Platelet receptors as therapeutic targets: Past, present and future

Janina Jamasbi1; Keng Ayabe2; Shinya Goto2; Bernhard Nieswandt; Karlheinz Peter3; Wolfgang Siess1,5

1Institute for the Prevention of Cardiovascular Diseases, LMU Munich, Munich, Germany; 2Department of Medicine (Cardiology), Tokai University School of Medicine, Isehara, Japan; 3Experimental Biomedicine, University Hospital and Rudolf Virchow Center, University of Würzburg, Würzburg, Germany; 4Atherothrombosis and Vascular Biology, Baker IDI Heart and Diabetes Institute, Melbourne, Australia; 5DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany

Summary
Anti-platelet drugs reduce arterial thrombosis after plaque rupture and erosion, prevent stent thrombosis and are used to prevent and treat myocardial infarction and ischaemic stroke. Some of them may also be helpful in treating less frequent diseases such as thrombotic thrombocytopenic purpura. The present concise review aims to cover current and future developments of anti-platelet drugs interfering with the interaction of von Willebrand factor (VWF) with glycoprotein Ib, and directed against GPVI, GPIb/IIa (integrin αIIbβ3), the thrombin receptor PAR-1, and the ADP receptor P2Y12. The high expectations of having novel antiplatelet drugs which selectively inhibit arterial thrombosis without interfering with normal haemostasis could possibly be met in the near future.

Keywords
Antiplatelet agents, GP Ibα, GP VI, GP IIb/IIIa, PAR-1

Introduction

Anti-platelet drugs reduce arterial thrombosis after plaque rupture and erosion, prevent stent thrombosis and are used to prevent and treat myocardial infarction (MI) and ischaemic stroke. However, there is a strong medical need to improve anti-platelet therapies, since standard anti-platelet drugs such as aspirin and P2Y12 antagonists have limited efficacy and as the major limiting factor increase the risk of bleeding, including fatal bleeding (1–3).

The present concise review aims to cover present anti-platelet drugs directed against platelet receptors of current interest, and to discuss future developments. For a more accurate and profound knowledge of specific platelet adhesion receptors (GPIbα, GPVI, integrin α2β1 and GPIIb/IIIa), G-protein coupled receptors (PAR-1, P2Y12) and their signalling pathways as therapeutic targets, the reader is referred to excellent comprehensive reviews (3–15).

Anti-platelet drugs may not only inhibit arterial thrombus formation after rupture and erosion of atherosclerotic plaques, but based on animal studies they may also retard the initiation and progression of atherosclerosis (16–21): platelets by interacting with activated monocytes, neutrophils and endothelial cells, and secretory chemokines and growth factors support through diverse mechanisms inflammation and cell proliferation underlying plaque growth (16, 22, 23). The results of clinical studies are, however, controversial in regard to inhibition of atherosclerosis by anti-platelet drugs (24–29).

von Willebrand factor and glycoprotein Ibα

The initial step for platelet adhesion is mediated by platelet specific glycoprotein (GP) Ibα interaction with von Willebrand factor (VWF) expressed on endothelial cells or bound to collagen at the site of endothelial injury (30). GPIbα is expressed exclusively on platelets (approximately 15,000 molecules/platelet). The VWF (monomer Mw 250 kDa) is present as multimers in circulating blood (Mw range from 500 kDa to 20,000 kDa (31)). Specific domains of the VWF monomer can bind to subendothelial collagen (domains A3 and A1), platelet GPIbα (domain A1), GPIIb/IIIa (domain C1), and factor VIII (domain D’, D3) (32), the latter linking platelet activation to coagulation (33) (▶Figure 1). Studies of VWF variants in mice showed that VWF-GPIbα interaction is critically important for the initiation of thrombus formation under...
blood flow conditions, whereas the VWF-collagen or VWF-GPIIb/IIIa interactions contribute mainly to thrombus growth (34). The exclusive role of VWF-GPIba interaction for platelet adhesion under high shear rate flow conditions was also shown with human blood (35).

