P2Y12 inhibitors in acute coronary syndromes: How do we choose the best drug for our patients?

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The development of oral inhibitors of the platelet P2Y12 receptor has improved outcomes in patients with acute coronary syndromes (ACS) and in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI) with stenting. The first thienopyridine drug, ticlopidine, proved to be effective after coronary stenting, but because of many side effects this drug was replaced by its sister compound, clopidogrel. Clopidogrel, when used in combination with low-dose aspirin was shown to be beneficial in patients with non ST-elevation ACS (1).

During the past five years, new P2Y12 inhibitors have been introduced, but large-scale head-to-head comparisons of the efficacy and side effects of these drugs are not available (2). In this issue of Thrombosis and Haemostasis, Steiner et al. (3) report the results of a network meta-analysis used to indirectly compare the efficacy and safety of prasugrel, ticagrelor, standard and high-dose clopidogrel in patients undergoing PCI.

Optimisation of clopidogrel dosing and the development of new drugs have been undertaken because the platelet inhibitory effect of clopidogrel has a relatively slow onset and also a variable efficacy. Several studies have shown that a low platelet response to clopidogrel is associated with a poor outcome (for review see [4, 5]). The cause of reduced platelet inhibition is multifactorial and in part due to genetic variability in the CYP-system, the presence of ACS especially acute ST-elevation myocardial infarction (STEMI), diabetes mellitus and other factors.

Prasugrel is a third generation thienopyridine agent. Like clopidogrel, prasugrel is a prodrug, although more efficiently converted to its active metabolite than clopidogrel. Prasugrel has a more rapid onset of action and provides a stronger and more consistent inhibition of platelet aggregation than clopidogrel (6, 7). Also, there is little evidence of rebound platelet hyperreactivity following cessation of prasugrel (8).

Ticagrelor, an ATP analogue, is a reversible P2Y12 ADP receptor antagonist. Ticagrelor does not require metabolism in the liver, thus leading to less inter-individual variability and a more consistent inhibition of platelet aggregation compared to clopidogrel (9). Regarding offset, surprisingly there was no significant difference in the extent of platelet inhibition between ticagrelor and clopidogrel at 24 and 84 hours following the final dose (9). Moreover, the pharmacodynamic properties of ticagrelor are not affected by the CYP2C19 genotype (10).

CURRENT-OASIS 7 was a randomised trial evaluating the efficacy of high- and low-dose antiplatelet therapy with aspirin and clopidogrel in patients with ACS (11, 12). More than 25,000 patients were recruited, and around 17,000 of these patients were deemed suitable for PCI. Patients were randomised to either high-dose (600 mg loading dose followed by 150 mg daily for one week followed by 75 mg daily) or low-dose (300 mg loading dose followed by 75 mg daily) clopidogrel and in a second randomisation assigned to either high-dose or low-dose aspirin. CURRENT-OASIS 7 did not demonstrate a reduction in the primary outcome (death, myocardial infarction [MI] or stroke at 30 days) in patients receiving high-dose clopidogrel (4.2% vs. 4.4%, p = 0.30), but there was a significant reduction of the secondary endpoint of stent thrombosis in the subgroup of patients undergoing PCI (1.6% vs. 2.3%, p = 0.001). This benefit, however, was obtained at the expense of more major bleeding (2.5% vs. 2.0%, p = 0.01). The dose of aspirin had no effect on the primary or secondary endpoints and no effect on bleeding rates (11).

The TRITON-TIMI 38 trial compared prasugrel and clopidogrel in ACS patients treated with aspirin (13). Double-blind randomisation was done in the catheterisation laboratory after angiography had revealed that the anatomy was suitable for PCI. More than 13,500 patients received either prasugrel (60 mg loading dose followed by 10 mg daily) or clopidogrel (300 mg loading dose followed by 75 mg daily) and treatment was continued for 6 to 15 months. The composite primary endpoint of cardiovascular death/MI/stroke favoured prasugrel (9.9% vs. 12.1%; p < 0.001); a benefit mainly driven by a reduction in non-fatal MI (7.3% vs. 9.5%, p < 0.001) and not by death (2.1% vs. 2.3%, p = 0.31) or non-fatal stroke (1% in both groups). Furthermore, there was a significant reduction in the need for target vessel revascularisation (3.7% vs. 2.5%, p < 0.001) and stent thrombosis with the use of prasugrel (2.4 vs. 1.1%, p < 0.001). However, the use of prasugrel conferred an increased incidence of non-coronary artery bypass grafting (CABG) TIMI major bleeding (2.4% vs. 1.8%, p = 0.03) and life-threatening bleeding (1.4% vs. 0.9%, p = 0.01).

A post-hoc subgroup analysis recognised three specific groups in which the benefit-to-harm risk profile differed from the overall study results. The first two...
groups included patients of 75 years or older and patients with a body weight of less than 60 kg; these patients had no overall benefit or harm. The third group, patients with a history of previous stroke or transient ischaemic attack (TIA), had an overall increase in adverse outcomes with no evidence of clinical benefit. In this group, the incidence of major bleeding was 2.3% with prasugrel vs. 0% in the equivalent group treated with clopidogrel (p < 0.02) (13). Accordingly, prasugrel should not be used in patients with a history of previous stroke or TIA, and the dose should be reduced to 10 mg/day in the elderly (>75 years) and those with a body weight less than 60 kg. Another subgroup analysis restricted to patients with diabetes mellitus showed that the reduction in the composite primary endpoint was significant in both diabetic and non-diabetic patients (14). However, the relative reduction was largest in patients with diabetes (30% vs. 14%), and the incidence of major bleeding was similar among diabetic patients, thus contrasting with the increased bleeding incidence seen with prasugrel in non-diabetic patients. Overall, the net clinical benefit of prasugrel seems larger in ACS patients with diabetes (14, 15). Also in the STEMI subgroup there was an overall benefit of prasugrel (16).

