Pharmacology and clinical trials of reversibly-binding P2Y₁₂ inhibitors

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Summary
The important role of the P2Y₁₂ receptor in amplification of platelet activation and associated responses and the limitations associated with clopidogrel therapy have led to the development of novel inhibitors of this receptor. Three reversibly-binding P2Y₁₂ inhibitors are in phase 3 development, ticagrelor, cangrelor and elinogrel. The pharmacology and clinical trial data for each of these inhibitors are discussed and compared with relevant data for the thienopyridines clopidogrel and prasugrel.

Keywords
ADP receptors, antiplatelet agents, arterial thrombosis, platelet pharmacology, antiplatelet drugs

The P2Y₁₂ receptor in platelet biology
Numerous platelet surface receptors mediate the actions of both soluble molecules in the plasma and subendothelial components of the vessel wall to regulate platelet function in a system that is designed to permit rapid aggregation at the site of vascular injury whilst limiting the risk of vascular occlusion. Collagen and other ligands in the vessel wall can bind platelets and lead to platelet activation, which subsequently causes the formation and/or release of soluble agonists such as thromboxane A₂, adenosine diphosphate (ADP) and 5-hydroxytryptamine (1,2). Activated platelets also form a catalytic surface for thrombin generation, a process known as platelet procoagulant activity that plays an important role in thrombogenesis and promotion of inflammation in the vessel wall (2).

ADP released from platelet dense granules as well as injured cells binds to two platelet surface receptors, the P₂Y₁ receptor, which initiates ADP-induced platelet activation, and the P₂Y₁₂ receptor, which plays a central role in amplification of platelet activation and the various platelet responses that culminate from this (3–5). Since all agonists induce ADP release and subsequent activation of the P₂Y receptors, the P₂Y₁₂ receptor is involved in the platelet response regardless of the stimulus (1). P₂Y₁₂ receptor activation amplifies and sustains platelet aggregation, including shear-induced aggregation, as well as strongly augmenting platelet granule release and procoagulant activity (4,6–10). Consequently, P₂Y₁₂ receptor activation is required in many experimental systems for stable thrombus growth such that blockade or deficiency of the receptor leads to smaller, unstable thrombi (11–14). The important role of the P₂Y₁₂ receptor in amplification of platelet activation and stable thrombus formation has made it an important target in the management and prevention of arterial thrombosis (1).

There are two principal types of drug that inhibit the P₂Y₁₂ receptor: thienopyridines (prodrugs such as ticlopidine, clopidogrel and prasugrel that act via irreversibly-binding active metabolites) and reversibly-binding inhibitors. This article will focus on the latter with relevant comparisons with the former. The antiplatelet effects of both types of inhibitors are proportional to the extent of receptor inhibition, either through prevention of ADP binding or inhibition of ADP-induced signalling (15,16).

Pharmacology of reversibly-binding P₂Y₁₂ inhibitors
Three reversibly-binding P₂Y₁₂ inhibitors are in phase 3 development, ticagrelor, cangrelor and elinogrel. These drugs belong to different chemical classes and have important differences in pharmacological properties as well as numerous similarities. All three drugs act by binding directly and reversibly to the P₂Y₁₂ receptor, without need for metabolic activation, and platelet function can recover when the plasma drug levels fall sufficiently to allow the drug to dissociate from the receptor. All three drugs can provide additional P₂Y₁₂ inhibition beyond the moderate mean level that is achieved with standard regimens of the thienopyridine clopidogrel, either when administered as alternative therapy to clopidogrel-naïve individuals or following prior clopidogrel treatment (17–20).