There are several studies showing that VWF needs to undergo a conformational change to bind to GPIba in a stable manner. Apparently the VWF A1 binding to GPIba is shielded by other VWF-domains and becomes uncovered by exposure to high shear forces stretching the molecule on collagen fibres or by VWF immobilisation (36, 37). Another study showed that the stable binding of VWF to GPIba depends on VWF binding to GPIIb/IIIa. Possibly the initial transient interaction mediated by GPIba leads to platelet activation and subsequent irreversible VWF binding supported by GP IIb/IIIa (38). Also the antibiotic ristocetin and botrocetin are able to induce stable binding of VWF to GPIba under static conditions, a feature which is used in platelet activation assays of VWF and diagnosis of von Willebrand disease (39). Approximately 15,000–25,000 molecules of GPIba are exclusively present on a single platelet (40, 41). The number of surface expressed GPIba decreases upon platelet activation (42).

GPIba binding to VWF shows unique binding characteristics with extremely fast on- and off-rates unless in the presence of specific mutations in either molecule or in the presence of ristocetin or botrocetin (38). These unique fast on- and off-characteristics of human VWF binding to GPIba wild-type prevented the clarification of the precise three-dimensional structure of the binding complex due to the difficulty of obtaining a stable complex of native GPIba bound to VWF. The crystal structure of VWF bound with GPIba was obtained only with recombinant GPIba constructs expressed in hamster ovary cells (43). Recent computational progress allowed to predict the dynamic three dimensional structure of GPIba bound to VWF (44). Facilitation of drug development using this new technology is awaited.

In contrast to GPIIb/IIIa, GPIba binds to immobilized VWF independently of platelet activation (40). The transient GPIba in-
Caplacizumab (ALX-0081), a humanised anti-VWF bivalent perfused with a phase II clinical trial with ARC1779, an anti-VWF aptamer, also effective.

α exchange which serves as a source of ADAMTS-13. In this specific to thrombocytopenia. Current standard therapy for TTP is plasma the whole body due to enhanced VWF binding to GPIb α meric VWF with a high affinity for GPIb (ADAMTS-13) leading to increased circulating ultra-large multi- It is caused by a dysfunction of VWF cleaving proteases (ADAMTS-13) leading to increased circulating ultra-large multimeric VWF with a high affinity for GPIbα. In patients with TTP, many micro-thrombi are induced in the microcirculation within the whole body due to enhanced VWF binding to GPIbα leading to thrombocytopenia. Current standard therapy for TTP is plasma exchange which serves as a source of ADAMTS-13. In this specific condition, drugs interrupting GPIbα binding to vWF should be also effective.

Several anti-VWF or GPIbα-inhibiting agents are under therapeutic development (Figure 1):

- Caplacizumab (ALX-0081), a humanised anti-VWF bivalent nanobody has already been tested in high-risk percutaneous coronary intervention (PCI) patients (patients with unstable angina, NSTEMI and stable angina associated with high-risk PCI) with favourable outcomes (4, 5). The beneficial effect of caplacizumab has also been tested in a phase III clinical study in aquired TTP with favourable outcome (57). Similarly, a phase III trial of caplacizumab is ongoing with the aim to demonstrare a rapid restoration of platelet counts in patients with microvascular thrombosis (HERCULES) (58).

- A phase II clinical trial with ARC1779, an anti-VWF aptamer, evaluated its effect for the treatment of TTP and von Willebrand disease 2b (39). There is an intention to test this drug in the prevention of arterial thrombotic diseases (60). ARC1779 effectively reduced VWF activity and increased platelet counts in TTP patients (61). ARC1779 was also effective in reducing platelet adhesion to damaged arteries ex vivo perfused with blood of patients with coronary artery disease on dual antiplatelet therapy (62). The 2nd generation anti-VWF aptamer, ARC15105, is under preclinical investigation (63).

