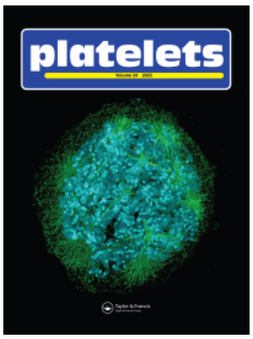

Platelets

ISSN: 0953-7104 (Print) 1369-1635 (Online) Journal homepage: informahealthcare.com/journals/iplt20

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To cite this article: Mark R. Thomas & Robert F. Storey (2015) The future of $P2Y_{12}$ receptor antagonists, Platelets, 26:5, 392-398, DOI: 10.3109/09537104.2015.1049519

To link to this article: https://doi.org/10.3109/09537104.2015.1049519

Published online: 04 Jun 2015.

platelets

http://informahealthcare.com/plt
ISSN: 0953-7104 (print), 1369-1635 (electronic)

Platelets, 2015; 26(5): 392–398
 DOI: 10.3109/09537104.2015.1049519

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INVITED ARTICLE: Celebrating the achievements of Professor Stan Heptinstall, Founder and Editor-in-Chief of Platelets (1990–2015)

The future of $P2Y_{12}$ receptor antagonists

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Abstract

Platelet $P2Y_{12}$ inhibitors have become a central component of the treatment strategy for patients with atherothrombosis due to the importance of platelet $P2Y_{12}$ receptors in arterial thrombosis. $P2Y_{12}$ inhibitors effectively reduce the risk of adverse cardiovascular events in patients with acute coronary syndromes (ACS) and patients undergoing percutaneous coronary intervention (PCI). However, despite this, patients with ACS continue to suffer from recurrent atherothrombosis and an increased risk of mortality. In addition, $P2Y_{12}$ inhibitors increase the risk of bleeding, thereby limiting their clinical benefit. It is therefore clear that further optimizations are needed in the pharmacology and treatment strategies of $P2Y_{12}$ inhibitors. The objective of these optimizations is to maximize cardiovascular benefit whilst minimizing adverse effects on haemostasis. This review article summarizes the most successful recent strategies in $P2Y_{12}$ inhibition in order to identify the optimizations and developments that are most likely to be successful in the future.

Keywords

Antiplatelet therapy, clopidogrel, platelets, $P2Y_{12}$ inhibitors, prasugrel, ticagrelor

History

Received 4 May 2015
Accepted 4 May 2015
Published online 4 June 2015

Introduction

Platelet $P2Y_{12}$ inhibitors are some of the most commonly used medications worldwide, due to their established benefit in the treatment and prevention of arterial thrombosis, as reviewed by Heptinstall and colleagues [1]. Following atherosclerotic plaque rupture, platelets are exposed to potent agonists that trigger platelet activation and aggregation. Subsequent platelet release of ADP and corresponding activation of platelet $P2Y_{12}$ ADP receptors has a central role in amplifying the response of platelets to the initial stimulus (Figure 1) [2]. Therefore, platelet $P2Y_{12}$ receptors are an attractive target for pharmacotherapy.

The first-generation thienopyridine ticlopidine was the first $P2Y_{12}$ inhibitor to be used in clinical practice, although its use was limited by adverse effects including neutropaenia [3]. The second-generation thienopyridine clopidogrel had a superior safety profile and therefore replaced ticlopidine. Clopidogrel is effective at reducing the risk of adverse cardiovascular events in patients with acute coronary syndromes (ACS) and following percutaneous coronary intervention (PCI) [4–6]. However, it has become increasingly clear that clopidogrel does not satisfactorily inhibit the platelets of approximately one-third of patients [7]. This is in part due to its reliance on multiple cytochrome P450 (CYP) enzymes for conversion into its active metabolite. The third-generation thienopyridine prasugrel is less dependent on CYP enzymes and therefore causes a more potent and consistent decrease in platelet reactivity [8]. In keeping with this, prasugrel decreases the risk of adverse cardiovascular events compared to clopidogrel in invasively-managed ACS patients, albeit at the expense of an increase in spontaneous and surgery-related bleeding [9]. Ticagrelor is another recently introduced potent $P2Y_{12}$ inhibitor, although it is a nucleoside analogue, representing a novel class of non-thienopyridine $P2Y_{12}$ inhibitor that is used in ACS, as reviewed by Heptinstall and colleagues [10]. Ticagrelor is also more effective than clopidogrel at reducing the risk of adverse cardiovascular events in patients with ACS, but also increases the risk of spontaneous bleeding [11].