Pharmacology of ticagrelor
Ticagrelor is an oral, reversibly-binding P₂Y₁₂ inhibitor belonging to the class cyclopentyl-triazolopyrimidine (CPTP). Although the
structure of adenosine triphosphate (ATP), the natural antagonist at the P2Y12 receptor, was used as a foundation for the design of orally active, reversibly-binding P2Y12 inhibitors, the CPTPs do not contain an adenosine group and so are distinct from true ATP analogues such as cangrelor (21). Unlike the active metabolites of thienopyridines which directly block the ADP binding site on P2Y12, ticagrelor binds to a distinct site on the receptor and prevents ADP from causing activation of the P2Y12 pathway in a non-competitive fashion without substantially inhibiting the binding of ADP (16). It may act through an allosteric mechanism to prevent G-protein mediated signal transduction following ADP binding. Ticagrelor has a rapid onset of action, achieving in approximately 30 minutes (min) a similar mean level of inhibition to that achieved after several hours by a 600-mg loading dose of clopidogrel and far exceeding this level of inhibition by 1 hour (h) in patients with coronary artery disease (22). The peak inhibitory effect is seen at approximately 2 h after a maintenance or loading dose of ticagrelor (17, 22, 23). The rate of onset of action and consistency of effect of a loading dose of ticagrelor are similar to the effects of a loading dose of the thienopyridine prasugrel (24) and, like prasugrel, ticagrelor achieves more consistent and greater mean levels of platelet inhibition during maintenance therapy compared to clopidogrel in patients with both stable coronary artery disease and acute coronary syndromes (ACS) (17, 22, 23). The plasma half-life of ticagrelor is approximately 6–8 h following loading or maintenance dosing (25–27) and may be prolonged by co-administration of cytochrome P450 (CYP)3A4 inhibitors, such as diltiazem, since hepatic metabolism via CYP3A is the principal mode of excretion of ticagrelor. An active metabolite of ticagrelor, AR-C 124910XX, is present at about one-third of the plasma concentration of ticagrelor and has a half-life of approximately 8–12 h. In the absence of CYP3A4 inhibitors, the inhibitory effects of ticagrelor decline rapidly over 72 h following cessation and near-normal platelet reactivity is achieved after approximately five days (22). In contrast, the effects of clopidogrel take 5–10 days to wear off, with patients having a high level of inhibition on clopidogrel taking 10 days to recover normal platelet reactivity following drug cessation (28). Unlike clopidogrel, the response to ticagrelor is not influenced by loss-of-function genetic variants of the CYP2C19 gene (29). Early findings indicate that ticagrelor has non-P2Y12-mediated effects on adenosine reuptake and enhances the coronary flow response to adenosine (30). Ticagrelor has been shown in an animal model to reduce myocardial infarction (MI) size in a coronary occlusion/reperfusion model (31) but it remains to be established whether an effect on adenosine (rather than just platelet inhibition) contributes to this observation.

**Pharmacology of cangrelor**

Cangrelor was the first reversible P2Y12 inhibitor to be designed for clinical development and is a true analogue of adenosine triphosphate (ATP) (32). It is not orally active and so must be administered intravenously, whereupon it binds rapidly to the P2Y12 receptor. The inhibitory effect of cangrelor on receptor activation by ADP is predominantly competitive (33). High levels of receptor inhibition are achieved within a few minutes when it is administered as a bolus dose, whilst continuous infusion without a bolus dose achieves steady state levels of inhibition within 15–30 min that are then sustained for the duration of infusion (34, 35). Cangrelor is rapidly inactivated through dephosphorylation and has a mean plasma half-life of less than 10 min in patients with ACS (34). The combination of this very short half-life and reversible binding underlie the rapid recovery of platelet function in 1–2 h following termination of intravenous infusion of cangrelor. Transition from intravenous cangrelor to oral clopidogrel is complicated by the fact that cangrelor bound to the P2Y12 receptor prevents thienopyri...
active metabolites binding to the receptor also (36–38). Since clopidogrel active metabolite levels peak at 1–2 h after dosing and have a short half-life (although the inhibitory effects of active metabolite bound to P2Y12 are irreversible) (39, 40), clopidogrel is ineffective if administered during cangrelor infusion (36) and, to avoid any negative interaction, the effects of cangrelor need time to wear off before clopidogrel active metabolite can achieve its inhibitory effect.