- A novel snake venom-derived GPIbα antagonist, anibatide, inhibiting the receptor binding sites for VWF as well as thrombin, reduced platelet thrombus formation in vivo in mice without prolonging tail bleeding time (64), and protected mice from acute experimental ischaemic stroke and reperfusion injury without inducing cranial bleeding (65, 66; see [67] for reference). A phase Ib-IIa clinical trial to investigate the safety and efficacy of anibatide in non-ST segment myocardial infarction (NSTEMI) patients has been completed in 2015 (68). Further agents interfering either with the VWF-GPIbα interaction are in preclinical investigation (3–5, 67).

However, so far, none of the agents are yet available for routine clinical practice.

Glycoprotein VI

Glycoprotein VI (GPVI) is the essential platelet collagen receptor in atherothrombosis while it has only little or no impact on normal haemostasis. Anti-GPVI antibodies cause only a mild bleeding tendency in mice, rat, rabbit, and non-human primates (69–73). However, in some patients with anti-GPVI autoantibodies bleeding is observed, which might be explained by concomitant GPVI-deficiency and thrombocytopenia (74). Indeed, injection of the anti-GPVI antibody IAQ1 into mice induces a significant prolongation of bleeding time, GPVI-deficiency and transient thrombocytopenia (70).

Of clinical importance, GPVI targeting might preferentially inhibit platelet activation after plaque rupture and erosion as shown by static and flow studies using human atherosclerotic plaque material (21, 75, 76), whereas in normal haemostasis loss of GPVI function may be, at least in part, compensated by the other major platelet collagen receptor, integrin αβ₃ (77–80). GPVI targeting is highly platelet-specific and is not expected to affect other cell types and to produce side effects, since the receptor is only expressed on platelets and megakaryocytes (81). Thus, GPVI has emerged as an attractive antithrombotic target. Interestingly, platelet adhesion onto immobilised VWF and VWF/GPIbα mediated Syk phos-
phorylation was inhibited in patients with GPVI deficiency and by anti-GPVI antibodies indicating that GPVI plays also a crucial role in vWF-GPIb triggered signalling and firm platelet thrombus formation, possibly by interaction of the GPVI/FcRy and GPIb/IX receptor complexes (82).

In addition to collagen fibres, GPVI has been shown to bind to fibronectin (20), vitronectin (83), laminin (84) and as recent studies suggest, also to fibrin (85, 86). Binding to some of these ligands in atherosclerotic plaques (laminin, fibronectin, vitronectin (87) could also explain the potent inhibition of atherosclerotic plaque-induced platelet activation by anti-GPVI antibodies. The GPVI-collagen interaction can be inhibited either by occupation of specific binding sites on collagen using GPVI mimetics such as recombinant dimeric GPVI-Fc fusion protein or by function blocking reagents such as antibodies directed against platelet GPVI (Figure 1). Whereas anti-GPVI antibodies are systemic platelet inhibitors, GPVI-Fc is expected to act locally at the site of plaque rupture and erosion whereas circulating platelets remain unaltered (10, 81, 88).

In a clinical phase I study in healthy human volunteers, a single intravenous application of GPVI-Fc (Revacept®) inhibited collagen-induced platelet aggregation ex vivo with high doses being effective up to seven days after injection (89). GPVI-Fc is currently tested for the treatment of acute ischaemic stroke, symptomatic carotid artery stenosis, transient ischaemic attacks (TIAs) or amaurosis fugax in a phase II clinical trial. As inhibition of human atherosclerotic plaque-induced platelet thrombus formation by GPVI-Fc in vitro increased with the rate of arterial shear, GPVI-Fc may exhibit locally enhanced antithrombotic properties at stenotic lesions which are particularly prone to rupture (90).

