Platelet activation and aggregation play a central role in the pathophysiology of thrombogenesis in ischemic heart disease. Dual antiplatelet therapy with aspirin and clopidogrel is currently the golden standard in the prevention of cardiovascular complications after percutaneous coronary intervention. Newer antiplatelet drugs are continuously marketed to respond to the limitations of clopidogrel, namely a delayed onset of action, an irreversible inhibition of platelet aggregation as well as a substantial variability in antiplatelet effect, in part due to genetic polymorphism. The second-generation thienopyridine prasugrel is more potent than clopidogrel, but also manifests a greater bleeding risk. Ticagrelor, a third-generation thienopyridine, seems to have a better safety profile and has recently been approved as a first-choice antiplatelet treatment in acute coronary syndrome in Europe. This article will review the different oral antiplatelet drugs currently available, compare pharmacology and safety/efficacy profiles, and discuss their limitations.

Rupture of atherosclerotic plaques or implantation of stents in coronary arteries leads to the endogenous production of platelet-activation agonists. This in turn leads to platelet aggregation and thrombotic occlusion of the artery, hence the importance of pharmaceutical platelet inhibition in ischemic heart disease.

Platelet activation and aggregation play a central role in the pathophysiology of thrombogenesis. Several antiplatelet drugs are available that target different platelet-activation pathways and aim at reducing the risk of recurrent thrombotic events and ischemic complications, both spontaneously and following percutaneous coronary intervention (PCI).

Platelet activation is primarily initiated by the adhesion of the agonist ADP to the P2Y1 and P2Y12 receptors on the surface of platelets [1]. The activated platelets in turn expose their GP IIb/IIIa receptors. The P2Y receptor is responsible for a positive feedback mechanism that amplifies platelet stimulation and, therefore, plays a central part in the final step of platelet aggregation and stabilization of aggregates.

Given the above, an antithrombotic regimen is the cornerstone in the treatment and prevention of peri- and post-procedural ischemic complications in patients treated with PCI. Dual antiplatelet treatment with acetylsalicylic acid (ASA) and a thienopyridine is currently the golden standard in antiplatelet treatment [2-5].

These two drugs act synergistically by inhibiting different steps of platelet adhesion and aggregation (Figure 1). The PCI-Cure trial corroborates the positive and cardio-protective effect of dual antiplatelet therapy in patients undergoing PCI [6].

Antithrombotic treatment is continuously being revised and newer drugs are marketed.
This article will review the different oral platelet inhibitors currently available; compare their pharmacology and safety/efficacy profile as well as discuss their limitations. Future perspectives regarding possible strategies in the treatment of ischemic heart disease will be discussed.

Pharmacological background
In order to understand the clinical implications of the different antiplatelet drugs available, it is important to understand their pharmacokinetics. The medications are subdivided into the following groups:

- **Aspirin**: a cyclooxygenase (COX) inhibitor that acts at an intracellular level;
- **P2Y12 antagonists**: these agents act on the receptor at the surface of platelets (thienopyridines, non-thienopyridines);
- **Protease-activated receptor (PAR) antagonists**: these inhibit PARs that normally interact with thrombin.

Figure 1 depicts the level at which the different antiplatelet agents act.

- **Aspirin**
  ASA (aspirin) is a salicylate drug whose antiplatelet effect relies on its ability to inhibit COX and thromboxane A2 (TXA2) production. Prostaglandin-endoperoxide synthase, also known as COX, is the key enzyme in the biosynthesis of prostacyclin, prostaglandins and thromboxanes. There are two isozymes of COX: a constitutive COX-1 and an inducible COX-2 that differ in their regulation of expression and tissue distribution. COX-2 is expressed in a limited number of cell types and regulated by specific stimulatory events. TXA2 is produced by activated platelets and has prothrombotic properties. It stimulates activation of new platelets and platelet aggregation by mediating expression of the glycoprotein complex GP IIb/IIIa in the cell membrane of platelets. Circulating fibrinogen binds these receptors on adjacent platelets, thus strengthening the clot.

ASA is the most widely used antiplatelet agent. It inhibits the enzymes COX-1 and COX-2 in their conversion of arachidonic acid to prostaglandin-H2 and -G2. Low-dose, long-term ASA use irreversibly blocks the formation of TXA2 in platelets, producing an inhibitory effect on platelet aggregation.

Higher doses of ASA are required for inhibition of COX-2, but an irreversible blockade of COX-1 results in irreversible platelet inhibition, thus, lower doses of ASA are sufficient to inhibit platelet aggregation.

Acetylsalicylic acid is rapidly absorbed from the bowel and hydrolyzed to salicylic acid by esterases in the bowel, blood and liver. Maximal plasma concentration is reached within 20 min to 2 h following administration. Salicylic acid is eliminated mainly by the liver and excreted with urine. Elimination half-life for ASA is less than 1 h. Although ASA is only detectable in plasma for a limited time, platelet inhibition can be demonstrated for approximately 7–10 days.

