Platelets and acute coronary syndromes

Acute coronary syndromes (ACS) are the leading cause of death worldwide and one of the main reasons for hospital admissions in developed countries. ACS thus represent a major public health concern.

Platelets play a pivotal role in the pathophysiology of ACS. They are small anuclear cell fragments, measuring 2-3 μm, produced in the bone marrow as a result of the fragmentation of megakaryocytes. The life span of a platelet is about 7-10 days, and around 10^{11} platelets are produced every day (1). Platelets also play an important role in normal haemostasis and healing processes.

Circulating platelets constantly interact with the vascular endothelium, but remain inactive due to the inhibitory action of e.g. nitric oxide and prostacyclin produced by endothelial cells. Upon endothelial injury, the subendothelium is exposed to the blood stream and the circulating platelet pool. This, in turn, promotes the release of mediators and cytokines that lead to the activation of receptors responsible for adhesion and aggregation, such as the P2Y12, thromboxane A2 and glycoprotein IIb/IIIa receptors.

Activation of these receptors induces platelet aggregation, temporarily sealing the breach in the vessel wall. Aggregated platelets provide a platform on which fibrin is incorporated once the full coagulation cascade has been activated. Regeneration of the damaged tissue is facilitated through the release of platelet growth factors. Once the healing process is complete the clot is broken down and reabsorbed (2,3).

Recently, the emergence of two new P2Y12 inhibitors, prasugrel and ticagrelor, has challenged the role of clopidogrel. Similar to clopidogrel, prasugrel is a prodrug that needs hepatic conversion to its active metabolite to provide irreversible P2Y12 inhibition. In contrast, ticagrelor is a direct-acting allosteric P2Y12 antagonist inhibiting the P2Y12 receptor reversibly. Both drugs provide a better protection against cardiovascular outcomes than clopidogrel as evidenced by large clinical trials. This benefit might partly reflect the rapid onset of action and the pronounced antiplatelet effect of these drugs compared to clopidogrel. So far, no direct comparison of prasugrel and ticagrelor has been performed, but ongoing trials will provide data to clarify the clinical role of these drugs.

The present review outlines the key milestones of the history of P2Y12 inhibitors and provides an up-to-date overview and comparison of the clinical applicability of these drugs.
Despite their key role in haemostasis, platelets may cause tissue damage once activated inappropriately. In particular, platelet aggregation is harmful in the lumen of a coronary artery already partly obstructed by the intraluminal extension of an atheromatous plaque. Rupture of an unstable plaque may have fatal consequences. The exposure of the lipid-rich centre of the plaque leads to the activation of platelets potentially initiating a platelet activation cascade. If platelet activation continues it may occlude the vessel and compromise blood flow to the part of the myocardium distal to the occlusion. Eventually, this results in myocardial injury and necrosis (2).

Although activation, adhesion and aggregation of platelets are necessary components during normal vascular healing processes, inhibiting their function is potentially beneficial. Sufficient inhibition of platelet aggregation is one of the main goals in the pharmacological management of ACS, and current guidelines advocate the use of dual antiplatelet therapy (4;5). The prevailing dual antiplatelet strategy is the use of aspirin and clopidogrel. However, new potent drugs have recently been introduced and may serve clinicians as strong alternatives to the traditional regimen for dual antiplatelet therapy. Important differences between currently available anti-platelet drugs are outlined in Table 1.

**Aspirin**

Aspirin (acetylsalicylic acid) was the first major drug used in the setting of preventive antiplatelet therapy. Aspirin inhibits platelet aggregation by reducing thromboxane A2 production. This is achieved through the acetylation of the cyclooxygenase (COX)-1 enzyme leading to its permanent deactivation and inability to produce the platelet activator thromboxane A2. Aspirin has a rapid onset of action, and the maximum effect is achieved within one hour of administration (6). In healthy individuals, a single dose of 20 mg, 325 mg and 600 mg leads to inhibition of COX function by 34%, 89% and 95%, respectively (7).

Residual platelet function results from the continued stimulation of aggregation through COX-1 independent pathways mediated by adenosine diphosphate (ADP) and thrombin.

Furthermore, as platelets are anuclear they are unable to regenerate enzymes, which is why the inhibition persists for the entire lifespan of the platelet (6). Aspirin has been proven to reduce morbidity and mortality in the context of secondary prevention, whereas its benefit in primary prevention is a modest reduction of vascular events although offset by the increased risk of major bleeding (8).