**Pharmacology of elinogrel**

Elinogrel is a reversibly-binding P2Y12 inhibitor that belongs to a different chemical class to both ticagrelor and cangrelor (41). It is being developed in both intravenous and oral formulations. In distinction to ticagrelor, elinogrel exhibits a competitive inhibitory effect on P2Y12 receptor activation by ADP and, as a result, it is substantially more effective at inhibiting platelet activation by lower, rather than higher, concentrations of ADP. Elinogrel has a plasma half-life of approximately 8 h. As expected from an intravenous platelet inhibitor, elinogrel produces much more rapid onset of action compared to clopidogrel and greater mean inhibition of platelet aggregation induced by ADP 5 μM both following the loading course and during maintenance therapy. Its rates of onset and offset of action have not yet been well characterised in patients with coronary artery disease.

**Clinical studies of reversibly-binding P2Y12 inhibitors**

**Clinical studies of ticagrelor**

The first phase 2 study of ticagrelor (the ‘DISPERSE’ study) was performed in patients with stable atherosclerotic disease and assessed four dose regimens of ticagrelor (50 mg, 100 mg and 200 mg twice daily and 400 mg once daily) compared to clopidogrel 75 mg daily (27). The three higher dose regimens of ticagrelor achieved substantially greater inhibition of ADP-induced platelet aggregation compared to clopidogrel during maintenance therapy over four weeks. Subsequently there was reformulation of the ticagrelor tablets and dose increments of 90 mg were developed to mirror the pharmacokinetics of the former 100 mg dose. The DISPERSE-2 study was a phase 2 comparison of ticagrelor 90 or 180 mg twice daily with clopidogrel 75 mg daily in patients with ACS. Three loading regimens of ticagrelor were studied (90 mg, 180 mg and 270 mg) in comparison to clopidogrel 300 mg loading dose (increased to 600 mg at the discretion of the investigator in patients undergoing percutaneous coronary intervention [PCI]) for clopidogrel-naive patients. Patients assigned to clopidogrel who had already received a loading dose simply continued on clopidogrel maintenance therapy. In the clopidogrel-naive patients, all the three loading regimens of ticagrelor achieved faster onset of action compared to the clopidogrel 300 mg loading dose with greater mean levels of inhibition of ADP-induced platelet aggregation (17). The ONSET/OFFSET study was designed to clarify further the pharmacodynamic profile of ticagrelor compared to clopidogrel in patients with stable coronary artery disease, assessing both onset of action and offset following discontinuation, and additionally to study cardiac and pulmonary function prospectively in this population (22, 42).

Generally ticagrelor was well tolerated compared to clopidogrel in the phase 2 studies, with similar incidences of gastrointestinal adverse effects. More minor bleeding occurred with ticagrelor in the ACS population as would be expected with a more effective P2Y12 inhibitor but there was no excess of major bleeding (43). In all the studies, dyspnoea was seen as an adverse effect of ticagrelor and was closely assessed in the ONSET/OFFSET study (42). Whilst dyspnoea is a common symptom in patients with coronary artery disease regardless of treatment, the dyspnoea related to ticagrelor appeared more likely to occur early in the course of treatment, sometimes spontaneously resolved with continued treatment or otherwise usually resolved after cessation of treatment, and was graded as mild or occasionally moderate in severity by the investigators. There was no apparent deterioration in either left ventricular systolic function or pulmonary function and no evidence of systemic acidosis associated with the ticagrelor-related dyspnoea (42). Currently the mechanism for ticagrelor-related dyspnoea remains to be determined. In the DISPERSE-2 study, continuous electrocardiogram (Holter) monitoring was performed to investigate whether ticagrelor reduced silent ischaemia compared to clopidogrel and in this Holter substudy it was incidentally discovered that ticagrelor treatment was associated with higher incidences of ventricular pauses (43). One hypothesis for both the dyspnoea and ventricular pauses is that ticagrelor may increase extracellular levels of adenosine which is known to cause both effects. Ticagrelor was noted also to cause asymptomatic increases in serum uric acid levels. A small numerical excess of syncope not overtly caused by bradycardia was noted in DISPERSE-2 though not statistically significant (43).