- **P2Y12 receptor antagonists**
  Adenosine diphosphate is an important activator of platelet aggregation. P2Y12 receptor antagonists refer to a class of selective inhibitors of ADP receptors that interfere with platelet aggregation by covalent modification of these receptors on the platelet surface. P2Y12 receptor antagonists are divided into two main categories: thienopyridines and nonthienopyridines.

  There are three main members of the thienopyridine family: ticlopidine, clopidogrel and prasugrel. The newer platelet inhibitors ticagrelor and elinogrel are...
direct-acting P2Y12 receptor inhibitors that reversibly change the conformation of the receptors. They belong to the class of nonthienopyridines.

- **Thienopyridines**

  Thienopyridines are prodrugs that require conversion in the intestine and liver to their active metabolites. These metabolites then selectively bind to the P2Y12 receptors on the platelet surface and cause irreversible platelet inhibition. This irreversible binding to the platelet surface inhibits activation of the GP IIb/IIIa receptor, which in turn inhibits platelet aggregation by inhibiting platelet binding to fibrinogen.

  Metabolism of the prodrugs requires hepatic CYP450 pathways, but there are important pharmacokinetic differences between the groups that in turn may induce differences in bioavailability and platelet response (Figure 2).

  - **Ticlopidine**

  Ticlopidine is 5-[(2-chlorophenyl), methyl]-4,5,6,7-tetrahydrothieno(3,2-c)pyridine hydrochloride. Its structural formula is depicted in Figure 2A.

    After oral administration of a single 250 mg dose, ticlopidine hydrochloride is rapidly absorbed and reaches peak plasma levels approximately 1–3 h after administration. Absorption is greater than 80%. Ticlopidine hydrochloride binds reversibly to plasma proteins, mainly to serum albumin and lipoproteins. The drug is metabolized extensively in the liver. Clearance decreases markedly on repeated dosing. Steady state concentrations are reached 3–5 days after standard dosing twice daily [7,8] but in elderly patients (mean age >70 years) these concentrations are approximately twice as high compared with younger volunteers, probably because of a decreased clearance seen with age.

    In healthy volunteers, substantial inhibition of ADP-induced platelet aggregation is obtained within 4 days after administration of ticlopidine 250 mg twice daily, and maximum platelet aggregation inhibition is reached after 8–11 days. Lower doses cause less and more delayed platelet inhibition, while higher doses do not give significantly greater platelet inhibition, only an increased rate of adverse events.

    After discontinuation of ticlopidine, platelet function returns to normal within 2 weeks in the majority of patients.

  - **Clopidogrel**

    Chemically it is methyl (+)-(S)-α-[(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). Its structural formula is depicted in Figure 2B.

    Together with ASA, clopidogrel has been the basis of antiplatelet treatment in acute coronary syndrome (ACS) patients since the results of the CURE trial were published in 2001. It is a first-generation thienopyridine that irreversibly and indirectly inhibits platelet aggregation. It is an inactive prodrug that requires in vivo conversion to its active metabolite, by the hepatic cytochrome P450 3A4 enzyme system.

    The majority of ingested clopidogrel is hydrolyzed by esterases to an inactive derivative. This derivative represents 85% of the clopidogrel metabolites detectable in plasma. The remaining unhydrolyzed clopidogrel undergoes hepatic transformation that relies mainly on the CYP1A2, CYP3A4/5 and CYP2C19 enzymes. This transformation to active metabolite requires two steps, namely oxidation of the thiophene ring to 2-oxoclopidogrel, which is then oxidized further by P450 forming a carboxyl and a thiol group. This thiol group forms a disulfide bond with the P2Y12 receptor on the platelet surface. The covalent transformation of the receptor inhibits ADP from binding, thus preventing activation of the GP IIb/IIIa receptor that binds fibrinogen. This cascade of events results in an inhibition of clot formation.

    The two-step activation of the prodrug is believed to account for some of the reasons for clopidogrel low response, where substantial residual platelet reactivity is detected in spite of optimal clopidogrel dosage. In fact, genetic polymorphisms have been shown to be related to substantial interindividual variability in the response to the antiplatelet effect of clopidogrel [9].

    Clopidogrel is six-times more potent than ticlopidine and has a better safety profile at a 50–100 mg daily dose. It requires 4–7 days to reach steady state, but the use of loading doses of 300–600 mg daily reduces this delay in maximal effect.

    Maximal level of its active metabolite is said to be reached 2–4 h after administration [10] and elimination half-life is approximately 7–8 h after a single dose. The effect is said to be dose-dependent up to a dose of 600 mg. There is no gain of effect with doses higher than 600 mg [11]. These findings are made from the determination of the plasma concentration of the inactive metabolite of clopidogrel, SR 26334.

    Following discontinuation, platelet function returns to normal levels within 7 days and depends on platelet turnover, since clopidogrel inhibits platelets irreversibly.