**Clopidogrel**

Clopidogrel is a second generation thienopyridine. It is a prodrug, which is well absorbed from the gut, but requires activation in the liver through the cytochrome P450 (CYP) system. The active metabolite of clopidogrel inhibits the ADP receptor-mediated platelet aggregation pathway. The need for activation partly accounts for the delayed onset of its antiplatelet effect. This delay can be reduced by the use of higher doses of clopidogrel (9).

CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) was a landmark trial, which established clopidogrel as a cornerstone in dual antiplatelet therapy and affirmed that increased platelet inhibition entails a reduction in cardiovascular events (10).

CURE was a randomised, double-blind, placebo-controlled trial in which a total of 12,562 ACS patients were included most being treated conservatively rather than invasively. Only patients without ST-segment elevation being hospitalised within 24 hours of symptom onset were included.

The study was later refined to only include patients with either electrocardiographic changes consistent with cardiac ischaemia and/or elevation in cardiac biomarkers suggestive of myocardial necrosis. All patients were randomly assigned to either clopidogrel (300 mg loading dose followed by 75 mg daily) or placebo on top of aspirin (75–325 mg daily). Treatment was continued for 3 to 12 months (mean duration 9 months).

### Table 1: Characteristics of oral antiplatelet drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary mode of action</th>
<th>Metabolism and platelet inhibition</th>
<th>Frequency of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX-1 inhibitor</td>
<td>Prodrug, irreversible</td>
<td>Daily</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>ADP P2Y12 receptor antagonist</td>
<td>Prodrug, irreversible</td>
<td>Daily</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>ADP P2Y12 receptor antagonist</td>
<td>Prodrug, irreversible</td>
<td>Daily</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Allosteric ADP P2Y12 receptor antagonist</td>
<td>Direct-acting, reversible</td>
<td>Twice daily</td>
</tr>
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</table>

ADP, adenosine diphosphate; COX, cyclooxygenase.
The occurrences of the first primary endpoint, a composite of death, non-fatal myocardial infarction (MI) and stroke, and of the second primary endpoint (the first primary in addition to refractory ischaemia) were both significantly reduced in the clopidogrel arm (9.3% vs. 11.4%, p < 0.001; 16.5% vs. 18.8%, p < 0.001, respectively). Furthermore, there was a reduction in the incidence of secondary endpoints; severe ischaemia (2.8% vs. 3.8, p = 0.007), revascularisation (20.8% vs. 22.7%, p = 0.03), and heart failure (3.7% vs. 4.4, p = 0.026). The benefits of dual antiplatelet therapy were apparent within the first few hours after administration. These benefits, however, were achieved at the cost of a significant increase in the number of major bleeding events (3.7% vs. 2.7%, p = 0.001), although this did not translate into a significant increase in life-threatening bleeding (2.1% vs. 1.8%, p = 0.13) (10).

Once the benchmark of dual antiplatelet therapy in ACS was established, the next question to arise was the optimal dosing required. This question was addressed in the CURRENT-OASIS 7 trial (11;12); a randomised, multinational, factorial trial evaluating the efficacy of high- and low-dose antiplatelet therapy with aspirin and clopidogrel in patients with ACS treated with percutaneous coronary intervention (PCI). More than 25,000 patients were recruited on the basis of electrocardiographic changes suggestive of ischaemia and/or raised levels of cardiac biomarkers.

Around 17,000 of these patients were deemed suitable for PCI and divided into four groups of 4,300 patients each. At first randomisation (double blind), patients were assigned to either high-dose (600 mg loading dose followed by 150 mg daily for one week followed by 75 mg daily) or low-dose dose (300 mg loading dose followed by 75 mg daily) clopidogrel. At second randomisation (open label), patients were assigned to either high-dose (300–325 mg daily) or low-dose (300 mg followed by 75-100 mg daily) aspirin.