In the PLATO study, ticagrelor (180 mg loading dose, 90 mg twice daily maintenance dose) was compared with clopidogrel (300 mg loading dose or 600 mg, if preferred, for those planned for PCI, 75 mg daily maintenance dose) in 18,624 patients with either i) moderate-to-high risk non-ST-elevation ACS within 24 h of symptom onset or ii) acute ST elevation myocardial infarction (STEMI) planned for primary PCI (44). Patients pre-treated with open-label clopidogrel were included and study medication was intended to be administered prior to coronary angiography in most cases and prior to PCI in all patients (45). Study medication was continued for up to 12 months, with study duration being reduced from 12 to nine months then six months towards the end of the trial. The study had a ‘double dummy’ design which meant that different strategies could be applied, in a blinded fashion, for the different study drugs prior to coronary artery bypass graft (CABG) surgery; clopidogrel (or its dummy in the ticagrelor arm) could be stopped five days prior to surgery according to standard practice whilst ticagrelor (or its dummy in the clopidogrel arm) was recom-
mended to be stopped only 24–72 h prior to surgery. The primary composite endpoint of cardiovascular death, MI or stroke was reduced to 9.8% from 11.7% (16% relative risk reduction) with ticagrelor compared to clopidogrel and there were significant reductions in the secondary endpoints of MI (5.8% vs. 6.9%) and cardiovascular death (4.0% vs. 5.1%) (44). There was no significant difference in the rates of major bleeding between the ticagrelor and clopidogrel arms (11.6% and 11.2%, respectively; p = 0.43), but there was a higher rate of non-CABG-related major bleeding with ticagrelor (4.5% vs. 3.8%, p = 0.03). There were more instances of fatal intracranial bleeding with ticagrelor but this was countered by fewer fatal bleeding events due to other causes such as gastrointestinal haemorrhage and so the fatal bleeding rates were not different between the groups (0.3% vs. 0.3%). The treatment effect of ticagrelor was observed regardless of whether an invasive or conservative management strategy was planned at randomisation and what loading regimen of clopidogrel was used (46). Although creatinine levels rose slightly more in the ticagrelor group compared to the clopidogrel group during the study, there was no difference in renal function between the groups after discontinuation of treatment and there was also a greater absolute benefit of ticagrelor over clopidogrel in patients with chronic kidney disease (47).

A 10,285 patient genetic substudy of PLATO has initially assessed the influence of relevant genetic variations in the gene for cytochrome P450 (CYP) 2C19, which plays an important role in the conversion of clopidogrel to its active metabolite (48), and also the gene for ABCB1, an efflux transporter in the intestine which is reported to influence clopidogrel absorption (49). This genetic substudy showed that carriers of loss-of-function alleles of CYP2C19 had higher events rates compared to non-carriers in the first 30 days but beyond this time point there was no further apparent influence and the superiority of ticagrelor over clopidogrel was not influenced by CYP2C19 genotype (50). Ticagrelor was also superior to clopidogrel regardless of ABCB1 genotype.

A total of 13.8% of ticagrelor-treated patients in PLATO reported an adverse event of dyspnoea compared to 7.8% of clopidogrel-treated patients (p < 0.001) and dyspnoea led to discontinuation of study drug in 0.9% of the ticagrelor group compared to 0.1% of the clopidogrel group (p < 0.001) (44). There was no attenuation of the mortality benefit of ticagrelor compared to clopidogrel in ticagrelor-treated patients who reported dyspnoea (51). A large Holter substudy in PLATO confirmed the higher incidence of ventricular pauses with ticagrelor compared to clopidogrel, particularly in the first week of treatment compared to after one month, but this did not lead to higher rates of pacemaker implantation or reported atrioventricular block (44). The excess of pauses were sinoatrial in origin and more frequently nocturnal (52).