  - **Prasugrel**

    Prasugrel is a second-generation thienopyridine and a potent alternative to clopidogrel [12]. Its structural formula is depicted in Figure 3.

    Prasugrel is, like clopidogrel, a prodrug that requires transformation to its active metabolite. It is
Prasugrel has a nearly similar elimination half-life compared with clopidogrel, but because of its simpler metabolism, it also displays a more rapid onset of action, as well as a higher and more consistent inhibition of platelet aggregation (IPA). It encounters the problem of low inter-patient variability. It competes directly with ADP for the P2Y12 receptor binding site on the platelet surface. Aspirin (the nonsteroidal anti-inflammatory drug) is a highly effective oral antiplatelet drug. It is proven to have greater antithrombotic properties, ASA considerably reduces events by 50–70% compared with placebo [18]. In patients with non-stent thrombosis (ST) elevation ACS, ASA has been shown to reduce the risk of ischemic events by 50–70% compared with placebo [19]. With its antithrombotic properties, ASA considerably reduces the risk of myocardial infarction (MI), vascular death and stroke.

The randomized trial ISIS-2 (Table 1) performed on 17,187 patients admitted for suspected acute MI, compared intravenous streptokinase and/or ASA. The use of ASA led to a significant reduction in all-cause mortality and 5-week vascular mortality. ASA also significantly reduced nonfatal reinfarction and nonfatal stroke without an increase in cerebral hemorrhage or major bleeds requiring transfusion [20]. A meta-analysis of 287 studies involving high-risk patients, that is, patients at increased risk of acute MI, ischemic stroke, both stable and unstable angina and peripheral arterial disease (with acute or previous vascular disease of all sorts), compared antiplatelet therapy versus control in 135,000 patients and different antiplatelet treatments in 77,000 patients. Investigators found that the use of an antiplatelet regimen reduced the composite end points of serious vascular events (nonfatal MI, nonfatal stroke or vascular death) by 50–70% compared with placebo [18].

Prasugrel is a selective inhibitor of the P2Y12 receptor, with low solubility and permeability and the first reversible oral antiplatelet drug. It is proven to have greater bioavailability than clopidogrel because it is quickly absorbed and does not require first-pass metabolic activation by hepatic enzymes prior to activation [19]. The bioavailability is 36% and it reaches its peak concentration after approximately 1.5 h. Ticagrelor as well as its main metabolite AR-C124910XX bind to plasma proteins and they are both pharmacologically active. Plasma concentrations are dose-dependent and both drug and metabolite are excreted via bile and feces [20].

Similarly to the thienopyridines, ticagrelor blocks P2Y12 ADP receptors on the platelet surface, but in contrast to thienopyridines, ticagrelor is an allosteric antagonist that reversibly changes the conformation of the receptor [21]. Its structural formula is depicted in Figure 4.

Elinogrel
Elinogrel is a novel platelet antagonist. Unlike the thienopyridines, it requires no metabolism prior to activation. As a result, it avoids the issue of delayed onset of action and inter-patient variability. It competes directly with ADP for the P2Y12 receptor binding site on the platelet surface. It is the only compound in its class with both an oral and an intravenous formulation, thus it can be used as well in both acute and chronic indications.

The intravenous form provides immediate onset and high levels of platelet inhibition with a maximal antiplatelet effect within 15 min of administration. It exhibits an elimination half-life of 12 h. It may be transitioned easily to the oral formulation, which similarly provides high levels of inhibition of platelet aggregation for chronic use.

PAR inhibitors
Thrombin (factor IIa) is a very potent platelet aggregation protein. PAR inhibitors are G-protein coupled receptors. PAR-1 is the main receptor in humans and it is proteolytically activated by thrombin. This alteration activates the autoreceptor, which results in platelet activation. PAR-1 is mainly found in platelets, fibroblasts and smooth muscle cells and it is the main thrombin receptor in arteries [22]. SCH 530348 is a high-affinity competitive PAR-1 antagonist that is rapidly absorbed and metabolized by the CYP3A4 hepatic system. The effect is dose-dependent and reversible, but the drug is slowly eliminated with an overall elimination half-life of 165–311 h. Steady state is reached within 21 days and the antiplatelet effect is consistent during the treatment period.

Clinical trials
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25% and the risk of nonfatal MI by 30%. The overall benefits of an antiplatelet regimen outweighed the risk of major bleeding. ASA was found to be protective in these high-risk patients [25].

ASA is used in primary as well as in secondary prevention of thrombotic events. A loading dose of 325 mg acutely is advised, followed by 75–100 mg daily for chronic therapy. Higher doses have been proven to increase the risk of bleeding, as shown in the CURRENT-OASIS 7 trial (Table 1) [26]. These results support earlier findings of a dose-dependent relationship between ASA and the risk of bleeding complications [26].