CURRENT-OASIS 7 did not demonstrate a reduction in the primary outcome (death, MI or stroke at 30 days) in patients receiving high-dose clopidogrel (4.2% vs. 4.4%, p = 0.3), 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 improved outcome in patients undergoing PCI obtained with the high-dose clopidogrel regimen were attributed to the more rapid onset of effect. Other concerns with clopidogrel are related to its metabolism through the CYP system in the liver where the active metabolites are formed. In this regard, drug interactions between clopidogrel and proton pump inhibitors, especially omeprazole, and other drugs that interfere with the CYP system might be important (13;14). Another major concern was the emergent evidence of genetic polymorphisms in the CYP system affecting the generation of the active metabolite and the platelet response to clopidogrel (15).

In light of these concerns, it became apparent that better antiplatelet agents were needed. Recently, two new antiplatelet agents, prasugrel and ticagrelor, have been approved for clinical use. These drugs have improved pharmacodynamic capacities compared to clopidogrel and large clinical trials have documented their potential to improve cardiovascular outcome.

**Prasugrel**

Prasugrel is a new thienopyridine agent. Like clopidogrel it requires activation to its active metabolite, which blocks the P2Y12 subtype of the ADP receptor. Accordingly, prasugrel is a prodrug, but it is more efficiently converted to its active metabolite than clopidogrel. The metabolism is dependent on hepatic CYP enzymes as well as intestinal carboxylesterases, but still, it has a more rapid onset of action and inhibits platelet aggregation stronger and more consistently than clopidogrel.

Thus, pharmacodynamic data suggest that the level of platelet inhibition attained 6 hours after the administration of clopidogrel can be achieved within 30 minutes with prasugrel (16). Moreover, the active metabolite of prasugrel inhibits ADP-induced platelet aggregation with the same potency as that of clopidogrel in vitro, but the in vivo differences in the metabolism of the drugs confer an approximately 12-fold greater exposure to prasugrel following a loading dose of prasugrel (60 mg) compared to clopidogrel (300 mg) (17). Also in terms of maintenance treatment, prasugrel (10 mg daily) provides a higher and more consistent level of platelet inhibition than clopidogrel even when using a relatively high dose of clopidogrel (150 mg daily) (18).

In view of these biochemical differences, the TRITON-TIMI 38 trial (TRial to Assess Improvement in Therapeutic Outcomes by Optimiz ing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) was designed to compare the efficacy and safety of prasugrel vs. clopidogrel in ACS patients planned to undergo PCI (19). TRITON-TIMI 38 was a randomised, double-blind trial in which more than 13,500 aspirin-treated patients received either prasugrel (60 mg loading dose followed by 10 mg daily) or clopidogrel (300 mg loading dose followed by 75 mg daily). Treatment was continued for 6 to 15 months.

The study demonstrated a significant reduction of the primary endpoint (death, non-fatal MI and non-fatal stroke) in the prasugrel group compared to the clopidogrel group (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, p = 0.93). 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) Thrombolysis In Myocardial Infarction (TII) major bleeding (2.4% vs. 1.8%, p = 0.03) and life-threatening bleeding (1.4% vs. 0.9%, p = 0.01) (19).

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) (19). 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 of less than 60 kg.
Another subgroup analysis restricted to patients with diabetes showed that the reduction in the composite primary endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke was significant in both diabetic (14%) and non-diabetic (30%) patients (20). Moreover, the incidence of major bleeding was similar among diabetic patients, thus contrasting with the increased bleeding incidence seen with prasugrel in the non-diabetic patients. Overall, the net clinical benefit of prasugrel seems larger in ACS patients with diabetes, and similar findings have been reported for a subgroup of ST-segment elevation MI (STEMI) patients (21).

In TRITON-TIMI 38, all patients were scheduled for PCI, but another large trial is currently evaluating the effect of prasugrel in similar patients not scheduled for PCI; TRILOGY ACS (the TaRgeted platelet Inhibition to clARify the Optimal stratEgy to medICally manage Acute Coronary Syndromes) is a randomised, double-blind trial planned to enrol 10,300 non-STEMI ACS patients within 10 days of presentation with either unstable angina or non-STEMI, who are not intended to undergo revascularisation procedures for their index event (22).

**Ticagrelor**

Ticagrelor, an ATP analogue, is a reversible P2Y$_{12}$ receptor antagonist. Ticagrelor does not require metabolism in the liver, thus leading to less inter-individual variability and more consistent platelet inhibition compared to clopidogrel. Furthermore, it has a more rapid onset and offset of action with more potent platelet inhibition than clopidogrel. A recent study demonstrated that platelet inhibition at 30 minutes with ticagrelor was equivalent to that achieved with clopidogrel at 4 hours. At 1 hour after loading, the degree of platelet inhibition with ticagrelor was greater than the maximal inhibition attained using clopidogrel, even though maximal platelet inhibition with ticagrelor was not reached until 2 hours after administration.