Numerous anti-GPVI antibodies such as human single domain antibodies (BLO8–1) (91) and humanised single-chain variable fragments (scFv derived from monoclonal 90I12) (92) have been developed as blocking antibodies, and would be ready to enter clinical trials. It could be that anti-GPVI antibodies which systematically inhibit all platelets in the circulation are less safe than GPVI-Fc. Indeed, anti-glycoprotein VI treatment severely compromised haemostasis in mice with concomitant aspirin therapy (79), whereas GPVI-Fc did not prolong mice tail bleeding time in combination with various anti-platelet drugs (19). On the other hand, GPVI-inhibition and even antibody-mediated depletion of GPVI from circulating platelets through shedding or internalisation has been shown to be beneficial in experimental models of thrombosis and thrombo-inflammatory diseases, such as stroke, without impairing haemostasis (9, 70).

GPVI-Fc application did not prolong bleeding time in humans, mice and rabbits (19, 89). Thus, GPVI-Fc might be tested in clinical trials as triple antiplatelet therapy with aspirin and a P2Y12 antagonist for the prevention of MI as recently proposed (93). In the future, subcutaneous application of GPVI-Fc might be envisioned for reasons of feasibility and efficacy. Indeed, a structurally similar protein, Etanercept (Enbrel®; a dimeric fusion protein of the extracellular domain of the TNF receptor 2 with Fc), used clinically for the treatment of rheumatic diseases, is injected subcutaneously once or twice a week (94, 95).

A recent study showed that the antithrombotic potential of GPVI-Fc could be highly improved by cross-linking GPVI-Fc with anti-Fc antibodies (96). Cross-linked GPVI-Fc inhibited collagen and human plaque-induced platelet aggregation as effectively as anti-GPVI antibodies. Despite the above mentioned potential merits of GPVI inhibition for prevention of arterial thrombosis, none of the drugs is currently in clinical practice.

**Glycoprotein IIb/IIIa inhibitors**

Glycoprotein (GP) IIb/IIIa (integrin αIIbβ<sub>3</sub>, CD41/CD61) is a most interesting target for anti-platelet therapy, having delivered both unprecedented clinical and commercial success but also one of the biggest failure and commercial losses in drug development (97).

The advantages of GPIIb/IIIa as a drug target are: 1) GPIIb/IIIa is the central receptor mediating binding to fibrinogen/fibrin, thereby crosslinking platelets and mediating platelet aggregation and ultimately the formation of thrombi. The blockade of this receptor effectively inhibits platelet aggregation and clot formation. 2) The receptor is only expressed on platelets and megakaryocytes, thereby avoiding off-target effects. 3) GPIIb/IIIa undergoes a conformational change upon platelet activation that allows to specifically block activated platelets only, which retains intact haemostasis.

However, GPIIb/IIIa as a drug target has disadvantages that indeed have caused problems in drug development: 1) GPIIb/IIIa is highly abundant with 60,000 to 80,000 receptors per platelet. Therefore, achieving full blockage of all receptors on all circulating platelets is a challenge, which requires high drug doses (e.g. 20 to 30 mg of the antibody fragment abciximab per patient) and often results in partial blockage of the receptor only. 2) Ligand mimicry is the basis of all GPIIb/IIIa blockers currently in clinical use and all those tested in clinical trials and ultimately abandoned. However, binding of ligand-mimetic blockers to GPIIb/IIIa induces a conformational change of the receptor potentially inducing fibrinogen binding (priming) (98). Also, this conformational change results in outside-in signalling (integrins are cell membrane sensors, signalling ligand engagement to the cell), thereby causing paradoxical platelet activation (98). 3) Blockade of GPIIb/IIIa independent on its activation state interferes with haemostasis and thus causes bleeding as also seen in the bleeding phenotype of Glanzmann thrombasthenia, the hereditary condition associated with a reduction of expression or function of GPIIIb/IIa. The increased risk of bleeding, especially rare events such as pulmonary bleeding, is particularly visible in patients who received the combination of GPIIb/IIIa blocker and fibrinolytic therapy (99).