- **Clopidogrel**
  
  Currently the combination of clopidogrel and ASA is the golden standard in antiplatelet treatment and prevention of cardiovascular (CV) complications in patients with ACS and/or undergoing PCI [5]. International guidelines suggest dual antiplatelet treatment with ASA 75–325 mg and clopidogrel 75 mg daily [27–29], and this strategy has proven efficient in the prevention of ischemic events and complications following intracoronary stent implantation [6,30]. There is still no definite consensus as to the duration of the antiplatelet treatment in ACS patients, as seen in the CREDO trial (Table 1) [31], although the CURE trial demonstrated that long-term clopidogrel therapy proved to be superior to placebo in high-risk ACS patients (Table 1).

  In the CAPRIE trial (Table 1) [32], clopidogrel proved to be significantly superior in the prevention of ischemic complications (stroke, MI and CV death) compared with ASA. The greater platelet inhibition seen with clopidogrel is even more substantial in patients at high risk of CV morbidity (diabetics, patients with high lipid levels and patients with former ischemic events) [33]. Mehta et al. demonstrated in the CURRENT-OASIS 7 trial (Table 1) that higher loading doses (600 mg bolus dose) of clopidogrel reduce the risk of MI in patients with ACS undergoing PCI [34,35]. In order to minimize the delay of onset of effect, current guidelines suggest the use of a loading dose of clopidogrel 600 mg prior to PCI, in order to ensure a sufficient IPA prior to stent implantation [36]. On the other hand, there is no gain of platelet inhibition with loading doses higher than 600 mg [11].

- **Prasugrel**

  Studies on prasugrel have mainly been conducted in patients with ACS and undergoing PCI; studies on stable angina patients are yet to be published.

  Analysis of platelet response has shown that a prasugrel loading dose of 60 mg results in faster onset, greater magnitude and more consistent levels of inhibition of platelet function compared with either clopidogrel 300 mg or 600 mg loading doses. Similarly, greater and more consistent levels of platelet inhibition were observed with maintenance doses (prasugrel 10 mg vs clopidogrel maintenance 75 mg) [19]. These properties have proven to be efficient in patients with a low response to clopidogrel, so-called ‘clopidogrel resistance’ in international literature. Although prasugrel entails a greater IPA, overall mortality did not differ significantly between clopidogrel and prasugrel.

  TRITON-TIMI 38 (Table 1) [37] is a large, randomized, multicenter, double-blind controlled Phase III prospective study of patients with ACS (unstable angina, non-ST-elevated MI and ST-elevated MI [STEMI]) undergoing PCI. It was performed in 30 countries and enrolled a total of 13,608 patients from 707 centers between November 2004 and January 2007. Patients with ACS treated with ASA and planned PCI were randomized to either clopidogrel 300 mg loading dose followed by 75 mg maintenance dose or prasugrel 60 mg loading dose followed by 10 mg daily. The primary end points were composite CV death, MI and stroke. The secondary end points were ST, composite CV death, MI, stroke and rehospitalization for recurrent ischemia. Safety was assessed by TIMI major and minor bleeding events and complications following intracoronary stent implantation [38].

  In a substudy, 3534 patients presenting with STEMI were randomly assigned prasugrel (60 mg loading dose followed by 10 mg maintenance dose) or clopidogrel (300 mg loading dose and 75 mg maintenance dose). At 30 days, 6.5% of patients allocated to prasugrel had met the primary end point of composite CV death, MI and stroke in the group receiving prasugrel compared with the group receiving clopidogrel (12.1 vs 9.9%, respectively; p = 0.001) [38]. Furthermore, rates of ST were lower in the prasugrel than the clopidogrel group (p < 0.001) [39].

  When it comes to safety end points, the study showed a significant increase in TIMI major bleeds in patients assigned for coronary artery bypass graft (CABG) surgery, but overall the net clinical outcome shows superiority of prasugrel versus clopidogrel. Subgroups of patients have been identified where prasugrel may induce increased bleeding risk and therefore harm patients older than 75 years of age, patients with a body-weight of <60 kg and patients with a history of stroke. In fact, patients with previous stroke or transient ischemic attack treated with prasugrel had a greater rate of TIMI major bleeding (p = 0.06) [40].

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Table 1. Major trials conducted on the different antithrombotic drugs.

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ACS: Acute coronary syndrome; ASA: Acetylsalicylic acid; CV: Cardiovascular; MI: Myocardial infarction; PAR: Protease-activated receptor; PCI: Percutaneous coronary intervention.
Oral antiplatelet agents in ischemic heart disease

Review: Clinical Trial Outcomes

point of either CV death, nonfatal stroke or nonfatal MI compared with 9.5% in the clopidogrel group (p = 0.0017). The same finding was made at 15 months (10 vs 12.4%; p=0.0221). Furthermore the risk of ST as well as a secondary end point (CV death, MI or urgent target vessel revascularization) was significantly reduced with prasugrel both at 30 days and 15 months. TIMI bleeding did not differ between the groups except for TIMI major bleeding related to CABG surgery where bleeding rates were significantly increased compared with the clopidogrel treatment arm (p = 0.0033). Thus, in patients undergoing primary PCI following STEMI, prasugrel has proven to be more potent in reducing thrombotic complications and CV death. An increase in bleeding risk was only shown in patients undergoing emergency CABG.

