New developments in oral antiplatelet therapy

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Oral antiplatelet therapy is central to the treatment of patients with thrombotic diseases. Yet, despite the proven efficacy of currently available agents such as aspirin and the P2Y12 receptor antagonist clopidogrel, and their advocacy in treatment guidelines, their efficacy and utilization remain suboptimal. This has prompted the search for more efficacious oral antiplatelet agents. Drug classes that have been, or continue to be, investigated include thromboxane A2/prostaglandin H2 (TXA2/PGH2; TP) receptor antagonists, protease-activated receptor (PAR) antagonists, and newer P2Y12 receptor antagonists.

TP receptors are G-protein-coupled receptors that, on agonist binding, activate the phospholipase C signalling cascade, resulting in platelet activation. The success of TP receptor antagonists has been limited to date; the majority of agents have been discontinued at phase I/II clinical trials following efficacy and safety concerns. However, S-18886 (terutroban) remains in development. Results from preclinical investigations demonstrate S-18886 to have comparable antiplatelet effects to clopidogrel, while data from phase II studies appear promising.

Inhibiting the actions of thrombin on platelets represents an emerging area of antiplatelet research, and compounds that target the PAR1 receptor are in early development. These include the PAR1-selective antagonist SCH 530348, which is currently being evaluated in phase III studies in patients with acute coronary syndromes (ACS), prior myocardial infarction, stroke, and existing peripheral arterial disease.

The P2Y12 G protein receptor is predominately located on platelets and is involved in the amplification of platelet activation. Owing to limitations of first- and second-generation thienopyridine P2Y12 antagonists such as clopidogrel, new antagonists are being evaluated. The irreversible thienopyridine P2Y12 antagonist prasugrel is currently in phase III development and has the potential to provide additional benefits over clopidogrel, including faster onset of action with improved inhibition of ADP-induced platelet aggregation and fewer non-responders. The differences in response are thought to be due to the more efficient generation of the active metabolite of prasugrel. The phase II JUMBO-TIMI 26 trial, which compared prasugrel with clopidogrel in patients undergoing elective or urgent percutaneous coronary intervention (PCI), reported low rates of bleeding with both drugs and a trend towards a reduction in ischaemic events with prasugrel relative to clopidogrel. However, the trial was not powered to show clinical outcomes.

Reversible, non-thienopyridine P2Y12 receptor antagonists are a further class of antiplatelet agents undergoing evaluation in clinical trials and include cangrelor, an ATP analogue. Cangrelor is a fast- and direct-acting, intravenous antiplatelet agent which has completed phase II clinical trials for the acute treatment of patients with ACS undergoing PCI. AZD6140 is a CPTP (cyclo-pentyl-triazolo-pyrimidine), and the first oral reversible antiplatelet agent in development for use in patients with ACS. Unlike the irreversible thienopyridines, AZD6140 does not require cytochrome P450
metabolic activation to exert its inhibitory effects on platelet aggregation. Data from the phase II DISPERSE trial demonstrates AZD6140 to have a more rapid onset of action and a significantly greater and more consistent inhibition of platelet aggregation when compared with clopidogrel in stable patients with atherosclerotic disease. Publication of the full analysis from the second phase II trial, DISPERSE2, is pending while recruitment is underway for the phase III PLATO (study of PLATElet inhibition and patient Outcomes). PLATO is a head-to-head outcomes study investigating the use of AZD6140 vs. clopidogrel for ACS in patients treated with medical therapy, PCI, or coronary artery bypass graft, with a planned recruitment of 18,000 patients worldwide.

Data from ongoing phase II and III clinical trials on the emerging antiplatelet agents are eagerly awaited. If these agents offer improvements over those currently available in terms of patient response to therapy, safety, and convenience, they are likely to influence the current prescribing patterns and guidelines.

**Introduction**

Oral antiplatelet therapies, such as the cyclooxygenase-1 inhibitor, aspirin, and the thienopyridine P2Y12 receptor antagonist clopidogrel, are central to the treatment of patients with thrombotic diseases. However, despite their proven efficacy and advocacy in treatment guidelines,1,2 many patients receiving these therapies continue to experience thrombotic events. There is thus a need to investigate new oral antiplatelet agents that could potentially offer patients improved efficacy, safety, and convenience. This article briefly examines the limitations of aspirin and clopidogrel, and profiles some of the new oral agents in clinical development.