Three GPIIb/IIIa inhibitors are currently approved for clinical use in most countries (Figure 1) (97, 100, 101). The first to be FDA approved in 1994 and extensively used in patients was the recombinant monoclonal antibody abciximab (ReoPro<sup>®</sup>). A second inhibitor, eptifibatide (Integrilin<sup>®</sup>), was approved in 1998 and is based on the disintegrin, barbourin, obtained from snake venom, a Lys-Gly-Asp (KGD) sequence. In contrast, the third ap-
proved inhibitor, tirofiban (Aggrastat®), is a small molecule non-peptide compound, which is modelled after the ligand-mimetic peptide RGD. In comparison to the wide spread use of GPIIb/IIIa blockers directly following their approval, the use of GPIIb/IIIa inhibitors is relatively limited nowadays. Based on bleeding complications associated with the inhibition of GPIIb/IIIa on all circulating platelets independent on its activation state and the availability of P2Y<sub>12</sub> receptor antagonists (causing less bleeding complications), the clinical role of GPIIb/IIIa inhibitors is now restricted to a small group of patients, who either undergo PCI without pre-treatment with P2Y<sub>12</sub> blockers or high-risk patients with a severe lesion pathology, e.g. large thrombus burden (101). In some countries clinical trials show negative outcomes for GPIIb/IIIa inhibitors (102). In Japan none of the GPIIb/IIIa inhibitors is available.

Orally available GPIIb/IIIa inhibitors were developed by numerous companies, potentially providing benefits to millions of patients. In total five major phase III trials (over 42,000 patients) testing four different compounds were completed (103). Either these studies did not find a significant improvement over existing therapy (aspirin) or they demonstrated excess mortality, including cardiovascular mortality. This negative clinical outcome ended the development of oral GPIIb/IIIa inhibitors with major financial losses of many pharmaceutical companies (103). The ligand-mimetic character of the developed oral GPIIb/IIIa inhibitors and its associated change of the integrin conformation potentially priming fibrinogen binding and outside-in signalling causing paradoxical platelet activation is the most probable explanation for these disappointing trial outcomes (97, 98).

Currently three innovative concepts targeting GPIIb/IIIa but avoiding previous mistakes are under development and have reignited the interest of GPIIb/IIIa as a target for future anti-platelet therapy: 1) Selective single-chain antibody based blockers of the activated conformation of GPIIb/IIIa on its own or in combination with the enrichment of anticoagulant or fibrinolytic drugs at the site of thrombus development. Effective inhibition of thrombosis without affecting haemostasis has been shown in preclinical studies (104, 105). Furthermore, priming of fibrinogen binding or paradoxical platelet activation is avoided as they do not bind to non-activated GPIIb/IIIa and thus do not induce a conformational change of the integrin receptor. 2) Several small molecules that selectively bind to the metal ion binding site of the β<sub>3</sub> subunit and thereby inhibit fibrinogen binding have also been shown not to induce conformational changes of GPIIb/IIIa, therefore avoiding priming of fibrinogen binding (106). 3) A recently described promising approach specifically targets GPIIb/IIIa outside-in signalling leaving inside-out signalling intact (107). This is achieved by the selective inhibition of the interaction between the intracellular domain of the β<sub>3</sub> subunit and Ga<sub>13</sub> using a myristoylated peptide with an ExE motif. This approach protects from occlusive thrombus formation in vivo but does not affect haemostasis (99, 108). These highly promising approaches for ‘advanced’ GPIIb/IIIa inhibition need to be tested in clinical trials.

Overall, GPIIb/IIIa is a highly attractive target for anti-platelet therapy. GPIIb/IIIa inhibitors have shown their efficacy and the observed problems in drug development have contributed to a better understanding of the role of GPIIb/IIIa and the lessons learned are now aiding the development of novel approaches for GPIIb/IIIa inhibition.