Patients with diabetes are known to have a higher risk of CV events in part because of greater platelet activity. In a TRITON-TIMI 38 substudy, Wiviott et al. found a significant reduction in both primary (CV death, nonfatal MI or nonfatal stroke; p < 0.001) as well as secondary end points (death, nonfatal MI, nonfatal stroke and nonfatal TIMI major bleeding) in diabetic patients treated with prasugrel compared with clopidogrel after PCI. Prasugrel entailed a 40% reduction in MI in patients with diabetes. As for bleeding risk, the rate was increased in prasugrel-treated patients without diabetes whereas there was found no significant increase in bleeding in patients with diabetes receiving prasugrel. Thus, the reduction in end points due to a greater platelet inhibition with prasugrel compared with clopidogrel was even more significant in patients with diabetes, without an accompanying significant increase in bleeding risk.

A recent trial has shown that switching directly from clopidogrel maintenance dose to either prasugrel loading dose or maintenance dose is well tolerated and results in significantly greater levels of platelet inhibition.

Ticagrelor

Ticagrelor is remarkable by its rapid onset and offset of antiplatelet effect and its action is closely time related to drug exposure, unlike thienopyridines that bind to the P2Y12 receptors for the entire lifetime of the platelet. It was designed to address the limitations of thienopyridines while achieving comparable or better antiplatelet effects with fewer adverse events. The DISPERSE-2 trial is a Phase II clinical study performed on 990 patients with NSTEMI-ACS comparing clopidogrel and AZD6140 (ticagrelor), and assessing safety and efficacy of the latter. Ticagrelor exhibited significantly greater levels of IPA both in clopidogrel-naive patients and in patients pretreated with clopidogrel. Ticagrelor had also a more rapid and consistent antiplatelet effect.
On the downside, side effects such as mild-to-moderate dyspnea and asymptomatic ventricular arrhythmias were observed.

The efficacy and safety of ticagrelor was further investigated in the PLATO study (Table 1) [44] conducted on 13,408 patients with ACS, planned to receive an invasive treatment. It is a prospective, randomized, double-blind, event-driven trial conducted on patients from 43 countries. Patients received, in addition to ASA, ticagrelor in a loading dose of 180 mg followed by 90 mg twice daily plus placebo tablets for clopidogrel or clopidogrel loading dose of 300 mg followed by a maintenance dose of 75 mg daily plus placebo tablets for ticagrelor. Study medication was continued for 6–12 months. Investigators demonstrated overall improved CV outcome with a significant reduction in total mortality, but also in MI, CV death and definite ST [45]. The rates of stroke did not differ between the two treatments. Safety was measured by the risk of total major bleeding, fatal or life-threatening bleeding, and no difference was found.

Dyspnea occurred more often as a side effect in the ticagrelor than the clopidogrel group (p < 0.0001) leading to discontinuation of treatment in 0.8 and 0.2%, respectively, of the ticagrelor- and clopidogrel-treated patients.

Ticagrelor does not require hepatic activation, which is especially advantageous in patients with genetic variants of the CYP2C19 enzymes that are prone to low response to clopidogrel [46,47]. It produces an overall superior platelet inhibition with less response variability than clopidogrel. It demonstrates comparable bleeding risks compared with clopidogrel, a property that may prove advantageous in candidates to immediate surgery.

■ Elinogrel

Elinogrel has a predictable effect because of its reversible antiplatelet effect [48]. This is advantageous for patients undergoing surgical procedures in which rapid restoration of platelet function is critical in order to reduce bleeding.

The Phase II INNOVATE-PCI study included 650 patients undergoing nonurgent PCI (Table 1). It is a randomized, double-blind trial comparing both intravenous and oral elinogrel with clopidogrel, in terms of safety, tolerability and preliminary efficacy. Data, presented at the European Society of Cardiology congress in August 2010, showed that elinogrel provides greater antiplatelet activity than clopidogrel as well as a more rapid onset of effect, without significant increase in the risk of bleeding [49].

In the ERASE MI pilot trial, the investigators evaluated intravenous elinogrel, when given to 70 patients undergoing primary PCI for STEMI. It was a Phase IIA, randomized, double-blind, placebo-controlled trial evaluating safety and tolerability of increasing doses (10, 20, 40 and 60 mg) of elinogrel, given as a bolus dose prior to primary PCI. Patients were randomized to elinogrel or placebo and all patients received a loading dose of clopidogrel 600 mg prior to PCI as well as a 300 mg single dose 4 h post PCI. The major outcome of in-hospital bleeding was evaluated using the TIMI and GUSTO classifications. Results showed that elinogrel was well tolerated without any major bleeds [50].