**Can we do better than aspirin and clopidogrel?**

**Limitations of aspirin**

Despite the proven benefits of aspirin, some 10–20% of aspirin-treated patients experience a recurrent vascular event within 5 years.3 This high risk of recurrence has been attributed, in part, to the inability of aspirin to inhibit platelet aggregation in certain patients—so-called aspirin ‘variability of response’—which is estimated to occur in 5–60% of aspirin-treated patients.3 For a detailed description of variability in response to aspirin (and clopidogrel), readers are referred to recent review articles on this subject.3–5 Evidence of a link between clinical outcome and variability in response to aspirin has been reported in a number of studies.6–8 For example, in patients with prior stroke, those who responded poorly to aspirin had an increased risk of subsequent stroke compared with aspirin-sensitive patients (40 vs. 4.4%, P < 0.000176).6

The mechanisms of variability in response to aspirin are not yet fully elucidated, but are considered to be multifactorial, ranging from clinical factors such as patient non-compliance, failure of physicians to prescribe aspirin appropriately, and drug–drug interactions, to genetic factors such as cyclooxygenase-1 polymorphisms.3–5 Another important limitation of aspirin, even at low doses, is the increased risk of gastrointestinal adverse effects, including bleeding.9

**Limitations of clopidogrel**

Clopidogrel and ticlopidine are the two irreversible thienopyridine P2Y12 receptor antagonists currently available, both of which have proven efficacy in reducing the risk of arterial thrombotic events.10 Clopidogrel has, however, largely superseded ticlopidine owing to its better safety and tolerability profile, in particular its lower incidence of thrombotic thrombocytopenic purpura and neutropenia.

Clopidogrel, a prodrug, requires hepatic cytochrome P450 metabolism to release its active metabolite, which binds irreversibly through covalent modification to the P2Y12 receptor such that recovery of platelet function is precluded. Evidence suggests that there is considerable interindividual variability in response to clopidogrel, as measured by platelet aggregation and activation tests, with 5–10% of patients not responding to its effects, and as many as 25% being only partially responsive to the drug.11,12 As with aspirin, the mechanisms underlying variability in response to clopidogrel are multifactorial. Failure of physicians to prescribe clopidogrel, inadequate dosing in patients with an increased body mass index, and, again, patient non-compliance may all contribute to therapy failure. Other causes include effects on the cytochrome P450 system, such as drug–drug interactions or gene polymorphisms of the CYP3A4 system affecting generation of the active metabolite, and polymorphisms of the P2Y12 receptor.3–5 Further limitations of clopidogrel include a relatively modest inhibition of the ex vivo platelet aggregation response to ADP, and suboptimal onset of action.

**Potential target receptors for new antiplatelet agents**

*Figure 1* highlights some of the targets for antiplatelet agents that have been, or continue to be, investigated. The following section provides further discussion on the
developmental status of thromboxane A2/prostaglandin H2 (TXA2/PGH2; TP) receptor antagonists,13 thrombin protease-activated receptor types 1 and 4 (PAR1/PAR4) antagonists,14 and P2Y12 antagonists.15

TP receptor antagonists

The TP receptors are G-protein-coupled receptors which, on agonist binding, activate a phospholipase C signalling cascade resulting in platelet activation. Several potent, orally administered, long-acting TP receptor antagonists have entered clinical development in recent years. These include ifetroban (BMS-180291),16–18 sulotroban (BS 13.177),19–21 and GR 32191.22–24 Despite the demonstration of antithrombotic effects of these agents in animal studies, phase II/III clinical trials have yielded disappointing results, and for the majority of agents, development appears to have been discontinued owing to efficacy and safety concerns.

However, at least one TP receptor antagonist remains in clinical development: terutroban (formerly S18886). In a preclinical study of ex vivo porcine platelet aggregation, terutroban (100 µg/kg/day) was more effective than clopidogrel (3 mg/kg/day) at inhibiting ADP-stimulated platelet aggregation and as effective as clopidogrel at inhibiting collagen-stimulated platelet aggregation and platelet deposition under both low- and high-shear conditions.25 These antithrombotic effects of terutroban and clopidogrel were superior to those of aspirin (5 mg/kg/day), which showed no significant effects. In humans, oral administration of terutroban for 12 weeks (1-30 mg/day) has been reported to produce dose-proportional inhibition of ex vivo platelet aggregation,26 and terutroban is now undergoing phase III clinical trials in stroke patients.