**Thrombin and PAR-1 antagonists**

Thrombin is an important potent platelet activator formed after vascular injury or plaque rupture from tissue factor in the vessel wall and by the procoagulant activity of activated platelets. Thus, the development of thrombin receptor antagonists is of potential clinical relevance. Thrombin mediates human platelet activation mainly through binding to protease activated receptors 1 (PAR-1) and 4 (PAR-4) on the platelet surface, but it can also bind to a thrombin binding site on GPIb (12, 109, 110). While PAR-1 is readily activated by low concentrations of thrombin, PAR-4 activation requires higher concentrations of the agonist (111). PAR-1 antagonists strongly inhibit thrombin-induced platelet aggregation and secretion (112). Vorapaxar (SCH 530348) and Atopaxar (E-5555) were developed as orally available competitive inhibitors of PAR-1; however, only Vorapaxar was approved by the FDA (Zontivity<sup>®</sup>), whereas the clinical development of Atopaxar was stopped due to safety concerns such as prolonged QT intervals despite promising results of phase II trials (12, 109, 113, 114).

A phase 2 trial with 1030 patients showed that the administration of Vorapaxar (SCH 530348) in combination with aspirin, clopidogrel and heparin or bivalirudin for 60 days in patients undergoing non-urgent PCI led to a reduction of major adverse cardiovascular events (non-significant). Of note high doses were not more efficient than low doses, but bleeding was not increased (115).

In another phase II clinical trial with 117 Japanese patients with non-ST segment elevation acute coronary syndrome, the addition of vorapaxar to standard antithrombotic treatment (aspirin, ticlopidine, and heparin) significantly reduced the incidence of MI during PCI from 42.9% to 16.9% (p=0.013) (116).

However, these positive results were not confirmed by the TRACER trial conducted in 12,944 patients, which showed that in patients with acute coronary syndromes without ST-segment elevation the addition of vorapaxar to standard therapy (aspirin and P2Y<sub>12</sub> inhibition) did not significantly reduce the primary composite end point (death from cardiovascular causes, MI, stroke, recurrent ischaemia with re-hospitalisation, or urgent coronary revascularisation), but significantly increased the risk of major bleeding and intracranial hemorrhage. Due to safety concerns the trial was prematurely terminated (110).

In contrast, the TRA 2P-TIMI 50 trial, which evaluated the effect of vorapaxar (in addition to standard therapy) in 26,449 patients with a history of MI, ischaemic stroke and peripheral arterial disease (PAD), showed a reduction of the risk of cardiovascular death, MI or stroke with Vorapaxar (9.3%) in comparison to placebo (10.5%) (p<0.001) (117). However, the study was discontinued in patients with a history of stroke due to increased risk of intracranial haemorrhage with Vorapaxar. Vorapaxar was ap-
proved by the FDA for the reduction of thrombotic cardiovascular events in patients with prior MI or with PAD (excluding patients with a history of stroke or TIA) (12, 109).

A clinical trial is currently under way recruiting stroke and TIA patients to evaluate the safety and efficacy of BMS-986141, an antagonist of PAR-4, in combination with aspirin for the prevention of recurrent stroke (118).

In conclusion, PAR-1 antagonists may be effective as anti-thrombotic drugs although the risk of bleeding is elevated. Vorapaxar is currently approved only in a small part of the world including the US.

**P2Y<sub>12</sub> ADP receptor**

The P2Y<sub>12</sub> ADP receptor is not only involved in a positive feedback in thrombin- and collagen platelet activation, it also mediates human plaque-induced platelet aggregation in blood under static conditions and participates in plaque-triggered, VWF-dependent platelet thrombus formation under flow at high arterial shear rate (119, 120).

Thienopyridine anti-platelet agents have been widely used for the prevention of stroke, MI, and stent thrombosis after coronary intervention (121–123). Their early clinical use such the use of ticlopidine to prevent stroke and stent thrombosis was mostly based on the results of clinical trials rather than understanding the mechanism of action. In this context, it is of note that the molecular target of thienopyridine(s) was cloned and published in Nature in 2001 (124) although two of the thienopyridines, ticlopidine and clopidogrel were registered for a wide spectrum of diseases already in the early nineties.