Phase III trial results are yet to be published. A Phase III trial of 24,000 patients is planned to start in 2011 and enroll chronic heart disease patients treated with ASA after an acute MI that has occurred 6 months to 5 years prior to randomization. It will compare low- and high-doses of oral elinogrel with placebo (ASA alone), administered for a period of 29 months on average. The end points are set to be CV death, MI or stroke.

■ PAR inhibitors

The Phase II trial TRA-PCI (Table 1) performed on 1030 patients undergoing nonurgent PCI was designed to assess the safety and tolerability of the PAR-1 antagonist SCH 530348. Investigators found that it was well tolerated with comparable rates of TIMI major and minor bleeding compared with placebo [51]. It thus showed promising results and investigators suggested it replaced clopidogrel in patients treated with warfarin, to ensure a better safety profile in patients receiving triple antithrombotic treatment.

TRACER (Table 1) is a Phase III, prospective, randomized, double-blind and placebo-controlled trial of approximately 13,000 non-ST elevation ACS patients from 800 sites. Patients would receive a 40 mg loading dose SCH 530348 or matching placebo and continue with a maintenance dose of 2.5 mg daily for at least 1 year. The goal of this study was to prove that, added to standard therapy, the PAR-1 SCH 530348 reduces the incidence of composite CV death, MI, stroke, recurrent ischemia with rehospitalization and urgent coronary revascularization, compared with standard therapy plus placebo [52]. However, the study was closed by the Data and Safety and Monitoring Board in February 2011 because of major safety issues with an increased risk of intracranial hemorrhage in patients with a history of stroke.

Clinical studies are necessary in order to assess the possible benefits especially in cases where triple antithrombotic medication is needed, for instance in the case of atrial fibrillation and PCI.

Assessment of antiplatelet response

Despite dual antiplatelet therapy, thrombotic complications such as ST still occur. One explanation is found in the phenomenon of clopidogrel low response.
Clopidogrel displays a delayed onset of action because of its complex pharmacokinetics and is also more vulnerable to genetic polymorphisms with defects in the CYP system, associated with clopidogrel low response [53–55]. The substantial inter-individual variation in the response to clopidogrel’s antiplatelet effect is in part due to reduced function alleles, mainly CYP2C19. With an altered DNA, the bioavailability of the active metabolite is affected, resulting in a lower degree of platelet inhibition. This multifactorial phenomenon [56,57] is described in subjects with high platelet reactivity in spite of antithrombotic medication [58].

Platelet response to clopidogrel, as assessed by point-of-care platelet function assays, varies widely and nonresponse rates range from 5–30% in various studies [59,60]. It has been determined that high residual platelet activity in spite of clopidogrel treatment is closely linked to adverse events after PCI [61], mainly with implantation of drug-eluting stents [62]. In fact, late as well as early ST have been related to an abnormal response to antiplatelet therapy [63–65].

Platelet function tests such as vasodilator-stimulated phosphoprotein, light transmission aggregometry, Multiplate® and Verify Now™ (Accumetrics, CA, USA) have been developed to detect patients with platelet hyperactivity. Platelet function analysis has, in smaller trials, been used for either shift of treatment or to optimize dosage of drugs in ‘low-responders’. This strategy has been shown to be feasible in a selected group of patients, but has also been very time consuming and has led to a delay of the scheduled invasive treatment for several days [66,67]. Newer techniques are less time consuming and do not require specially trained technicians, which makes them more attractive as point-of-care assays.

Genetic polymorphism can also be detected by analyzing DNA samples from each patient, for instance with the recent Spartan RX CYP2C19*2 tests where a sample of the patient’s saliva is quickly analyzed to determine whether there is genetic polymorphism and, therefore, substantial residual platelet reactivity in spite of optimal antiplatelet therapy.

**Clinical challenges**

The phenomenon of low response to ASA has been evaluated in smaller trials but the exact incidence and its clinical impact remain unknown. Würtz et al. evaluated the platelet response to ASA in 117 patients undergoing PCI and of whom 39 had suffered previous ST. All patients received ASA 75 mg daily and platelet function was evaluated by Verify Now™ ASA assay and Multiplate® with citrated and hirudinized blood. Platelet turnover was assessed by determining the fraction of immature platelets. Results clearly showed that in patients with previous ST, platelet response to ASA was impaired with a resulting increased platelet aggregation [68]. Also, the fraction of immature platelets was increased (p = 0.13).

Ticlopidine has limited clinical use and has been widely substituted with clopidogrel because of the latter’s better safety profile (Table 1) [69]. Serious adverse events have been reported. In fact, ticlopidine can cause life-threatening hematological adverse reactions, including neutropenia/agranulocytosis, thrombotic thrombocytopenic purpura and aplastic anemia.

Current antiplatelet medication used in addition to ASA includes the thienopyridines clopidogrel and prasugrel, but there are several limitations to their use. Clopidogrel and prasugrel provide a prolonged antiplatelet effect by irreversibly binding to the P2Y12 receptor on the platelet surface. As there is no antidote to these drugs, the irreversible effect may lead to prolonged bleeding complications, namely in the case of urgent surgery.