PAR antagonists

In addition to stimulating fibrin production in the coagulation cascade, thrombin may also activate platelets via PAR receptors. These receptors are a category of G-protein-coupled receptors implicated in a range of cellular responses such as haemostasis and thrombosis, and inflammation.27 PAR1 and PAR4 are expressed on the surface of human platelets, with the PAR1 receptor proposed as the principal thrombin receptor.28 Inhibiting the actions of thrombin on platelets by targeting PAR1 receptors is, therefore, another potential antiplatelet therapy. At least two oral PAR1 receptor antagonists are currently in development: SCH 530348 and E5555.

SCH 530348 has demonstrated good oral bioavailability in phase I studies and is currently being evaluated in patients with acute coronary syndromes (ACS), prior myocardial infarction (MI), or stroke, and patients with peripheral arterial disease. The recently completed phase II trial, Thrombin Receptor Antagonist in Percutaneous Coronary Intervention (TRA–PCI), has reported positive findings regarding the safety and efficacy of SCH 530348.29 This trial randomized 1030 patients, aged >45 years, to receive a 10, 20, or 40 mg loading dose (LD) of SCH 530348 or placebo, in addition to aspirin, clopidogrel, and antithrombin therapy. Patients undergoing PCI (n = 573) were further randomized to a 0.5, 1.0, or 2.5 mg/day maintenance dose (MD) of SCH 530348 or placebo for 60 days. In the PCI cohort, treatment with SCH 530348, across all dosages, decreased (non-significantly) the incidence of death and major adverse cardiovascular events [MACE (5.9 vs. 8.6% with placebo)] without increasing major or minor bleeding [primary endpoint (2.8 vs. 3.3% with placebo)]. Phase III trials (using 40 mg LD with 2.5 mg MD) are now underway.
E5555 has been reported to inhibit platelet aggregation with no change in bleeding time in phase I studies and is being developed as a potential treatment for critical care ACS. Five drug–drug interaction studies and a food effects study have been completed, and a phase II proof-of-concept trial in patients with coronary artery disease (CAD) is soon to commence. This randomized, double-blind, placebo-controlled study, in approximately 600 patients, aged 55–80 years, with CAD and an elevated high-sensitivity C-reactive protein, will assess the incidence of MACE and a range of markers of intravascular inflammation. Secondary endpoints include the incidences of major and minor bleeding.

P2Y12 receptor antagonists

The P2Y12 G-protein receptor belongs to a superfamily of at least three purinoceptors (P2X1, P2Y1, and P2Y12) that selectively contribute to platelet aggregation. The P2Y12 receptor is predominantly located on platelets and, through signal activation by ADP, reduces levels of cyclic-AMP, promoting platelet activation. In contrast to the P2XY1 receptor (an ATP-gated channel) and the P2Y1 receptor (a platelet receptor coupled to Gq that initiates ADP-induced activation), the P2Y12 receptor is linked to Gi and is involved in the amplification of platelet activation initiated by ADP and numerous other pathways. As P2Y12 receptor activation yields powerful amplification of platelet aggregation, dense and alpha-granule secretion, and procoagulant activity, P2Y12 receptor antagonists have the potential to have dramatic inhibitory effects on platelet function, regardless of the activating stimuli.

As discussed, ticlopidine and clopidogrel represent the first- and second-generation P2Y12 receptor antagonists, respectively. Due to their limitations, however, other P2Y12 receptor antagonists, both oral and intravenous, are being evaluated for the treatment of patients with atherothrombotic disease. Among these are the thienopyridine prasugrel, an ATP analogue, cangrelor, and a cyclopentyl-triazolo-pyrimidine (CPTP), AZD6140 (Figure 2), all of which have entered phase III development.

Thienopyridine P2Y12 receptor antagonists

Prasugrel

Prasugrel (formerly CS-747, LY-640315) principally differs from the other irreversible thienopyridine P2Y12 receptor antagonists by having an ester group close to the reactive thiol group and a fluorine atom replacing the chlorine atom (Figure 2A). Like clopidogrel, prasugrel is a produg that requires hepatic metabolism to form its active metabolite which irreversibly inhibits the P2Y12 receptor. However, the active metabolite of prasugrel is generated much faster and at higher concentrations compared with clopidogrel, resulting in improved inhibition of ADP-induced platelet aggregation and fewer non-responders, as measured by inhibition of platelet aggregation (IPA).

