

# Novel antiplatelet drugs in clinical development

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## Summary

The clinical value of antiplatelet compounds strongly depends on the benefit-risk balance between their anti-thrombotic effects and the

bleeding risk they incur. This ratio is especially important in the treatment of cerebro-vascular disease. Several novel compounds in clinical development hold promise to improve this benefit-risk ratio.

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## Introduction

Atherothrombotic disease and, more specifically, plaque rupture lead to platelet activation and, consecutively, to thrombus formation. Therefore, platelets play a very relevant role in many acute and chronic cardiovascular diseases. Acute coronary syndromes (ACS), such as myocardial infarction (MI), have been successfully treated with platelet inhibitors. Treatment of stroke with these compounds, however, was less successful, mainly due to an over proportionate increase in bleeding complications. Ischaemic stroke is the most frequent disabling disease and a leading cause of death above the age of 60 years (1). Frequently, the underlying cause is rupture of atherosclerotic plaques which leads to platelet adhesion and thrombus formation or embolisation into cerebral arteries. A significant medical need remains for the treatment of this condition.

A large amount of surface receptors and intraplatelet molecules support and regulate platelet activation, which has been intensively investigated during the recent decades. These findings led to the development of novel antiplatelet agents. Because of limited space, this review only focuses on novel platelet drugs in clinical development which have so far not been approved for the treatment of patients, including those whose clinical development has recently been terminated (see overview in ►Figure 1). We thought that such a combined overview should enhance the understanding of the current state, as well as of benefits, pitfalls, pros and cons of these novel drug classes. Therefore, many recent achievements including, but not limited to platelet ADP receptor inhibitors clopidogrel, prasugrel, ticagrelor, as well as to novel glycoprotein (GP)IIb/IIIa antagonists and directly acting thrombin and factor Xa inhibitors are not described in this review article, and are outlined in many recent excellent reviews elsewhere (for example, please see references [2–4]).

In the flowing arterial or venous blood, platelet activation can be triggered by several extra-cellular agonists, such as thromboxane A<sub>2</sub>, ADP and thrombin. All these mechanisms are targeted by

approved drugs, and additional compounds are in clinical development for each of these target mechanisms.

## Inhibitors of platelet P2Y<sub>12</sub> receptors

Platelet ADP receptor inhibitors have been introduced into the treatment of patients who suffer from cardiovascular diseases, and have been shown to provide relevant benefit in large clinical studies. Several novel drugs as well as novel formulations of existing compounds are in clinical development (see ►Table 1 for overview).

Cangrelor (The Medicines Company, Parsippany, NJ, USA) is administered intravenously, and is being studied as a pharmacologically directly active, reversible P2Y<sub>12</sub> antagonist (5). This non-thienopyridine is characterised by a rapid reversal of effects after the end of the infusion – a specific peculiarity which is not found with the other currently approved P2Y<sub>12</sub> antagonists. Similar to prasugrel and ticagrelor, cangrelor is characterised by a faster onset of action and stronger platelet inhibition than clopidogrel, and showed no significant increase in major bleeding compared with clopidogrel in phase II studies (5). Cangrelor has already been studied in two phase III trials, CHAMPION-PCI and CHAMPION-PLATFORM, which were, however, both stopped early because of lacking efficacy (6, 7). According to the authors of the study reports, this negative outcome might be due to an inappropriate inclusion based on biomarkers of MI. Cangrelor has also been studied as a bridge for patients on clopidogrel who need to terminate treatment before surgery (8) – the results included prolonged platelet inhibition with cangrelor. Cangrelor is currently being investigated in the CHAMPION-PHOENIX phase III trial, which is still enrolling patients (trial NCT01156571; www.clinicaltrials.gov/ct2/show/NCT01156571). The trial compares the efficacy and safety profile of cangrelor with standard of care (clopidogrel) in patients who require percutaneous coronary intervention (PCI).

Elinogrel (PRT060128; Novartis, purchased from Portola, San Francisco, CA, USA) is also a non-thienopyridine, directly active, reversible P2Y<sub>12</sub> antagonist, which can be administered orally or intravenously (9). It has been shown that patients who are subject to high remaining platelet reactivity to ADP after administration of clopidogrel can be reversibly treated with elinogrel (10). It was shown in a phase II study that elinogrel, as compared to clopidogrel, did not increase the general incidence of bleeding, although a specific endpoint of infarction-combined bleeding which required medical attention was more common (INNOVATE-PCI, 11). Novartis therefore communicated a discontinuation of further development in 2012.