Patients with ACS who, in spite of clopidogrel therapy, have high residual platelet activity, are prone to have a greater risk of CV complications, in particular ST, after PCI [64]. It has been shown that patients with poor response to clopidogrel, have an 11-fold increased risk of ST after stent implantation. The association between low response to clopidogrel and the development of ischemic events is substantial in the acute phase and in the 30 day period following PCI. The therapeutic management of low response is still undefined. Low responders could potentially obtain greater clinical benefit from higher doses of clopidogrel or from a shift of therapy to a more potent drug. Several larger trials, such as the GRAVITAS trial (Table 1) [70], have been designed to evaluate the effect of tailored therapy in patients with platelet hyperactivity who have received PCI with implantation of a drug-eluting stent.

The issue of low or nonresponsiveness to clopidogrel has led to the development of alternative antiplatelet therapies [71].

In the past, scientific efforts were turned to anatomic pathology and disease predisposition in order to offer optimal primary as well as secondary prevention of disease development. Great advances have been made in the field of pharmacogenetics and there is now also awareness of the fact that genetic differences influence each individual’s response to various drugs. Understanding the genetic influence on the effect of various drugs has become a key factor in tailoring treatment according to each patient’s overall profile. Great advances have been made in this field, but a significant clinical effect of a tailored treatment strategy remains to be shown in a large trial [72].
Prasugrel has a simpler metabolism than clopidogrel and thus a greater bioavailability and a more rapid onset of effect [73,74]. The drug is therefore less prone to poor responsiveness. However, this greater antiplatelet effect also leads to greater bleeding risks. In TRITON-TIMI 38, Montalescot et al. found that prasugrel was associated with a significantly higher rate of TIMI major bleeding compared with the clopidogrel group (2.4 vs 1.8%, respectively; \( p = 0.03 \)) [37]. A significantly greater amount of patients in the prasugrel group than in the clopidogrel group experienced life-threatening bleeding events (1.4 vs 0.9%; \( p = 0.01 \)).

Another limitation to this potent drug is that it is not advised in patients with previous stroke, patients aged ≥75 years and patients who weigh <60 kg as these risk factors have been associated with higher risk of bleeding in the TRITON trial. The increased risk of intracranial hemorrhage in the prasugrel group was in fact significant compared with that in the clopidogrel group (2.3 vs 0%, respectively; \( p = 0.02 \)) [19].

In a TRITON substudy, ACS patients referred to an initial PCI strategy and who received dual antiplatelet treatment with ASA plus either prasugrel or clopidogrel, were finally referred to CABG surgery because of their substantial coronary pathophysiology. Montalescot et al. found significant increases in rates of TIMI major bleeds in the prasugrel group compared with the clopidogrel group (\( p = 0.003 \)) [37].

Newer antiplatelet drugs such as ticagrelor are now available and have shown promising results or reversible platelet inhibition, especially desirable in a setting of emergency surgery and in patients with increased bleeding risk. Although ticagrelor has proven to be more potent than clopidogrel in inhibiting platelet aggregation, it has not demonstrated any significant difference in minor and major bleeding events [75]. However, the adverse events of dyspnea and ventricular arrhythmias may lead to an inappropriate interruption of the treatment.

The problem of side effects was also seen with the use of PAR-1 antagonists in the TRACER trial, where the study was prematurely closed because of an increased incidence of intracranial hemorrhage.

The emergence of antiplatelet function tests was meant to help detect clopidogrel low responders, but there is a major limitation to these tests, namely the fact that there is no consensus on cut-offs and no definite definition of antiplatelet drug low response. This explains the variability in the prevalence of low response ranging from 5–30% according to different clinical trials.

Furthermore, the legitimacy of antiplatelet function tests is still a matter of discussion with the continuous development of still more potent drugs. In fact, several studies have faced difficulties, such as the TRIGGER-PCI trial where investigators compared treatment with prasugrel and clopidogrel in patients with stable coronary artery disease based on platelet reactivity testing. The study was recently halted because of the lack of sufficient primary end points.

Future perspective

The continued improvement of existing antiplatelet therapies is necessary to meet with the complex pathophysiology of platelet activation. Great advances have been made with newer point-of-care assays to measure platelet reactivity [76]. These tests are now more efficient, sensitive and rapid and they no longer necessitate specially trained technicians. This enables each physician to quickly determine a given patient’s platelet aggregation profile and decide whether a tailoring of the antiplatelet regimen is necessary. With the complexity of patients referred to interventional cardiology, a tailoring of their antiplatelet treatment may reduce the occurrence of ischemic complications. A number of point-of-care platelet function assays are now available, but systematic testing of platelet function is not yet implemented. This requires the emergence of larger clinical trials demonstrating a significant clinical benefit of tailoring antiplatelet treatment.