The PLATO trial included ACS patients with either a planned invasive or non-invasive treatment strategy (17). The composite endpoint of death from vascular causes, MI or stroke was significantly lower with ticagrelor compared with clopidogrel (9.8% vs. 11.7%; p<0.001). Furthermore, there was a significant reduction in the occurrence of the secondary endpoints (a composite of death from any cause, MI and stroke) in the ticagrelor group (10.2% vs. 12.3%, p < 0.001), and a significant reduction in a composite of death from any cause, MI and stroke in addition to recurrent ischaemia, TIA or other arterial thrombotic events (14.6% vs. 16.7%, p < 0.001). In the ticagrelor group, a significant reduction in the incidence of MI alone was seen (5.8% vs. 6.9%, p = 0.005), and, importantly, the rate of death from any cause was also reduced with ticagrelor (4.5% vs. 5.9%, p < 0.001). In terms of safety, there was no significant difference in TIMI major bleeding (7.9% vs. 7.7%, p = 0.57), and there was no difference in the incidence of fatal or life-threatening bleeding (5.8% in both groups). Ticagrelor conferred an increased incidence of non-CABG TIMI major bleeding (4.5% vs. 3.8%, p = 0.03) and intracranial bleeding as a whole (0.3% vs. 0.2%, p = 0.06), including fatal intracranial bleeding (0.1% vs. 0.01%, p = 0.02). In contrast, the occurrence of other types of major bleeding was reduced with ticagrelor (0.1% vs. 0.3%, p = 0.03) (17). The effect of ticagrelor compared with clopidogrel on the primary endpoint in the subgroup of patients with STEMI with planned PCI was consistent with the overall study population (10.8% vs. 9.4%; p = 0.07) (18) and the benefit of ticagrelor was present whether patients were treated invasively or conservatively (19). Patients with impaired renal function appear to profit particularly from ticagrelor (20). Finally, in the subgroup of ACS patients with a history of ischemic stroke or TIA the efficacy and bleeding results of ticagrelor were consistent with the overall trial population (21).

At first glance, data from TRITON-TIMI 38 and PLATO suggest that prasugrel and ticagrelor are superior to clopidogrel. However, it should be acknowledged that TRITON-TIMI 38 was designed for patients scheduled for PCI. Additionally, the dose of clopidogrel used in this study was lower than what is recommended by the most recent ESC NSTEMI guidelines (22).

In summary, these trials have proven that new stronger platelet inhibitors are beneficial for ACS patients with a price to pay of an increase in non-CABG TIMI major bleedings, but as the overall benefit is clear, these new drugs are now recommended in the guidelines. Unfortunately, we have very little clinical comparative data between prasugrel and ticagrelor.

Steiner et al. (3) systematically searched the literature and identified head-to-head randomised controlled trials in order to indirectly compare the efficacy and safety of prasugrel, ticagrelor, standard and high-dose clopidogrel in patients undergoing PCI. A total of 14 randomised trials were included, three of which provided almost 90% of all patients. Some of the drug comparisons were only performed in one (ticagrelor vs. clopidogrel) or a few studies.

Network meta-analysis was performed using generalised linear mixed models with adjustment for length of follow-up. The method of network meta-analysis is considered to be able to attenuate the bias inherent to indirect comparisons.

No significant differences were found for efficacy outcomes except for stent thrombosis favouring prasugrel. Prasugrel exhibited a similar bleeding risk as high-dose clopidogrel, but more bleeding compared to ticagrelor. Ticagrelor was associated with less bleeding compared to high-dose clopidogrel. No differences were seen for non-CABG-related major bleeding between the three strategies, which were all associated with higher bleeding rates than standard dose clopidogrel. Steiner et al. restricted their study to patients undergoing PCI, but the results were corroborated in a subgroup analysis comprising only patients with ACS.

Our guidelines from the European Society of Cardiology (ESC) and the American Heart Association (AHA)/American College of Cardiologists (ACC) are helping us to practice evidence-based medicine. The recommendation and level of evidence is mainly based on randomised clinical trials and to some extent also on subgroup analyses from such trials. High-quality traditional meta-analyses are also taken into account. The use of network meta-analysis enables several treatments to be compared using both direct comparisons of the intervention within randomised controlled trials and indirect comparisons across trials based on a common comparator (23). Thus, network meta-analysis allows comparison of drugs that have not been directly compared in head-to-head trials.

Whether and how results from network meta-analyses will have impact on guidelines is an open question. We hope that it will be possible to perform a head-to-head comparison of the three treatment strategies evaluated by Steiner et al. in order to provide a more definitive answer to the question: “Which P2Y12 inhibitor should we use?”

Conflicts of interest
SDK has received lecture fees from AstraZeneca, Daiichii-Sankyo, Eli Lilly, and Sanofi-Aventis. ELG has received lecture fees...
invited editorial focus

from Bayer, Boehringer Ingelheim, and Pfizer, and serves on the advisory board for AstraZeneca. AMH has no conflicts of interest to declare.

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