By identifying the most successful advancements in $P2Y_{12}$ inhibitors to date, this review article aims to predict the optimizations and developments that are likely to be most successful in the future.

Optimizing the pharmacology of $P2Y_{12}$ inhibition

Pharmacokinetics

Thienopyridines, such as clopidogrel and prasugrel, are prodrugs that require conversion into their active metabolites by hepatic cytochrome P450 (CYP) enzymes *in vivo* to reduce platelet reactivity. Clopidogrel is converted into its active metabolite in two metabolic steps by CYP enzymes, in particular CYP2C19 [12]. Generation of the active metabolite of clopidogrel is therefore influenced by drugs that affect CYP2C19 [13] and by loss-of-function polymorphisms of the *CYP2C19* gene [14]. In contrast, prasugrel is converted into its intermediate form by plasma esterases, requiring just one CYP-mediated step to generate its active metabolite, and has little dependence on CYP2C19 [15, 16]. Whilst the active metabolites of clopidogrel and prasugrel are structurally very similar (but not identical), the more efficient and extensive metabolism of prasugrel compared to clopidogrel results in higher and more consistent generation of the active metabolite of prasugrel [17]. Consequently, the pharmacokinetics of prasugrel are not significantly affected by drugs that affect CYP2C19 [13] or by genetic polymorphisms of *CYP2C19* [14]. In contrast to the thienopyridines, ticagrelor is direct acting and therefore does not require conversion into an active metabolite to reduce platelet reactivity, thereby resulting in a

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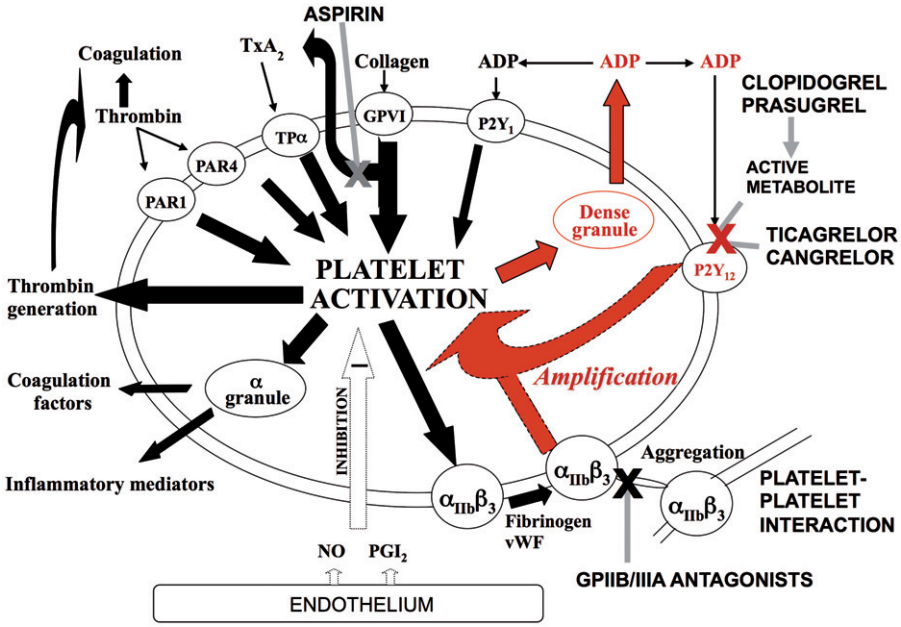

Figure 1. The role of P2Y$_{12}$ receptors in platelet activation. Platelet activation is induced by collagen, thromboxane A$_2$, thrombin and ADP, as well as other agonists. This triggers the release of dense granules, which contain ADP. The released ADP then acts on platelet ADP receptors, of which, the P2Y$_{12}$ receptor has a major role in amplifying the response of the platelet to the initial agonist (highlighted in red).

predictable pharmacokinetic profile [18]. However, ticagrelor is metabolized by CYP3A into at least 10 different active metabolites (some of which are equipotent with ticagrelor) and therefore has drug–drug interactions with CYP3A inhibitors [19].