As expected, the clinical event rates in PLATO were highest in patients with diabetes mellitus, renal impairment or age greater than 65 years but the relative risk reduction for ischaemic events with ticagrelor compared to clopidogrel remained consistent across these subgroups so that the absolute benefit was highest in these higher risk patients (44, 47, 53).

Clinical studies of cangrelor

The CHAMPION-PCI study was a randomised, double-blind study that compared intravenous cangrelor (30 μg/kg bolus then 4 μg/kg/min infusion for at least 2 h) started within 30 min before PCI, with a loading dose of clopidogrel 600 mg started at the same time (54). The study predominantly included patients with non-ST-elevation ACS although a minority of patients had either stable angina or STEMI. The cangrelor group received clopidogrel 600 mg at the time the infusion was discontinued. The primary composite endpoint was death from any cause, MI or ischaemia-driven revascularisation at 48 h and this was not significantly different between the groups, occurring in 7.5% of cangrelor-treated patients and 7.1% of patients in the clopidogrel-only group (odds ratio, 1.05; 95% confidence interval [CI], 0.88 to 1.24; P = 0.59). Dosing cangrelor at the time of cangrelor discontinuation creates a window of higher platelet reactivity in between the offset of cangrelor and the onset of clopidogrel effect (36) and it is possible that this could have attenuated the clinical efficacy of this combination. Furthermore, it is not clear whether dosing clopidogrel at the time of cessation of cangrelor infusion was sufficient to avoid any negative interaction between clopidogrel and cangrelor for some patients in this study, which might further compromise the efficacy of cangrelor. The CHAMPION-PLATFORM study was performed in parallel and compared cangrelor infusion (30 μg/kg bolus then 4 μg/kg/min infusion for 2–4 h) with a placebo infusion for patients with, predominantly, non-ST-elevation ACS undergoing PCI who had not yet received any thienopyridine (55). Patients receiving cangrelor then received clopidogrel 600 mg when the infusion was stopped whilst patients receiving placebo received this clopidogrel loading dose at the end of the procedure. The primary endpoint was the same as for CHAMPION-PCI and, again, was not significantly different between the groups although there was a trend towards benefit (7.0% cangrelor vs. 8.0% placebo, p = 0.18) underlying which were reductions, at 48 h, in death (0.2% cangrelor vs. 0.7% placebo, p = 0.02) and stent thrombosis (0.2% cangrelor vs. 0.6% placebo, p = 0.02). There was more femoral access site bleeding but no excess of transfusions or TIMI-major bleeding in the cangrelor group.

In view of the negative primary outcomes of the CHAMPION studies, a further efficacy study will be required to establish cangrelor as an option for patients undergoing PCI and such a study is currently ongoing (CHAMPION PHOENIX, clinicaltrials.gov identifier NCT01156571). The BRIDGE study is considering an alternative application for cangrelor in patients who are treated with thienopyridine and need to stop thienopyridine prior to CABG surgery. This study will compare cangrelor with placebo infusion continued up until the day of surgery as a potential means of continuing protection with P2Y12 inhibition during the window of vulnerability when the effects of clopidogrel are wearing off in high-risk patients.

Similar to ticagrelor, cangrelor was associated with an increased incidence of dyspnoea compared to placebo in the CHAMPION studies (54, 55). The incidence of dyspnoea associated with cangrelor (1 to 1.4%) was lower than that seen in the ticagrelor studies but
this may simply reflect the short duration of infusion of cangrelor, administered in the busy setting of PCI when mild episodes of dyspnoea may be overlooked.