A recent study involving 101 aspirin-treated patients with atherosclerotic disease who were randomized to either prasugrel (either a 40 mg LD and 5 mg/day or 7.5 mg/day MD, or a 60 mg LD and 10 mg/day or 15 mg/day MD) or clopidogrel (300 mg LD and 75 mg/day MD) reported there to be fewer non-responders in the prasugrel groups. At 4 h post-LD, 52% of clopidogrel patients were non-responders (defined as IPA ≤ 20% in response to 20 μM ADP) compared with only 3% of prasugrel patients (both 40 mg and 60 mg, \( P = 0.0002 \) vs. clopidogrel). Furthermore, at pre-MD on day 28, 45% of clopidogrel patients were non-responders compared with 0% of prasugrel patients treated with MD of either 10 mg or 15 mg (\( P = 0.0007 \)).

Prasugrel was also compared with clopidogrel in the Joint Utilization of Medications to Block platelets Optimally - Thrombosis In Myocardial Infarction 26 (JUMBO-TIMI 26) trial. This phase II, randomized, dose-ranging trial compared three different dose regimens of prasugrel with a standard dose of clopidogrel.
in 904 patients undergoing elective or urgent PCI. Overall, no significant difference between patients treated with prasugrel and those treated with clopidogrel was observed in terms of the primary safety endpoint, the rate of significant major and minor non-coronary artery bypass graft-related bleeding at 30 days (1.7 vs. 1.2%; hazard ratio: 1.42; 95% confidence interval: 0.40, 5.08). There was no obvious difference between the three prasugrel dose regimens for this parameter (1.5, 2.0, and 1.6% for 40/7.5, 60/10, and 60/15 mg, respectively). For the primary efficacy endpoint—a composite endpoint of MACE [comprising death (all cause mortality), MI, stroke, recurrent myocardial ischaemia requiring hospitalization, and clinical target vessel thrombosis] at 30 days—there was a consistent, but not statistically significant, trend towards a benefit for patients treated with prasugrel compared with those treated with clopidogrel (7.2 vs. 9.4%, P = 0.26) (Figure 3). The effects observed with prasugrel did not appear to be dose dependent.

The phase III trial, TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel - Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38), which is comparing prasugrel with clopidogrel in ACS patients, is currently underway.37 This randomized, double-blind, parallel-group, multinational clinical trial has enrolled 13,614 patients from 30 countries, with moderate- to high-risk ACS undergoing PCI to receive prasugrel (60 mg LD followed by 10 mg/day MD) or clopidogrel (300 mg LD followed by 75 mg/day MD) for up to 15 months. In patients with unstable angina or non-ST-elevation myocardial infarction (NSTEMI), or who enrolled post-STEMI, randomization will occur only after the coronary anatomy is known to be suitable for PCI. The primary endpoint in this study is time of the first event of cardiovascular death, MI, or stroke.

Reversible P2Y12 receptor antagonists

Reversible P2Y12 receptor antagonists, such as cangrelor and AZD6140, have chemical structures that differ substantially from those of the irreversible thienopyridine P2Y12 receptor antagonists (Figure 2B).

Cangrelor

Phase II clinical trials evaluating cangrelor (formerly AR-C69931MX) for the acute treatment of patients with ACS undergoing PCI have been completed. Cangrelor, which is administered intravenously, inhibits platelet aggregation with rapid onset and offset of action and does not require metabolism for therapeutic activity, thus offering potential benefits over clopidogrel.38 Initial experience with cangrelor during PCI suggests that it is associated with an acceptable risk of bleeding and adverse cardiac events, and results in platelet inhibition with less prolongation of bleeding time than the glycoprotein IIb/IIIa receptor antagonist abciximab, a commonly used antiplatelet therapy for this patient group.39

A two-part, multicentre, randomized, placebo- and active-controlled phase II study assessed cangrelor in patients undergoing PCI. In part 1 of the study, 200 patients were randomized to either placebo or cangrelor (1, 2, or 4 μg/kg/min) administered intravenously for 18–24 h just before the start of the revascularization procedure (in addition to aspirin and heparin). In the second part of the study, an additional 199 patients were randomized to either cangrelor (4 μg/kg/min) or a standard dose of abciximab (0.25 mg/kg bolus followed by 0.125 μg/kg/min up to a maximum of 10 μg/min for up to 12 h) 10–60 min before the start of the revascularization procedure.39 Combined major and minor bleeding (the primary endpoint) occurred in 13% of patients receiving cangrelor compared with 8% receiving placebo.
in part 1 ($P = \text{not significant}$) and in 7% of patients receiving cangrelor during part 2, compared with 10% receiving abciximab ($P = \text{not significant}$). In part 2, the occurrence of the composite endpoint of a MACE (death, MI, and unplanned repeat coronary intervention) was similar between patients receiving cangrelor and those receiving abciximab at both 7 days (5.7% vs. 5.4%, respectively, $P = \text{not significant}$) and 30 days (7.6% vs. 5.3%, respectively, $P = \text{not significant}$). These data suggest that there is no difference between cangrelor and abciximab in terms of either ischaemic events or bleeding risk.