Since they provide a more predictable pharmacokinetic profile, direct acting P2Y$_{12}$ inhibitors or P2Y$_{12}$ inhibitors that require minimal biotransformation are likely to be the most successful in the future. Avoidance of CYP metabolism is also preferable to minimize drug–drug interactions.

Pharmacodynamics

A major limitation of the use of clopidogrel is its variability of response, since approximately one-third of clopidogrel-treated patients do not achieve satisfactory platelet inhibition [7]. A poor response to clopidogrel can be detected using platelet function testing, including a P-selectin-based test developed by Heptinstall and colleagues, and is associated with an increased risk of cardiovascular events [20, 21]. Conversely, a high level of response to clopidogrel is associated with an increased risk of bleeding [21–23]. This has led to the concept of a therapeutic window of P2Y$_{12}$ inhibition, which aims to achieve an optimal balance between maximizing cardiovascular benefit whilst minimizing bleeding [21–23]. Tailoring antiplatelet therapy on the basis of measurements of platelet reactivity is an attractive concept for achieving an optimal level of P2Y$_{12}$ inhibition. Various attempts have been made to personalize antiplatelet therapy in clopidogrel-treated patients, but the strategies tested so far have not provided additional cardiovascular benefit compared to traditional antiplatelet therapy [24–26]. The more favourable pharmacokinetics of prasugrel and ticagrelor compared to clopidogrel result in more rapid, consistent and potent platelet inhibition than clopidogrel [8, 27]. Prasugrel reduces the risk of adverse cardiovascular events compared to clopidogrel in invasively-managed ACS patients [9]. Similarly, ticagrelor reduces the risk of adverse cardiovascular events compared to clopidogrel in patients with ACS managed both invasively and non-invasively, including a reduced risk of cardiovascular death [11, 28]. However, the cardiovascular benefit of both drugs is counter-balanced by increased rates of spontaneous bleeding [9, 11]. Ideal strategies for P2Y$_{12}$ inhibition would achieve an optimal level of P2Y$_{12}$ inhibition that maximizes reductions in risk of adverse cardiovascular events without an excessive increase in risk of bleeding. Ticagrelor maintenance therapy achieves a very high level of P2Y$_{12}$ inhibition [27, 29], so aiming for a higher level than this is not necessary or desirable since this may only result in increases in bleeding that outweigh potential cardiovascular benefits. It is therefore unlikely that future strategies of P2Y$_{12}$ inhibition will involve greater levels of P2Y$_{12}$ inhibition than current strategies, in the majority of patients at least.

The active metabolites of clopidogrel and prasugrel covalently bind to P2Y$_{12}$ receptors, causing irreversible inhibition that lasts for the lifespan of the platelet, which is approximately 10 days. Since new, uninhibited platelets are constantly generated, platelet function recovers approximately 5–7 days after clopidogrel and prasugrel discontinuation [30]. In contrast, ticagrelor is a reversibly-binding P2Y$_{12}$ inhibitor, which results in a more rapid offset of platelet inhibition, within approximately 72 hours [31]. This may have contributed to the particular benefit of ticagrelor over clopidogrel in patients undergoing CABG, with a reduction in all-cause mortality of approximately 50% and bleeding contributing to more deaths in the clopidogrel group following CABG surgery [32]. Whilst the rapid offset of ticagrelor potentially allows for a shorter interruption of P2Y$_{12}$ inhibition than clopidogrel, it would theoretically be appealing to continue P2Y$_{12}$ inhibition until immediately prior to surgery. In the BRIDGE study, treatment with cangrelor after discontinuation of thienopyridine was able to reduce platelet reactivity in the interval before surgery without increasing bleeding [33]. An antidote to ticagrelor has recently been developed and its efficacy is currently being tested [34]. In the future, it may be possible to continue ticagrelor up until the time of surgery and reverse its effect immediately prior to surgery. This strategy could only be possible with P2Y$_{12}$ inhibitors that do not cause irreversible inhibition of the P2Y$_{12}$ receptor.