Currently used thienopyridines are ticlopidine, clopidogrel and prasugrel. They are orally administered prodrugs, which require metabolism by the cytochrome P450 enzymes in the liver to generate the active metabolites in circulating blood (125). It is of note that the active metabolite(s) of thienopyridines are so unstable that the majority of them immediately binds to the P2Y<sub>12</sub> receptor of platelets present in the hepatic microcirculation (126). The clinical problem of clopidogrel, but not of prasugrel, are patients carrying the CYP2C19 poor metaboliser genotype, who have a higher rate of major adverse cardiovascular events, including stent thrombosis after clopidogrel treatment than noncarriers (127, 128). However, it should be considered that prasugrel is also a prodrug, but with a different metabolic pathway, and specific cytochrome P450 genotypes with a low metabolism of prasugrel might be found in the future.

The new P2Y<sub>12</sub> receptor antagonists, the oral ticagrelor and the intravenously applied cangrelor have a structure different to that of thienopyridines. They bind directly to the P2Y<sub>12</sub> receptor and do not require hepatic biotransformation. Cangrelor and ticagrelor are reversible P2Y<sub>12</sub> receptor antagonists (119). Ticagrelor seems to have off-target effects such as the inhibition of uptake of adenosine into red cells via inhibition of type 1 equilibrative nucleoside transporter (ENT-1) (129). Enhanced circulating adenosine might mediate additional platelet inhibition by ticagrelor through binding to the Gs-coupled platelet adenosine A<sub>2A</sub> receptor and increasing intracellular c-AMP levels (130).

There is positive relationship between the extent of P2Y<sub>12</sub> receptor antagonism and the inhibition of ADP-induced platelet aggregation (131). The most important question, for which there is no answer at present, is: “How much of the P2Y<sub>12</sub> receptors are actually blocked by the current treatment with P2Y<sub>12</sub> antagonists, and how much of the P2Y<sub>12</sub> receptors should be blocked to achieve the ideal balance between reduction of thrombosis and increase in bleeding?” (126). It is clear that the P2Y<sub>12</sub> ADP receptor should not be blocked by 100%, because genetic P2Y<sub>12</sub> ADP deficiency is a spontaneous bleeding disorder (132, 133). The establishment of an easy-to-use clinical test measuring the platelet P2Y<sub>12</sub> receptor drug occupancy may solve these problems.

Due to lack of an appropriate assay system to standardise the dose of P2Y<sub>12</sub> receptor inhibitors in patients, standard doses of even the new generation P2Y<sub>12</sub> receptor antagonists differ across the world. In patients with acute coronary syndrome, 60 mg loading dose followed by a 20 mg maintenance dose of prasugrel is approved in the majority of countries in the world including China and Korea except for Japan due to the results of global TRITON TIMI 38 trials (134). Based on a huge number of phase I and II dose-finding studies, the PRASFIT-ACS trial of prasugrel with a 20 mg loading dose followed by a 3.75 mg/day maintenance dose has been tested and is now approved in Japan (135). On the other hand, for ticagrelor, the global dose was tested in Japan in the PHILO trial (136). Unlike the global trial of PLATO, the PHILO trial did not show better results of ticagrelor compared to clopidogrel. Small doses of a P2Y<sub>12</sub> inhibitor may be better suited in the relative small body sized East Asian patients (131), but clear scientific evidence is missing.

**Conflicts of interest**

SG received consulting fees from Sanofi, Astra Zeneca, Bayer, Artmehron, Roche Diagnostics and is a member of steering and executive committees of various clinical trials. KP is listed as inventor on patents describing single-chain antibodies directed against GPIIb/IIIa. The other authors report no conflict of interest.

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