AZD6140

AZD6140 is a CPTP (Figure 2B) which acts directly on the P2Y12 receptor without the need for metabolic activation and with a plasma half-life of approximately 12 h. AZD6140 has a rapid onset of action, with the peak IPA (induced by 20 μM ADP and measured by optical aggregometry of platelet-rich plasma) occurring within 2–4 h of dosing. As such, it is the first rapidly acting, reversible oral P2Y12 receptor antagonist in development for the treatment of ACS.

AZD6140 has been evaluated in the Dose-finding Investigative Study to assess the Pharmacodynamic Effects of AZD6140 in atherosclerotic disease (DISPERSE) phase II studies. The phase IIa DISPERSE study compared AZD6140 with clopidogrel in 200 patients with confirmed stable atherosclerotic disease in any vascular bed. DISPERSE randomized patients, aged 25–85 years, to one of four different dose regimens of AZD6140 (50, 100, or 200 mg twice daily, or 400 mg once daily) or clopidogrel (75 mg once daily) for 28 days, without any LD in any treatment group. Patients also received low-dose aspirin (75–100 mg once daily).

On treatment with AZD6140 at 100 and 200 mg twice daily, and 400 mg once daily, the magnitude of IPA (final extent) observed was greater than with 50 mg of AZD6140 twice daily or 75 mg of clopidogrel once daily. At 4 h post-dose on day 14, the least square mean differences between the three higher doses of AZD6140 and clopidogrel with regard to percentage IPA ranged from 25–30%. There was no substantial difference between the three highest doses of AZD6140 with respect to mean percentage IPA. Figure 4A and B presents individual patient data from this study, showing the final extent of mean IPA on day 1 and day 14 for the clopidogrel group and the AZD6140 100 mg twice-daily group, respectively.

AZD6140 was further investigated in the phase Ib Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs. clopidogrel in NSTEMI (DISPERSE2) trial which compared AZD6140 with clopidogrel in ACS patients with either unstable angina or NSTEMI ACS. All patients were treated with aspirin (325 mg LD followed by 75–100 mg once daily) and heparin/low-molecular-weight heparin and/or glycoprotein IIb/IIIa inhibition as selected by the local physician. This phase Ib study randomized 984 patients, aged ≥18 years, to one of two different dose regimens of AZD6140 (90 or 180 mg twice-daily maintenance therapy) or clopidogrel (75 mg once-daily maintenance therapy) for 4–12 weeks. Half of the patients in each AZD6140 arm were sub-randomized to receive a 270 mg LD while the other half started therapy with the MD. In the clopidogrel group, thienopyridine-naive patients received a 300 mg LD with the option to give an additional double-blind clopidogrel 300 mg dose pre-PCI (total 600 mg dose). Preliminary data from the DISPERSE2 trial was presented at the 2006 American College of Cardiology meeting in Atlanta. Publication of the final detailed analysis from the DISPERSE2 study is pending.

AZD6140 is currently being further evaluated in the PLATelet inhibition and patient Outcomes (PLATO) study.
This large \((n = 18,000)\), randomized, multinational, event-driven phase III clinical trial commenced in mid-2006 with the aim of comparing AZD6140 with clopidogrel in a broad ACS patient population (including STEMI, NSTEMI, and unstable angina), from 1000 centres in 45 countries.\(^{44}\)

**Summary**

Oral antiplatelet therapy is central to the treatment of patients with atherothrombotic disease, but patients experience varied responses to currently available antiplatelet therapies, such as aspirin and clopidogrel. Therefore, there is a need to optimize antiplatelet therapy in terms of efficacy and tolerability. Several potential new antiplatelet therapies are now being evaluated. Among these are TP receptor antagonists, such as SCH 530348 and E5555, and P2Y\(_{12}\) receptor antagonists, such as prasugrel, cangrelor, and AZD6140. Phase III data for these emerging compounds is eagerly awaited. If these agents are proven to offer improvement over currently available antiplatelet non-responders among patients with stable angina pectoris scheduled for elective coronary stent placement. *Thromb Haemost* 2003;89:783–787.

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New developments in oral antiplatelet therapy


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