LG Life Science develops the reversible P2Y<sub>12</sub> receptor antagonist LG 231306 in phase I, for a future indication in atherothrombosis.

In summary, novel ADP receptor blockers are promising, but any increases in efficacy were always accompanied by an increased bleeding risk. This problem was even more obvious when combinations of these drugs with other antiplatelet agents were used in clinical or in previous preclinical animal studies (12).

In addition to the new chemical entities, novel formulations of the drug clopidogrel are being studied. A clopidogrel formulation to be used for intravenous administration is being investigated in a phase III trial by The Medicines Company. Fixed dose combinations of clopidogrel and aspirin are being investigated by YuHan and by Dong A Pharmaceuticals.

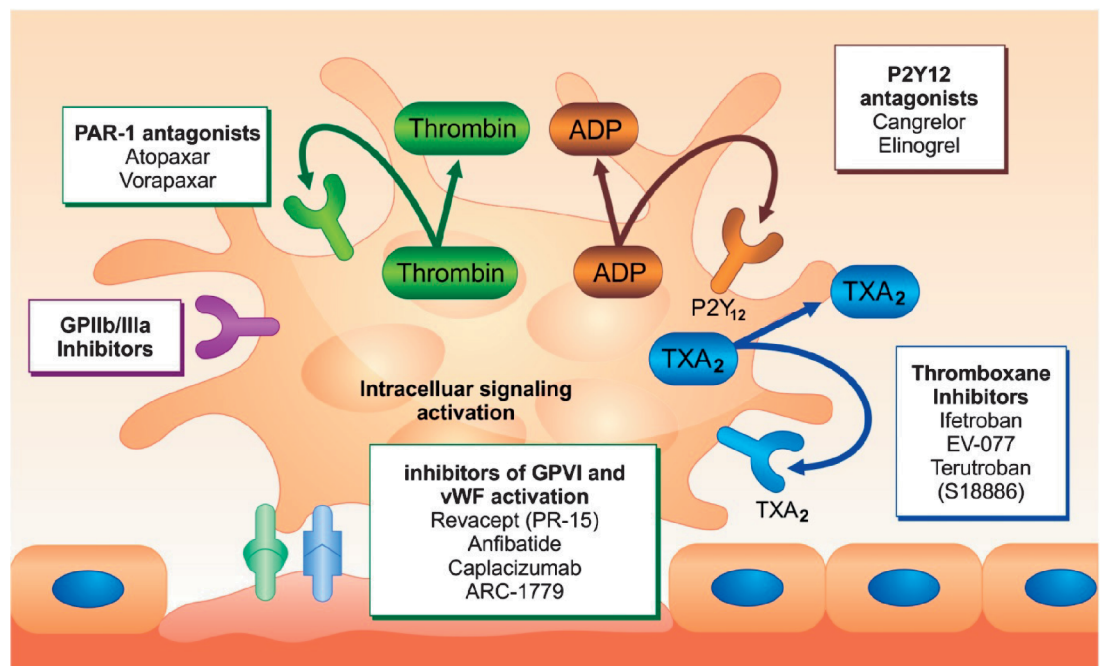
## Thrombin receptor PAR-1 antagonists

Besides its activity in the coagulation cascade, thrombin acts on two platelet G-protein coupled receptors, protease-activated recep-

tor 1 (PAR-1) and PAR-4 (13), and strongly activates several platelet signalling pathways. PAR-1 is activated by lower concentrations of thrombin than PAR-4 and mediates a more rapid platelet activation response (14). PAR-1 antagonists are therefore inhibitors of thrombin-induced platelet activation but not of thrombin-induced cleavage of fibrinogen (the final step in coagulation). Preclinical studies have shown that selective PAR-1 blockade with an analogue to vorapaxar (SCH 530348; Schering-Plough, now Merck Inc., Whitehouse Station, NJ, USA) results in a potent reduction of platelet aggregation mediated by thrombin, but preserved haemostasis (15). Administration of vorapaxar had a systemic effect *in vivo* and specifically suppressed thrombin-induced aggregation *ex vivo* (16).