Route of administration

In healthy volunteers and stable patients, both prasugrel and ticagrelor achieve a high level of P2Y$_{12}$ inhibition within approximately 30 minutes [31, 35]. However, in patients with

ST-elevation myocardial infarction (MI), the inhibitory effect of both drugs is delayed by as much as 2–6 hours [36]. This may be due to delayed absorption and the effect of morphine on delaying gastric emptying has been implicated as a likely cause for this [37, 38]. Strategies that can help to overcome this have therefore been investigated. In the Mashed Or Just Integral Tablets of ticagrelOr (MOJITO) study, crushed tablets achieved a significantly greater reduction in platelet reactivity than ordinary tablets [39]. Another intuitive pharmacological strategy to address this would be initiation of immediate parenteral $P2Y_{12}$ inhibitors in patients with ACS, followed by oral maintenance therapy once sufficient platelet inhibition has been achieved. The intravenous $P2Y_{12}$ inhibitor cangrelor can achieve almost immediate potent $P2Y_{12}$ inhibition [40]. Meta-analysis of studies investigating cangrelor shows that it reduces the risk of periprocedural thrombotic events in patients undergoing PCI, but increases the risk of bleeding [41]. Elinogrel was developed as a direct acting $P2Y_{12}$ inhibitor that could be administered intravenously or orally. In the phase II study INNOVATE PCI, elinogrel did not increase major bleeding compared to clopidogrel [42] but was subsequently withdrawn from further development.

Logically, a strategy of intravenous administration of $P2Y_{12}$ inhibitor followed by oral maintenance therapy is particularly appealing. Recently cangrelor has been approved by the European Commission and has received favourable opinion from the FDA advisory committee. The availability of cangrelor therefore offers the opportunity to circumvent the problem of delayed absorption of oral $P2Y_{12}$ inhibitors in opiate-treated patients undergoing emergency coronary stenting. This will likely reduce the subsequent risk of acute stent thrombosis in these patients, as long as clinicians take care in transitioning to oral $P2Y_{12}$ inhibitors. This is a concern as cangrelor blocks the binding of clopidogrel and prasugrel active metabolites to the receptor, as shown by Heptinstall and colleagues and other groups [43–45].

Safety, tolerability and minimization of adverse effects

Although bleeding is clearly a core concern in the development of antiplatelet strategies, other adverse effects are also important considerations. The first thienopyridine $P2Y_{12}$ inhibitor to be used in clinical practice, ticlopidine, caused neutropaenia [3], leading to its replacement by clopidogrel. Whilst subsequent thienopyridines have been generally well-tolerated, it has become apparent that the reversibly-binding agents ticagrelor, cangrelor and elinogrel cause dyspnoea [46]. In the case of ticagrelor, it has been hypothesized that this may be related to the finding that ticagrelor inhibits cellular uptake of adenosine [47] and therefore increases plasma levels of adenosine [48], which can cause dyspnoea [49]. Alternatively, it has been suggested that reversible $P2Y_{12}$ inhibitors may affect $P2Y_{12}$ receptors on sensory neurons to a greater degree than thienopyridines, thereby causing dyspnoea [46]. As dyspnoea can rarely lead to discontinuation of the $P2Y_{12}$ inhibitor, it would be preferable to avoid dyspnoea. However, in the case of ticagrelor, it is unknown whether the mechanism that causes dyspnoea contributes to the clinical benefit of the medication. For example, a significant reduction in sudden cardiac death was noted in PLATO with ticagrelor compared to clopidogrel [50], raising the hypothesis that ischaemic preconditioning by increased extracellular adenosine might reduce the risk of arrhythmic death, although reduction in MI via platelet $P2Y_{12}$ inhibition is an alternative explanation. The Trial of Caffeine to Alleviate Dyspnoea Related to Ticagrelor (TROCADERO) study (clinicaltrials.gov reference NCT02311088) will clarify the cause of ticagrelor-associated dyspnoea by investigating whether it can be relieved by caffeine, which is an adenosine antagonist.

