ACS to receive twice-daily dosing of either placebo, rivaroxaban 2.5 mg, or rivaroxaban 5 mg. The absolute 0.6% excess of TIMI (thrombolysis in

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myocardial ischaemia) major bleeding with rivaroxaban is similar to what was observed with prasugrel or ticagrelor in similar ACS populations. The safety was significantly better with the low dose of 2.5 mg than with 5 mg, including a significant decreased rate of fatal bleeding ($P = 0.04$). In addition, the 2.5 mg dose group showed a significant reduction in all-cause mortality [hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.53–0.87; $P = 0.002$] the best safety criterion, if any. Stent thrombosis and MI were also reduced compared with placebo. These results suggest that prolonged factor-Xa blockade in addition to DAPT is an attractive strategy in patients without co-morbidities, a strategy that may compete with DAPT using a new P2Y12 inhibitor. Leonardi et al. now report the effect of vorapaxar on MI. This was a pre-specified substudy of the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome trial (TRACER). This study showed vorapaxar vs. placebo in nearly 13,000 patients with non-ST-segment elevation ACS that was terminated prematurely, after completion of enrolment, and after the target endpoint was reached, following an unplanned independent safety review. Vorapaxar is an antagonist of protease-activated receptor 1, the main thrombin receptor on human platelets, which inhibits thrombin-induced platelet activation—the most important link between coagulation and platelet aggregation. Phase II investigations performed in the setting of ACS and PCI demonstrated that vorapaxar on top of DAPT did not increase risk of bleeding compared with placebo, and reduced the occurrence of MI. Therefore, vorapaxar might have been seen as ideal for ACS, acutely and for long-term secondary prevention.

The authors assessed vorapaxar effects in reducing total occurrences of MI, post-randomization (both the first and subsequent), which are in fact recurrent events as 94% of participants experienced an MI as their qualifying event for study inclusion. Both recurrent (HR 0.88; 95% CI 0.79–0.98; $P = 0.021$) and total infarctions (HR 0.86; 95% CI 0.77–0.97; $P = 0.014$) were reduced. This effect was not specifically related to the size of infarction but directionally consistent, as previously reported with prasugrel and ticagrelor when compared with clopidogrel. Of interest, patients who were not treated with thienopyridine at baseline were the only subgroup who experienced fewer MIs on vorapaxar. In addition, type 4a MIs, the major driver of the clinical benefit of new P2Y12 inhibitors, were not significantly reduced by vorapaxar (HR 0.90; 95% CI 0.73–1.12; $P = 0.35$).

Although these data are convincing, they need to be put in perspective with the exploratory nature of the analysis, focused on a secondary endpoint when the main study was negative in terms of its primary endpoint. Moreover, the analysis is performed according to 2007 universal definitions of MI, when a new version of these definitions has been now published. The safety of the drug also poses a question, with a three-fold excess in intracranial haemorrhage (0.24% vs. 1.07%) (Figure 2). The interaction between thienopyridine use over time and vorapaxar effect is another unsolved issue.

**Figure 1** Risk reduction of first and recurrent cardiovascular events according to different antiplatelet strategies. MI, myocardial infarction; RR, relative risk.

**Figure 2** Safety profile of various antithrombotic strategies in secondary prevention of ACS. HR, hazard ratio; TIMI, thrombolysis in myocardial ischaemia.
So far, DAPT including aspirin and P2Y$_{12}$ receptor inhibitors remains the easiest strategy during and after the acute phase of an ACS among the various strategic options. Whether the DAPT strategy must be changed during the first year following an ACS (addition of a third antiplatelet agent or of an oral Xa inhibitor) remains uncertain and can only be determined on a case by case evaluation of the risk and benefit. PEGASUS will tell us if there is a benefit for a prolongation of strong DAPT in patients at high risk (prior myocardial infarction). TRA2P and CHARISMA suggest that it may well be the case. More drugs, including PAR-4 inhibitors, are also on the horizon with the usual expectation of an ischaemic benefit without excess bleeding.

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**References**