The PAR-1 antagonist vorapaxar, a tricyclic 3-phenylpyridine, is administered orally, and is rapidly absorbed (16). The molecule binds almost irreversibly to an unusual superficial binding pocket of the receptor protein (17). The phase II trial TRA-PCI demonstrated that vorapaxar inhibited thrombin receptor activating peptide (TRAP)-induced platelet aggregation in a dose-dependent manner, was generally well tolerated, and did not cause an increase in major bleeding, also when administered concomitantly with aspirin or clopidogrel (18). Two phase III trials of vorapaxar have been recently completed: TRACER (19) and TRA 2P-TIMI 50 (20). TRACER was a randomised double-blinded trial comparing vorapaxar with placebo in addition to standard therapy in 12,944 patients who had ACS without ST segment elevation. The TRACER study was terminated early because of safety concerns. There was a significant reduction to 14.7% (vs 16.4% in controls) in a composite endpoint of death from cardiovascular causes, MI, or stroke. However, there was increased risk of moderate or severe bleeding, as well as of intracranial haemorrhage (ICH). The trial did not result in any change in all cause mortality.

**Figure 1: Schematic overview of new anti-platelet drugs in clinical development which inhibit platelet surface receptors and signalling pathways.** The initial step of platelet activation depends on plaques and arterial lesions, and occurs mainly via vWF-GPIb and GPVI, which then lead to intraplatelet signal activation, and consecutive release of agents thrombin, ADP, thromboxane and others. These agents can then stimulate the respective receptors on the same and other platelets, and activate the fibrinogen receptor, GPIIb/IIIa.



TRA 2P - TIMI 50 included 26,449 patients with a history of either MI, stroke or peripheral vascular disease, which were analysed as three study arms (20). The Data and Safety Monitoring Committee recommended stopping one of these arms of TRA 2P - TIMI 50, patients with a history of ischaemic stroke, because of an excess of ICH in the patients randomised to vorapaxar. There was a significant reduction to 9.3% (vs 10.5% in controls) in a composite endpoint of death from cardiovascular causes, MI, stroke, recurrent ischaemia with rehospitalisation, or urgent coronary revascularisation. However, there was increased risk of moderate or severe bleeding, as well as of ICH. A prespecified subgroup analysis on 17,779 patients with previous MI found an even more pronounced relative reduction of 20% of the combined end point, which, however, also coincided with increased bleeding events (21).

Consecutively, the clinical trials being conducted by Merck / Schering-Plough were halted for patients with stroke and mild heart conditions. However, Merck communicated in August 2012 that it would seek approval of the drug in the USA and Europe in a limited indication, of patients with a history of MI, but not of stroke, and an age below 75 years, based on the TRACER subgroup analysis (21).

Another PAR-1 antagonist, atopaxar (E5555, Eisai, Tokyo, Japan), inhibits thrombin- and TRAP-mediated CD40 release from human platelets (22). Two phase II trials (LANCLOT-ACS and -CAD) investigated 603 and 720 patients with acute or high-risk stable coronary artery disease, respectively (23-25). The trials found signs of the expected platelet inhibition, and reduction of ischaemia on 24-hour electrocardiogram (ECG, Holter) monitoring. The overall number of bleeding complications was low, but numerically higher in the atopaxar groups. In summary, these results could be considered sufficiently positive to embark on a phase III trial. However, the numerically higher incidence of major bleeding complications, liver dysfunction, and QTc prolongation and the lack of a convincing dose-related trend for bleeding risk and efficacy were considered troublesome (23), and may caution any further development.

A recently published meta-analysis on the risk of ICH with PAR-1 antagonists (26) showed that on the basis of nine trials including 42,000 patients, that risk was almost two-fold increased.

Many of these patients had been treated with PAR-1 antagonists in combination with aspirin or/and ADP receptor inhibitors. Previous preclinical studies of combinations of the PAR-1 antagonists vorapaxar with aspirin or clopidogrel in cynomolgus monkeys (27) and of atopaxar with rtPA in guinea pigs (28) had not shown any additive increase of bleeding compared to the respective compounds alone. In contrast, investigation of PAR-1 knock-out mice did show a potentiating increase in bleeding time when these mice were also treated with clopidogrel (29). For an overview of thrombin receptor inhibitors in clinical investigation see ► Table 2.