Summary of predictions for developments in the pharmacology of $P2Y_{12}$ inhibitors

Following on from the most successful developments to date described above, drugs with the following pharmacological features are likely to be most successful in the future: (1) direct acting or requiring minimal biotransformation; (2) minimal interaction with CYP enzymes; (3) level of $P2Y_{12}$ inhibition no greater than currently achieved by standard doses of ticagrelor; (4) reversible; (5) readily available antidote; (6) safe and well-tolerated. Intravenous $P2Y_{12}$ inhibitors offer an attractive adjunct to oral inhibitors in particular clinical settings such as opiate-treated patients undergoing emergency PCI.

Optimizing the application of $P2Y_{12}$ inhibitors

Patient populations

Clopidogrel, in addition to aspirin, reduces the risk of adverse cardiovascular events in patients with ST-elevation MI, non-ST-elevation MI and in patients undergoing PCI compared to placebo [4–6]. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON – TIMI) 38 study, prasugrel reduced the incidence of adverse cardiovascular events compared to clopidogrel in ACS patients with a planned invasive strategy [9.9% vs. 12.1%; hazard ratio (HR), 0.81; 95% confidence interval (CI), 0.73–0.90; $p<0.001$] [9]. However, prasugrel did not significantly reduce the incidence of adverse cardiovascular events compared to clopidogrel in medically managed ACS patients in the TRILOGY study (13.9% vs. 16.0%; HR, 0.91; 95% CI, 0.79–1.05; $p=0.21$) [51]. In contrast, ticagrelor reduces the risk of adverse cardiovascular events compared to clopidogrel in both medically-managed and invasively-managed ACS patients [11, 52]. It has not yet been shown whether potent $P2Y_{12}$ inhibitors offer additional benefit compared to clopidogrel in patients with stable coronary artery disease undergoing PCI. The STEEL PCI study (clinicaltrials.gov reference NCT02327624) will investigate two doses of ticagrelor compared to clopidogrel in these patients. In the future, it is clear that potent $P2Y_{12}$ inhibitors will be used in ACS patients with a planned invasive strategy. Further investigation is needed to determine the reason why ticagrelor is of benefit to medically-managed ACS patients, whilst it would appear that prasugrel is not [28, 51].

Duration of $P2Y_{12}$ inhibition

The treatment options for patients with ACS are complex and have evolved substantially over the last decade. There is an increasing focus on treatment with PCI and drug-eluting stents in particular. Whilst drug-eluting stents are effective at preventing restenosis compared to bare metal stents, there has been concern that a prolonged duration of $P2Y_{12}$ inhibition may be required to prevent stent thrombosis. Guidelines have previously recommended 12 months of dual antiplatelet therapy following PCI for ACS [53, 54]. However, the recent Dual Antiplatelet Therapy (DAPT) study has shown that 30 months of dual antiplatelet therapy reduces the risk of stent thrombosis and adverse cardiovascular events compared to 12 months at the expense of an increased risk of bleeding [55]. On the other hand, recent meta-analyses have suggested that prolonged dual therapy with aspirin and either clopidogrel or prasugrel might increase all-cause mortality [56]. The recent Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) study showed that ticagrelor reduces the risk of adverse cardiovascular events

when started 1–3 years after MI at the expense of an increased risk of bleeding [57]. Interestingly, in this setting, a lower dose of ticagrelor (60 mg twice daily) provided as much cardiovascular benefit as the dose normally used after ACS (90 mg twice daily) but caused slightly less bleeding. Although longer durations of dual antiplatelet therapy provide a reduction in adverse cardiovascular events, this is to some extent balanced by an increase in bleeding. Therefore, in the future, it is likely that there will be an increased focus on determining which patients are likely to benefit the most from long-term dual antiplatelet therapy. In the future, higher doses of P2Y$_{12}$ inhibitors may be used for a set period of time following ACS, followed by a lower long-term dose, particularly in patients who may not tolerate higher doses.