**Clinical studies of elinogrel**

The ERASE-MI study assessed single intravenous bolus doses of elinogrel 10 mg, 20 mg, 40 mg or 60 mg compared to placebo in patients with STEMI planned for primary PCI but this trial was terminated early after enrolment of only 70 patients so provided limited information about safety and efficacy of elinogrel in this clinical setting (56). A pharmacodynamic study showed that a single oral dose of elinogrel 60 mg suppressed platelet aggregation responses in patients with high platelet reactivity during clopidogrel therapy following PCI (20). The INNOVATE-PCI study was a larger study that assessed combinations of intravenous bolus and oral dosing of elinogrel compared to clopidogrel in patients undergoing non-urgent PCI, excluding patients within seven days of MI (57). Patients received either 80 mg or 120 mg bolus of intravenous elinogrel followed by 50 mg, 100 mg or 150 mg twice-daily oral elinogrel or oral clopidogrel 300 to 600 mg loading dose followed by 75 mg daily. Following an interim safety analysis, the 80 mg bolus was dropped in favour of the 120 mg dose and the lowest oral dose of elinogrel was also dropped (58). A total of 616 patients received either elinogrel 100 mg or 150 mg twice-daily or clopidogrel 75 mg daily for up to 120 days. There was a dose-dependent trend towards higher rates of femoral access site bleeding with elinogrel but no significant excess of TIMI-defined major or minor bleeding. Similar to ticagrelor, patients treated with elinogrel had higher incidence of dyspnoea which was usually mild, often transient and infrequently led to discontinuation. Mild increases in liver function tests were also associated with elinogrel treatment and there was a slight numerical excess of cases of syncope. Much larger phase 3 studies are now planned to assess the efficacy of elinogrel.

**Comparison of the clinical studies of thienopyridines and reversibly-binding P2Y12 inhibitors**

There is a unifying theme across the spectrum of trials targeting the P2Y12 receptor: increasing levels of P2Y12 receptor inhibition are associated with reducing risk of arterial thrombotic events including MI, stent thrombosis and cardiovascular death, but at the expense of increasing risk of spontaneous bleeding. These clinical results are predictable from the preclinical studies of the receptor showing its profound role in thrombosis and its contribution to haemostasis. Stroke has been more refractory to prevention by P2Y12 inhibitors, likely reflecting the heterogeneity of aetiologies for stroke and contribution of impaired haemostasis to the occurrence or exacerbation of severity of some strokes.

Fundamental differences in study design are likely to explain why prasugrel in the TRITON study showed a greater early benefit over clopidogrel (24) compared to ticagrelor in the PLATO study (44). The early benefit of prasugrel in TRITON, particularly in patients with diabetes or STEMI or carriers of a loss-of-function allele in the CYP2C19 gene associated with reduced active metabolite formation with clopidogrel (59–61), is likely to have been amplified by the lack of adequate pre-treatment with clopidogrel prior to PCI in the majority of patients and the relatively low loading dose of clopidogrel (300 mg) (62), which is recognised to have slower onset of action and less consistent effect than a 600 mg loading dose (63). This might explain the reduction in early mortality in the STEMI cohort treated with prasugrel and the dramatic difference in early outcomes in the diabetic patients in TRITON. Indeed, the results of CHAMPION PLATFORM study support the need for adequate P2Y12 receptor inhibition at the time of PCI in order to prevent acute stent thrombosis and death (55). However, other mechanisms involving non-P2Y12-mediated (‘off-target’) effects of thienopyridines and their active metabolites warrant investigation to explore possible additional effects on thrombosis and haemostasis. In contrast to TRITON, more effective pre-treatment regimens of clopidogrel were employed in the PLATO study, with 46% of patients receiving open-label clopidogrel prior to randomisation and nearly 20% of patients receiving at least 600 mg total loading dose, and this is likely to explain why the difference between ticagrelor and clopidogrel in the first 30 days was less marked, except perhaps for carriers of a loss-of-function allele for CYP2C19 (44, 50).