Regarding offset, there was no significant difference in the extent of platelet inhibition between ticagrelor and clopidogrel at 24 and 84 hours following the final dose. Ticagrelor has been shown to lower platelet aggregation more than clopidogrel at 72 and 120 hours after the last dose (23). A recent study evaluated and compared the pharmacodynamic properties of ticagrelor and clopidogrel in relation to CYP2C19 genotype. The study confirmed that the antiplatelet effect of clopidogrel is dependent on CYP2C19 genotype, whereas this is not the case for ticagrelor (24). This lends further support to the use of ticagrelor in patients carrying the loss-of-function CYP2C19 alleles.

To assess the effect of ticagrelor on clinical outcomes, the PLATO trial (PLATElet inhibition and patient Outcomes) was designed as a randomised, double-blind study comparing the efficacy and safety of ticagrelor and clopidogrel in patients with ACS (25). The diagnosis of ACS was evidenced by two of the following criteria: electrocardiographic changes suggestive of coronary ischaemia (unless it was ST-segment elevation with planned PCI; then this criterion alone did suffice), positive biomarkers consistent with myocardial necrosis or one of a number of predefined risk factors. Furthermore, all patients were included in the study within 24 hours of symptom onset. A total of 18,624 patients were recruited and followed for up to 12 months. Most patients were treated with aspirin at a dose of 75 mg to 100 mg daily. If not already on aspirin they were given a loading dose of 300-325 mg. Patients were randomly assigned to either ticagrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 mg loading dose followed by 75 mg daily). Patients undergoing PCI after randomisation received an additional dose of their study drug at the time of PCI: 300 mg of clopidogrel, at the investigator’s discretion, or 90 mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomisation (26).

PLATO demonstrated a significant reduction in the occurrence of the primary endpoint (a composite of vascular death, MI or stroke) with the use of ticagrelor vs. clopidogrel (9.8% vs. 11.7%, p < 0.001). Furthermore, there was a significant reduction in the occurrence of the secondary endpoint (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). Moreover, death from vascular causes was reduced (4.0% vs. 5.1%, p = 0.001), whereas the incidence of stroke was not (1.5% vs. 1.3%, p = 0.22). These effects were evident at 30 days and were sustained during the entire study (23).

Regarding safety, there were no significant differences between groups in terms of the occurrence of TIMI major bleeding (7.9% vs. 7.7%, p = 0.57), and there were no differences in the incidence of fatal or life-threatening bleeding (5.8% in both, p = 0.70). 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), particularly fatal intracranial bleeding (0.1% vs. 0.01%, p = 0.02). In contrast, the occurrence of other types of fatal bleeding was reduced with ticagrelor (0.1% vs. 0.3%, p = 0.03) (25). Recent data have shown that treatment with ticagrelor results in a significantly lower prevalence of high on-treatment platelet reactivity than clopidogrel (26), and that ticagrelor overcomes low-responsiveness in patients with coronary artery disease treated with clopidogrel (27).

These findings are in line with the improved clinical outcome reported from the PLATO trial (23) and may be explained by the pharmacodynamic differences between the drugs. Moreover, a PLATO substudy revealed that the superiority of ticagrelor is present irrespective of CYP2C19 and ABCB1 polymorphisms (28). Also, the subgroups of STEMI patients (29) and patients undergoing CABG (30) had benefit of ticagrelor compared to clopidogrel although not statistically significant. Moreover, the excess benefit of ticagrelor was present whether patients were treated invasively or conservatively (31). Finally, patients with impaired renal function appear to profit particularly from ticagrelor (32).