## Novel fibrinogen receptor GPIIb/IIIa inhibitors

The platelet fibrinogen receptor, the GPIIb/IIIa, is a pivotal protein mediating platelet aggregation. Inhibition has been achieved by a number of compounds, either antibodies or small molecules. Although to our knowledge, no novel chemical entities in this drug class are in clinical development, some new combinations and formulations of inhibitors of this receptor have been developed, and are currently being investigated. A novel combination of a known GPIIb/IIIa inhibitor with iloprost (ilomedin) (<http://www.clinicaltrial.gov/ct2/show/NCT01532544>), as well as a transdermal formulation of tirofiban are in clinical development.

Despite tremendous progress in using these agents for the treatment of patients with ACS, this concept did not yet translate into improvement of patient care with transient ischaemic attack (TIA) or stroke: Abciximab, a GPIIb/IIIa-inhibitor, which has been successfully used for the treatment of ACS, was also investigated for the treatment of acute ischaemic stroke in the Abciximab emergent stroke treatment trial (AbESTT), and yielded initial promising results (30). However, a consecutive clinical phase III trial (AbESTT-II) was discontinued due to increased fatal ICH and poor outcomes (31). Therapy with these drugs alone or in combination with other antiplatelet agents markedly increased bleeding risk in clinical or in preclinical animal studies (32, 33, 39). This risk might only be overcome in the future by novel conformation-specific blockers of GPIIb/IIIa (32). For an overview of novel GPIIa/IIb inhibitors in clinical development see ► Table 3.

**Table 1: P2Y12 inhibitors in clinical investigation.**

Cangrelor, The Medicines Company, Parsippany, NJ, USA – phase III
Elinogrel, Novartis, Basel, Switzerland and Portola Pharmaceuticals – discontinued
LC 231306, LG Life Sciences, Seoul, Korea – phase I
MDCO-157, The Medicines Company, Parsippany, NJ, USA, intravenous clopidogrel, – phase III.
YH14659, Yuhan, Seoul, Korea, fixed dose combination of aspirin and clopidogrel, – phase I
G-0041, Dong-A, Seoul, Korea, fixed dose combination of aspirin and clopidogrel, – phase I

**Table 2: Thrombin receptor inhibitors in clinical investigation.**

Vorapaxar (SCH 530348), Merck / Schering Plough, Whitehouse Station, NJ, USA – phase III
Atopaxar (E5555), Eisai, Tokyo, Japan, phase II

**Table 3: Novel GPIIa/IIb inhibitors in clinical development.**

Iloprost (trometamol+eptifibatide, Thr-B7), Thrombologic, Copenhagen, Denmark -phase II
Transdermal tirofiban, Mediceur, Winnipeg, Canada – phase I

## Targeting platelet activation by subendothelial tissue or matrix: Von Willebrand factor/GPIIb and GPVI antagonists

GPVI-mediated and von Willebrand Factor (vWF)-mediated platelet adhesion and activation play an important role in thrombus formation (34). vWF binds to the platelet receptor GPIIb via its A1 domain, and plays an important role in primary haemostasis (reviewed in [35–38]). The multimeric structure of vWF undergoes a conformational change by binding to a specific site on collagen fibers, enabling vWF to interact with GPIIb. GPVI is the major signalling receptor for collagen and exclusively expressed on platelets and megakaryocytes initiating platelet recruitment at sites of vascular injury (39, 40). Both blocking of GPIIb and GPVI with specific antibodies led to a reduced infarct volume and a significantly improved functional outcome in an acute stroke model in mice (36, 41). This finding was confirmed in vWF<sup>-/-</sup> mice (42). These animals did not show any increased incidence of ICH but tail bleeding time was increased in mice treated with anti-GPIIb antibodies (40, 41).

The initial platelet activation via the platelet receptors GPIIb or GPVI by collagen-bound vWF or collagen, leads to activation of the integrin  $\alpha$ IIb $\beta$ 3 (GPIIb/IIIa) platelet receptor, and to the consecutive steps of platelet aggregation and spreading, and to pathological thrombus formation (for review see [34, 43, 44]). Inhibition of collagen/GPVI interaction can be achieved both by anti-GPVI antibodies and by the soluble GPVI receptor. For an overview of novel platelet adhesion inhibitors interfering with von Willebrand factor (vWF) and/or glycoprotein VI (GP VI) which were tested in clinical studies see ► Table 4.