Higher rates of non-CABG-related major bleeding were seen with both prasugrel and ticagrelor in the TRITON and PLATO studies, respectively. The higher rates of CABG-related bleeding seen with prasugrel likely reflect both the irreversible P2Y12 inhibition by prasugrel and the study design of TRITON since it was not intended that patients would proceed to CABG surgery and so there may have been a disproportionate number of urgent CABG cases occurring before the effects of the drug had been allowed to wear off. Despite these higher rates of bleeding, mortality was lower in the prasugrel-treated compared to clopidogrel-treated patients undergoing CABG (reported at www.theheart.org/article/1154085.do). On the other hand, the more rapid reversibility of inhibitory effects of ticagrelor provided an advantage in patients proceeding to CABG surgery in PLATO and investigators were advised to stop ticagrelor 24 to 72 h prior to surgery in order to allow the level of platelet inhibition to decline substantially. As a result, there was no excess of CABG-related bleeding with ticagrelor (64). Despite this lack of clinical evidence of differences in platelet inhibition at the time of CABG surgery, there was an impressive reduction in mortality following surgery in the ticagrelor group compared to the clopidogrel group (HR: 0.49; 95% CI: 0.32 to 0.77; p < 0.01) (64), and further work is required to elucidate the mechanisms for this.

A further difference between the results of TRITON and PLATO is that fatal bleeding was increased with prasugrel compared to clopidogrel (0.4% vs. 0.1%), which was not the case for ticagrelor compared to clopidogrel (0.3% vs. 0.3%). The reason for this difference is unclear and, again, off-target effects of the drugs must be considered as potential explanations. In TRITON, out-
comes were worse in the prasugrel group for patients with a prior history of stroke or transient ischaemic attack, mainly due to higher levels of intracranial haemorrhage with prasugrel, whilst in PLATO the treatment effect of ticagrelor was preserved in patients with a history of transient ischaemic attack or ischaemic stroke. However, neither prasugrel nor ticagrelor can be considered safe in patients with a history of intracranial haemorrhage. The excess of fatal bleeding with prasugrel had a neutralising effect on mortality over the follow-up phase so that ultimately mortality rates were the same in the prasugrel and clopidogrel groups. There was also an excess of cancer-related deaths in the prasugrel group (65). On the other hand, there was a progressive reduction of cardiovascular and total mortality with ticagrelor compared to clopidogrel in the PLATO study leading to a 22% relative risk reduction for total mortality in the ticagrelor arm. This extent of mortality reduction was unexpected and prompts the need for further work to explore whether some of the beneficial effects of ticagrelor are related to off-target effects.

Dyspnea has been noted as an adverse effect for all the above reversibly-binding P2Y₁₂ inhibitors (ticagrelor, cangrelor and elinogrel) whilst this is not the case for the thienopyridines. The fact that three different chemical classes of reversibly-binding inhibitors are associated with this adverse effect should give some insights into future studies assessing the mechanism for this adverse effect. Similarly, ventricular pauses have been noted as an adverse effect of ticagrelor but not the thienopyridines.

The common and different attributes of the reversibly-binding P2Y₁₂ inhibitors and the thienopyridines provide an increasingly comprehensive armamentarium for targeting this receptor and optimising the clinical outcomes of patients with ACS and other manifestations of atherothrombosis.

Conflict of interest
This work was supported by an unrestricted educational grant to the University of Sheffield from Eli Lilly and Daiichi Sankyo alliance to support the European Platelet Academy. Prof. Storey has received consultancy fees, honoraria and/or institutional research grants from AstraZeneca, Eli Lilly, Daiichi Sankyo, The Medicines Company, Novartis, Sanofi Aventis, Bristol Myers Squibb, GlaxoSmithKline, Eisai, Schering Plough, Merck, Teva, Dynabyte, Accumetics and Medscape.

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