Initiation of P2Y$_{12}$ inhibition

Guidelines recommend that antiplatelet therapy should be initiated as early as possible after the diagnosis of ACS is made [53, 54]. In patients with non-ST-elevation ACS, the ACCOAST trial recently showed that pretreatment with prasugrel before coronary angiography offers no additional benefit compared to later administration once coronary anatomy has been defined [58]. However, studies that have shown a benefit of clopidogrel and ticagrelor in non-ST-elevation ACS have used pretreatment strategies and so the findings from ACCOAST cannot be extrapolated to these drugs. In patients with ST-elevation ACS, the Administration of Ticagrelor in the Cath Lab or in the Ambulance for New ST Elevation Myocardial Infarction to Open the Coronary Artery (ATLANTIC) study showed a similar effect of ticagrelor on parameters of reperfusion regardless of whether it was administered before or after arrival at the hospital, although a benefit of early ticagrelor treatment might have been masked by morphine treatment [59]. Further studies are required to determine the optimal time for starting ticagrelor in different clinical settings and to assess how intravenous P2Y$_{12}$ inhibitors may be used as adjunctive therapy to optimize risk.

Summary of predictions for future optimizations in use of P2Y$_{12}$ inhibitors

It is clear that potent P2Y$_{12}$ inhibitors will continue to play an important role in invasively-managed ACS patients in the future. There may be an increasing focus on identifying patients who are also likely to receive a cardiovascular benefit from long-term P2Y$_{12}$ inhibition without an excessive risk of bleeding. Pretreatment with P2Y$_{12}$ inhibitors prior to coronary angiography is likely to continue in ticagrelor- and clopidogrel-treated patients, unless future studies indicate a more favourable alternative, such as initial use of an intravenous P2Y$_{12}$ inhibitor.

Table 1. Summary of our predictions for the most successful strategies for P2Y$_{12}$ inhibition in the future.

	Predicted strategies for the future
Pharmacology	Use of P2Y$_{12}$ inhibitors that have the following properties: 1. Direct acting or require minimal biotransformation 2. Minimal interaction with CYP enzymes 3. Cause a level of P2Y$_{12}$ inhibition that is no greater than the level currently achieved by ticagrelor and prasugrel 4. Bind reversibly 5. Antidote readily available 6. Safe and well-tolerated 7. Can be administered intravenously or can be used in conjunction with intravenous inhibitors
Clinical usage	Clinical strategies that involve: 1. Administration of intravenous P2Y$_{12}$ inhibitors or, otherwise, oral P2Y$_{12}$ inhibitors prior to coronary angiography 2. Identification of patients likely to benefit from long-term P2Y$_{12}$ inhibition 3. Possible increased prominence of P2Y$_{12}$ inhibitors in the management of stroke and peripheral arterial disease 4. Possible new indications for P2Y$_{12}$ inhibitors in stable patients with diabetes and patients with pneumonia 5. Use of P2Y$_{12}$ inhibitors without aspirin in certain clinical contexts

New frontiers of P2Y$_{12}$ inhibition

New indications for P2Y$_{12}$ inhibitors

In the PLATO study, ticagrelor was unexpectedly associated with fewer deaths following pulmonary infections and sepsis than clopidogrel [32, 50, 60]. It is unclear whether this was due to ticagrelor causing greater P2Y$_{12}$ inhibition than clopidogrel or whether it was due to inhibition of adenosine uptake by ticagrelor. Alternatively, it could have been due to an adverse off-target effect of clopidogrel or could simply have been due to chance. The Examining the Effect of Ticagrelor on Platelet Activation, Platelet-Leukocyte Aggregates, and Acute Lung Injury in Pneumonia (XANTHIPPE) study (clinicaltrials.gov reference NCT01883869) and the Randomized Trial of Ticagrelor for Severe Community Acquired Pneumonia (TCAP) trial (clinicaltrials.gov reference NCT01998399) will investigate this by determining whether ticagrelor is of benefit compared to placebo in patients with pneumonia.