### Specific compounds which inhibit soluble vWF

Compounds which interact in these pathways may target either the GPIIb receptor on platelets, or the collagen-binding A3 domain of soluble vWF, or the GPIIb receptor-binding A1 domain, and hence block collagen-induced vWF binding and activation.

The anti-vWF antibody, AJW 200 (Ajinomoto, Yokohama, Japan), is directed against the A1 domain, and has been shown to be safe in human volunteers - no bleeding complications were observed (45). The development has not been continued since 2003.

ARC-1779, (Archemix - Baxter, Deerfield, IL, USA), is an aptamer which targets the A1 domain of activated vWF, and thereby inhibits the binding of vWF to GPIIb (46). A phase I study showed dose-dependent inhibition of vWF plasma activity (46). A Phase II study investigated patients with carotid artery stenosis undergoing surgical desobliteration (endarterectomy) (47). Microembolisms (MES) were recorded by transcranial doppler. Postoperative MES were delayed significantly but perioperative bleeding was increased. The sponsor Archemix - Baxter decided to stop funding the trial after inclusion of 36 patients, instead of the planned 100 patients (47). Another phase II study in patients with acquired

**Table 4: Novel platelet adhesion inhibitors: interfering with von Willebrand factor (vWF) and/or glycoprotein VI (GP VI) which were tested in clinical studies.**

Anfibatide, Lee's Pharmaceuticals, Hong Kong and China, a snake venom-derived compound which blocks glycoprotein Ib – phase II
Caplacizumab (ALX-0081), Ablynx, Ghent, Belgium, an antibody fragment (nanobody) against the A1 domain of vWF – discontinued after phase II for lack of further funding
ARC-1779, Archemix Corporation, Cambridge, MA, USA (acquired by Baxter), an aptamer directed against the A1 domain of vWF – discontinued for CV indications after phase II
Revacept (PR-15), Advancecor (previously, Procorde), Martinsried, Germany, a specific GPVI-Fc fusion protein, acting as an inhibitor of vascular lesion-induced GP VI or vWF activation – phase II

thrombotic thrombocytopenic purpura (TTP) is under way. The inhibition of GPIIb-vWF interaction thus seems to result in increased bleeding complications, similar to the pathological loss of vWF in vW disease.

Caplacizumab (ALX-0081), (Ablynx, Ghent, Belgium), is a bivalent humanised antibody fragment (nanobody) which was also raised against the A1 domain of vWF (48). A phase I study showed promising characteristics (49). A phase II study which included 380 patients with ACS was completed in early 2012 (<http://clinicaltrials.gov/ct2/show/NCT01020383>). The primary endpoint was to reduce bleeding complications compared to a therapy with abciximab. This endpoint was missed, since bleeding events within 30 days tended to be increased in the group treated with therapeutic doses of caplacizumab compared with abciximab, although no statistical difference was reached (<http://hugin.info/137912/R/1562875/484367.pdf>), despite the fact that the drug was not overdosed (50). A phase II study in patients with acquired thrombotic thrombocytopenic purpura (TTP) (TITAN study) is ongoing; results are expected by end of 2013.

Anfibatide (Declotana, Lee's Pharmaceuticals, Shatin, Hong Kong), is a botops atrox viper venom-derived compound which serves as an inhibitor of the platelet receptor for vWF, GPIIb. Animal studies have shown that intravenous injection of anfibatide effectively abolishes cyclic flow reductions in a canine model of unstable angina with less prolongation of bleeding time than GPIIb/IIIa antagonists. The drug was reported to be safe in a phase I trial (NCT01588132; <http://www.clinicaltrials.gov/ct2/show/NCT01588132>). A phase Ib/IIa study NCT01585259 has recently been initiated in patients with non-STEMI myocardial infarction (<http://www.clinicaltrials.gov/ct2/show/NCT01585259>).

### Glycoprotein VI (GPVI)

The GPVI pathway may be inhibited by compounds which induce depletion of platelet GPVI, or by blocking antibodies, or by using mimics of GPVI which bind to collagen, thereby masking the activating GPO-epitopes in collagen in vascular lesions and plaques.