Newer drugs that meet with the requirements of consistent antiplatelet effect, rapid and reversible onset and offset of action, limited metabolization necessary for activation as well as a better safety profile with lower bleeding risks are yet to be marketed. Ticagrelor is the latest drug on the market that matches the mentioned criteria, but the question of compliance remains to be answered as this drug is to be administered twice daily.

A standardized definition of response to antiplatelet drug as well as a consensus on how to individualize treatment based on platelet reactivity and bleeding risk remains to be determined.

Financial & competing interests disclosure

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Executive summary
- Platelet activation and aggregation are the main factors in thrombus formation.
- Dual antiplatelet regimen with ASA and clopidogrel has so far been the gold standard in the prevention of thrombotic events in acute coronary syndrome patients.
- Newer drugs are continuously being marketed to address the limitations of available antiplatelet regimens.

Pharmacological background
- Aspirin is a salicylate drug that inhibits cyclooxygenase and thromboxane A2 production.
- Thienopyridines are prodrugs that irreversibly and selectively bind the P2Y12 receptors on platelet surface.
- Clopidogrel necessitates a two-step transformation via the hepatic CYP3A4 system.
- Prasugrel is also transformed in the liver, but exhibits greater bioavailability compared with clopidogrel.
- Nonthienopyridines, such as ticagrelor and elinogrel are reversible P2Y12 antagonists that do not require hepatic transformation prior to activation and, therefore, exhibit greater bioavailability.
- Protease-activated receptor (PAR)-1 antagonists act on G-coupled receptors and on thrombin receptors in arteries.

Clinical trials
- The ISIS-2 trial showed a significant reduction in all-cause mortality with ASA.
- The CURE trial demonstrated benefits with long-term use of clopidogrel therapy.
- The CURRENT-OASIS 7 trial demonstrated a reduced risk of stent thrombosis when doubling the doses of clopidogrel.
- TRITON-TIMI 38 showed a significant reduction in the composite end points of cardiovascular death, nonfatal MI and nonfatal stroke in patients receiving prasugrel.
- The PLATO trial demonstrated overall improved cardiovascular outcome with a significant reduction in total mortality with the use of ticagrelor.
- A Phase II trial, INNOVATE-PCI showed that elinogrel provides greater antiplatelet effect than clopidogrel as well as a more rapid onset of effect.
- The TRA-PCI, a Phase II trial performed on patients undergoing nonurgent percutaneous coronary intervention, has shown that SCH 530348, a PAR-1 antagonist, was well tolerated and did not cause increased bleeding when administered as a supplement to ASA and clopidogrel.

Assessment of antiplatelet response
- Despite dual antiplatelet therapy, thrombotic complications such as stent thrombosis still occur and have been linked to clopidogrel low response.
- Platelet function tests such as Multiplate® and Verify Now™ have been developed to assess residual platelet reactivity and detect patients that, despite optimal antiplatelet regimen, exhibit a high degree of platelet activity.
- Mutations of the cytochrome P450 enzyme system inducing genetic polymorphisms provide part of the explanation for clopidogrel low response and can be assessed by genetic tests such as the Spartan RX CYP2C19 DNA testing system.

Clinical challenges
- Ticlopidine has limited clinical use because of side effects such as neutropenia, agranulocytosis, thrombotic thrombocytopenic purpura and aplastic anemia.
- Clopidogrel provides an irreversible antiplatelet effect with subsequent bleeding risks mainly in the setting of emergency surgery and a delayed onset of action because of a complicated first-pass metabolization necessary prior to activation of its prodrug.
- Clopidogrel also exhibits substantial interindividual variability in antiplatelet effect. The phenomenon of clopidogrel low response is mainly due to genetic polymorphisms.
- The limitations of prasugrel are mainly due to an increased risk of bleeding and the drug is contraindicated in patients with previous stroke, aged ≥75 years and weighing <60 kg.
- Ticagrelor faces side effects such as dyspnea and ventricular arrhythmias.
- Although several platelet function tests are currently available, no consensus has been reached on cut-off levels of platelet reactivity, nor is there an established therapeutic approach for the management of high residual platelet reactivity and low response to clopidogrel as there still is no evidence that a tailoring of antiplatelet regimens entails significant clinical benefits.

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In patients with ST elevated myocardial infarction undergoing percutaneous coronary intervention, prasugrel is more effective than clopidogrel in preventing ischemic events without increasing bleeding risks.


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In patients with ST elevated myocardial infarction undergoing percutaneous coronary intervention, prasugrel is more effective than clopidogrel in preventing ischemic events without increasing bleeding risks.
 Patients referred to planned percutaneous coronary intervention were pre-loaded with clopidogrel 600 mg and platelet function was assessed with multiplate electrode platelet aggregation. Results showed that patients with low response to clopidogrel had a significantly higher incidence of stent thrombosis.


 Patients with previous stent thrombosis were shown to have a reduced antiplatelet effect to aspirin. This may be linked to an increased platelet turnover.