**DISCUSSION**

As platelets play an integral role in the pathophysiology of ACS, inhibiting platelet activation and aggregation is a logical approach when aiming to improve ACS outcome. Numerous pathways contribute to platelet activation, and several drugs have been developed to inhibit these pathways and improve treatment of platelet-dependent thrombosis.
From the data outlined above, it is apparent that various strategies of intense platelet inhibition do indeed improve clinical outcome. The combination of aspirin and clopidogrel set the benchmark for dual antiplatelet therapy in the wake of the CURE study. However, concerns have emerged regarding the efficacy of clopidogrel due to its delayed onset of action, interaction with other drugs and a highly variable inter-individual platelet inhibitory effect. These limitations have highlighted the need for new antiplatelet agents capable of overcoming the drawbacks of clopidogrel. Ideally, these drugs should have a rapid onset of action and display a potent and more reliable antiplatelet effect. Furthermore, they should have a predictable and consistent antiplatelet effect in all individuals.

At first glance, examination of the data presented from TRITON-TIMI 38 and PLATO suggests that prasugrel and ticagrelor meet the high expectations as both drugs have a more rapid and pronounced antiplatelet effect than clopidogrel. However, it is important to consider 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 current guidelines (4). Moreover, as outlined above, in some specific patient groups prasugrel is actually associated with an unfavourable benefit-to-harm risk profile.

By contrast, in the PLATO study ticagrelor was used to treat all patients presenting with ACS regardless of planned PCI or not. In keeping with current guidelines, patients undergoing PCI were given high loading doses of antiplatelet treatment. Thus, they received an additional dose of the study drug at the time of PCI: 300 mg of clopidogrel or 90 mg of ticagrelor for patients undergoing PCI more than 24 hours after randomisation. Disadvantages of ticagrelor are the side effect of transient dyspnoea (33) and the need for twice daily dosing.

The benefits derived from platelet inhibition in ACS are usually obtained at the expense of an increased risk of bleeding (34). This is an important consideration given the increased mortality associated with peri-interventional bleeding (35). However, there was no increase in the incidence of major bleeding events when comparing clopidogrel and ticagrelor whether employing the PLATO or the TIMI bleeding definitions.

This is in contrast to the comparison of clopidogrel and prasugrel, in which the incidence of TIMI major bleeding was increased in patients treated with prasugrel. However, in the PLATO study the number of non-CABG TIMI major bleeding was also significantly increased in the ticagrelor group confirming the dogma that stronger platelet inhibition provides a reduction in ischaemic events at the cost of more spontaneous bleeding events.

The offset of action is another important aspect of antiplatelet agents used in the context of ACS, as a number of these patients require CABG instead of PCI. Antiplatelet therapy is likely to either delay surgery or precipitate bleeding-related complications. In TRITON-TIMI 38, a total of 368 patients underwent CABG. There was a significant increase in the number CABG-related TIMI major bleeding in the prasugrel group (13.4% vs. 3.2%, p < 0.001) (21).

In the PLATO study, a total of 782 patients were triaged to CABG. In these patients, ticagrelor was associated with a slightly lower rate of CABG-related TIMI major bleeding (5.3% vs. 5.8%, p = 0.32) (25).

This might be a result of the more rapid offset of ticagrelor’s effect, owing to the reversibility of the P2Y12 receptor inhibition provided by this drug as demonstrated in patients with stable coronary artery disease (23). Similarly, the DISPERSE-2 study demonstrated that patients undergoing CABG 1-5 days after stopping ticagrelor therapy had a numerically lower incidence of major bleeding than patients treated with clopidogrel (36% vs. 64%) (36). Treatment with ticagrelor can be initiated prior to coronary angiography and may be administered to patients who have already received clopidogrel. There is no requirement to modify the dose according to age or body weight.

Prasugrel and ticagrelor have emerged as potent and effective alternatives to clopidogrel in the management of ACS (45). So far, no direct comparison of these drugs has been performed. Currently, an ongoing randomised crossover trial on ACS patients is comparing the efficacy of prasugrel and ticagrelor in terms of overcoming high on-clopidogrel platelet reactivity (NCT01360437). Importantly, Bonello et al. recently demonstrated that the concern of on-treatment platelet reactivity persists even with the new drugs. In ACS patients treated with PCI, high on-prasugrel platelet reactivity was frequent (25.2%) and associated with an increased rate of cardiovascular events (37).

In conclusion, antiplatelet therapy remains a cornerstone in ACS treatment and has improved clinical outcome substantially. Despite the advantage of clopidogrel as a part of a dual antiplatelet treatment strategy, this drug has important limitations. New drugs with more rapid and sustained action, more predictable function and improved safety profiles are available heralding the advent of a new era in the treatment of ACS.

REFERENCES
REFERENCES (Continued)