Early anti-GPVI antibody developments (OM4 – Otsuka, Fab390 – Sanofi, Paris, France) were discontinued because they led to acute thrombocytopenia or platelet GPVI depletion. In murine studies, chronic administration of the anti-GPVI antibody JAQ1 led to a depletion of the GPVI protein on the surface of circulating platelets resulting in a long-term antithrombotic protection (51). This finding was, however, accompanied by an inhibition of other platelet signalling pathways, such as thrombin-dependent activation (52, 53). As a result of this broad range inhibition, a significant reduction in platelet adhesion and aggregation to injured arterial vessel walls (53) as well as a significant reduction in infarct volume in stroke was described (41). A humanised anti-human GPVI antibody was tested in hGPVI-transgenic mice, and shown to be effective (54). Another tool to interfere with the GPVI-mediated platelet activation is a dimeric form of a soluble GPVI fusion protein, in which the extracellular domain of GPVI was fused to Fc and forms dimers (GPVI-Fc, Revacept, AdvanceCor GmbH, Martinsried, Germany), which led to a reduction in platelet adhesion to the injured vessel wall in healthy mice (55) as well as in cholesterol-fed ApoE  $-/-$  mice (56) and reduced neointima formation (57). In a mouse model of ischaemic stroke after introduction of a wire into the middle cerebral artery, Revacept also led to an improvement in motor function, reduction in infarct volume and oedema, without increasing the risk of ICH (58). Revacept does not interact with platelets, but binds to collagen, perhaps also to fibronectin, on the vessel wall, covering them like a plaster. These specific activation sites of GPVI-mediated platelet activation do not only occur in vessel wall erosions, but also in plaques (59). Revacept is also supposed to inhibit the lesion-induced activation of vWF by allosteric hindrance of the binding site of vWF to collagen (58). Accordingly, preclinical studies showed that addi-

tion of Revacept to any approved anti-platelet drug, or to combinations of these drugs, had no additional impact on bleeding times compared to the respective drugs alone, even in triple therapy (60). In contrast, a combination therapy of anti-GPVI antibodies with ASA (acetylsalicylic acid, aspirin) led to a marked increase in bleeding time in mice (61).

In a phase I study in humans, Revacept proved safe with regard to bleeding time, general coagulation (all haemostasis parameters unchanged) and platelet counts in healthy volunteers (62); no impact on general, ADP- or thrombin-induced platelet activation was found (62). These findings are in contrast to the broad-range inhibition seen with anti-GPVI antibodies in animal models (51), and to those exerted by other anti-vWF-directed compounds which are summarised in this chapter. In accordance with the long-term biological activity of fully human antibodies or Fc fusion proteins, the effect of Revacept was maintained for about two weeks after single dosing in humans (62), so that an extended protection interval was suggested.

Revacept is being further investigated in a phase II study NCT01645306 in patients with stroke or TIA (<http://www.clinicaltrials.gov/ct2/show/NCT01645306>).

## P-selectin antagonism

P-selectin is a cell adhesion molecule which is expressed on activated platelets and endothelial cells, and which is secreted from platelet alpha granules and endothelial Weibel-Palade bodies. It promotes platelet rolling and adhesion on activated endothelium, and leukocyte recruitment to these sites (63). Studies in mice (63), rats and pigs have suggested that inhibition of P-selectin with either a monoclonal antibody or P-selectin glycoprotein ligand 1 Ig complex (PSGL-1) significantly decreases cellular infiltration and neointimal formation. Inclamumab (F. Hoffman-LaRoche, Basel, Switzerland) is a monoclonal antibody which targets P-selectin. A recent phase II study showed that administration of this agent in patients with non-ST elevation MI reduced the myocardial damage after an intervention, as determined by measuring creatine kinase and troponin I levels (64).

## Thromboxane -prostaglandin inhibitors, serotonin and phosphodiesterase inhibitors

Based on the success of ASA (aspirin), novel compounds have been developed which interfere in the metabolism or inhibit the action of thromboxane or prostaglandin, e. g. by blocking the respective receptors (for overview see [65]).