Clopidogrel is currently used in the management of stroke and peripheral arterial disease. AstraZeneca's PARTHENON programme of clinical trials includes EUCLID, SOCRATES and THEMIS, which will determine the benefit of ticagrelor in peripheral arterial disease, stroke and patients with type 2 diabetes, respectively. It is therefore possible that P2Y$_{12}$ inhibitors, particularly ticagrelor, may take more important roles in the management of stroke and peripheral arterial disease in the future and may develop new indications for the treatment of stable patients with diabetes and patients with pneumonia.

Combination of P2Y$_{12}$ inhibitors with other platelet inhibitors

Platelet P2Y$_{12}$ inhibitors are routinely used in combination with low dose aspirin at an optimal dose of 75–100 mg [61]. However, it is not known whether aspirin is still needed in all situations when a potent P2Y$_{12}$ inhibitor such as prasugrel or ticagrelor is used. The GLOBAL LEADERS study (clinicaltrials.gov reference NCT01813435) will investigate this by randomizing PCI patients to receive 1 month of aspirin in combination with ticagrelor, followed by 23 months of ticagrelor alone compared to a normal treatment strategy (12 months of dual antiplatelet therapy, followed by aspirin alone). There is also interest in whether a third antiplatelet medication can be added in on top of aspirin and a P2Y$_{12}$ inhibitor. The thrombin receptor inhibitor vorapaxar initially showed potential in this role, but unfortunately did not significantly reduce the risk of adverse cardiovascular events when commenced urgently in ACS patients and increased the risk of bleeding, including intracranial haemorrhage [62]. However, vorapaxar has been approved by the FDA for use in combination

with other antiplatelet drugs as secondary prevention therapy. The prostaglandin E receptor 3 (EP_3) antagonist DG-041 has been identified as a promising platelet inhibitor for use in conjunction with aspirin and $P2Y_{12}$ inhibitors by Heptinstall and colleagues [63–66]. *In vitro, ex vivo* and animal studies have suggested that DG-041 inhibits platelets without significantly impairing haemostasis [67, 68], which holds promise for future clinical investigation. Strategies involving dual antiplatelet therapy with aspirin and a potent $P2Y_{12}$ inhibitor currently have the most momentum, although it is possible that aspirin may play a lesser role in this relationship in the future.

Conclusion

There is still much scope for optimizing the pharmacology and treatment strategies of $P2Y_{12}$ inhibitors (Table 1). $P2Y_{12}$ inhibitors used in the future are likely to be direct acting and reversible and are unlikely to be significantly more potent than current treatments. Theoretically, compounds that are available in both oral and intravenous formulations would be ideal although different oral and intravenous agents that interact favourably should suffice. Invasively-managed ACS patients are likely to continue to derive the most benefit from $P2Y_{12}$ inhibitors in the future. There may also be an increasing focus on risk stratification to determine whether patients may benefit from long-term $P2Y_{12}$ inhibition and which patients may be optimally treated by $P2Y_{12}$ inhibitors alone without aspirin. In addition, $P2Y_{12}$ inhibitors may find a more prominent role in stroke, peripheral arterial disease and stable patients with diabetes.

Acknowledgements

The views expressed are those of the authors and not necessarily those of the MRC.

Declaration of interest

Dr. Mark Thomas is funded by a Medical Research Council (MRC) Clinical Research Training Fellowship. Dr Mark Thomas has no conflicts of interest. Prof Robert Storey reports institutional grants from AstraZeneca and Merck; research support from Accumetrics; honoraria from AstraZeneca, Accumetrics, and Medscape; consultancy fees from AstraZeneca, Correvio, Merck, Accumetrics, Sanofi-Aventis, Regeneron, Roche, The Medicines Company, Aspen, PlaqueTec and Thermo Fisher Scientific.

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