Terutroban (SI88886, Servier, Neuilly-sur-Seine, France) is a thromboxane receptor antagonist, which is effective in a Folts model of cyclic coronary flow reductions (66), and has an inhibitory effect on the ADP-, collagen- and PMA-induced aggregation in human platelets (66). It was investigated in the PERFORM trial including 19,120 patients in a head-to-head comparison vs aspirin. Compared to aspirin, no significant additional

**Table 5: Novel inhibitors of thromboxane, prostaglandin, serotonin or phosphodiesterase.**

Terutroban (SI88886), Servier, Neuilly-sur-Seine, France, thromboxane/prostaglandin receptor antagonist – discontinued after phase III
Ifetroban, Cumberland Pharmaceuticals, Nashville, TN, USA, thromboxane-2/prostaglandin endoperoxide receptor antagonist – phase II
EV-077, Evolva, Reinach, Switzerland, thromboxane receptor inhibitor – phase I
Ncx-4016, Nicox, Sophia Antipolis, France, NO-releasing aspirin – discontinued after phase II
DG-041, Decode Genetics, Reykjavik, Iceland, prostaglandin EP3 receptor antagonist – discontinued after phase II
APD-791, Arena Pharmaceuticals, San Diego, USA, 5HT2a serotonin receptor inverse agonist – phase I
K-134, Kowa, Koriyama, Japan, phosphodiesterase (PDE) III inhibitor – phase I/II
AZD 6482, AstraZeneca, London/Södertälje, GB/Sweden, PIP3 kinase inhibitor – phase I
Omeprazole+aspirin (PA 32540), Pozen, Chapel Hill, NC, USA – phase III
ASA+niacin, Cerenis, Toulouse, France – phase II

benefit was observed on an endpoint of ischaemic stroke, MI or vascular death (67). Therefore, further development was discontinued.

Ifetroban (Cumberland Pharmaceuticals, Nashville, TN, USA) is a thromboxane-2/prostaglandin endoperoxide receptor antagonist, and is currently being investigated in a phase II study in hepatorenal syndrome (<http://www.clinicaltrials.gov/ct2/show/NCT01436500>). EV-077 is a thromboxane receptor inhibitor which has been investigated in a phase I study (68). A recent review commented that antagonism at the thromboxane prostanoid receptor might not be much different from therapy with low-dose aspirin in terms of efficacy and side effects (65).

DG-041 (Decode Genetics, recently acquired by Amgen, Thousand Oaks, CA, USA), an antagonist of prostaglandin EP3 receptors, which mediates platelet activation by prostaglandin E2 (65), and Ncx 4016, a nitric oxide (NO)-releasing aspirin, as well as APD-791 (Arena Pharma, San Diego, CA, USA), a serotonin receptor inverse agonist, were all evaluated in phase Ib or II studies. Further developments seem to have been recently discontinued.

Serotonin 2A receptor antagonism is considered beneficial because serotonin released from dense granules upon platelet activation is an agonist of platelet activation. Serotonin 2A receptor antagonists have been shown to attenuate recurrent thrombosis in a canine model *in vivo* (69). However, they are ineffective in inhibiting platelet activation by physiological stimuli and plaque in human blood (70).

Inhibition of phospho-diesterase type III (PDE-3) increases intraplatelet cAMP, and thereby inhibits aggregation, and is the dominant effect of the approved drug cilostazol (71). Besides, PDE-3 inhibition also exerts a beneficial effect on the endothelium (71). A novel selective inhibitor of PDE-3 is K-134 (Kowa Pharmaceuticals, Koriyama, Japan), for which a phase II study in patients with intermittent claudication has been completed (NCT00783081, <http://www.clinicaltrials.gov/ct2/show/NCT00783081>), and resulted in improved walking distance in intermittent claudication. Some other drug preparations are combinations of existing drugs.

Please see ► Table 5 for an overview on these drugs.

## Conclusion

Many interesting novel antiplatelet compounds are being clinically developed. Recent outcome reports from smaller, mid-sized as well as very large clinical trials have reconfirmed that the clinical value of platelet inhibitors heavily depends on the benefit-risk balance between their anti-thrombotic effects and the bleeding risk they incur. It should be kept in mind that even long-term treatment with low-dose aspirin incurs a relevant risk of bleeding, particularly from gastrointestinal sources (72). This is of particular importance in the treatment of stroke, since the combination of aspirin with other anti-platelet drugs has so far failed to improve outcome due to disproportional increase in bleeding complications (73, 74). We would anticipate that new drugs which specifically target the initial steps of plaque-mediated activation of

platelet signalling pathways, but leave basal platelet signalling unchanged, should represent a significant improvement compared to existing approved drugs. In this regard, the preclinical evaluation of such compounds on general haemostasis and platelet function especially in combination to existing drugs might be predictive and help to decide on further development.

## Conflicts of interest

Martin Ungerer and Götz Münch are both employed of AdvanceCOR, a private biotech company which develops anti-platelet drugs.

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