Thrombosis Therapy: Focus on Antiplatelet Agents

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Abstract
Platelet adhesion, activation and aggregation to the injured vessel wall are crucially involved in the pathogenesis of thrombus formation. Agents in theory thwarting these phases would have significant clinical value. The current antiplatelet drugs used in daily clinical practice include COX-1 inhibitor aspirin, ADP P2Y₁₂ receptor antagonist clopidogrel, and the GPIIb-IIIa antagonists (abciximab, epifibatide and tirofiban). However, confined curative ratio along with unforeseen bleeding risk remains a major puzzle of antiplatelet therapy. With advances in understanding of the molecular basis of platelet in thrombosis, newer antiplatelet agents that targets different stage of thrombus formation have been recently developed, mostly including agents targeting platelet adhesion (GPIV, vWF), activation (GPVI, P2Y₁₂, Tpa, PAR1, phosphodiesterase, cyclooxygenase), and aggregation (GPIIb/IIIa). In this article, we will review the advantages and limitations of various antiplatelet agents that have been approved by the US Food and Drug Administration (FDA) or under development.

Keywords: Platelet; Thrombus formation; Antiplatelet drugs

Introduction
Thrombosis precipitating cardio-cerebrovascular diseases is the most common cause of morbidity and death. Platelets have a central role in thrombus formation [1]. At the cellular level (Figure 1), thrombosis is initiated by platelets tethering to subendothelial von Willebrand factor (vWF) via the glycoprotein Ib (GPIb) [2,3]. GPIbα-vWF interactions mediates the initial adhesion step of platelets to the extracellular matrix (ECM) at high shear rates (>500 s⁻¹). GPIbα may also contribute to platelet adhesion to the intact vessel wall by interacting with P-selectin exposed on activated endothelial cells. At sites of vascular injury, GPVI-collagen interactions initiate intracellular signaling pathway followed by shifting of integrins to high-affinity state and the release of secondarily acting agonists (ie, ADP, serotonin, and calcium), as well as synthesizing thromboxane from arachidonic acid (AA). At the same time, exposed tissue factor (TF) locally triggers the formation of thrombin (extrinsic pathway). Activation of FXII and FXI also lead to thrombin formation. Platelet activation is subsequently propagated through agonist-receptor interaction, mostly including ADP/via P2Y₁/P2Y₁₂, thrombin via protease-activated receptor 1(PAR1) and PAR4, and thromboxane via the thromboxane receptor (TP). At the same time, activated platelets act as a catalytic surface for thrombin generation from its plasma pro-enzymes (intrinsic pathway) [4,5]. Finally, the activated platelets co-aggregate with fibrinogen and vWF via GPIb/IIIa [6,7]. This leads to thrombus stabilization by insoluble fibrin intermeshed within and around the platelet thrombus. The three dimensional platelet plugs under pathophysiological conditions can obstruct circulatory system patency leading to ischemic heart disease (myocardial infarction, unstable angina), ischemic stroke, and related conditions [8]. Antiplatelet therapy is a well-established thrombolytic approach for patients with thromboembolic disorders. In this article, we will review the advantages and limitations of FDA-approved or investigational antiplatelet agents in the treatment of thrombotic events.

Anti-platelet Agents Targeting Platelet Adhesion
Pharmacological agents targeting vWF or GPIIbα are a promising antiplatelet strategy. As listed in Table 1, nine these agents are currently under investigation. It includes ARC1779, AJW200, 82D6A3, ARC-15105, ALX-0081 and ALX-0681, h6B4-Fab, GPGP-290, SZ2.

Agents Targeting vWF
ARC1779 (Archemix Corp) is a novel aptamer-based chemical antibody that binds to vWF A1 domain with high affinity and little immunogenicity [9,10]. In vitro, ARC1779 inhibits vWF A1-dependent or shear stress-induced platelet aggregation as well as platelet adhesion to collagen-coated matrices [11]. In vivo, injection of ARC1779 leads to reduced thrombus formation on porcine arteries, and reduced carotid artery thrombosis in primates [11]. Incubation of ARC1779 with platelets from coronary artery disease (CAD) patients impaired shear stress-induced platelet adhesion [12]. A Phase II clinical trial showed that continuing injection of ARC1779 may prevent platelet aggregation and increase platelet counts in thrombotic thrombocytopenic purpura patients [13].

AJW200 is a humanized monoclonal antibody (mAb) against vWF A1 domain. In vitro, AJW200 inhibits high-shear-stress-induced human platelet aggregation in a dose-dependent manner [14]. A further clinical trial to verify its safety and efficacy is still ongoing.

Other vWF antagonists including 82D6A3, ARC15105, ALX-0081, and ALX-0681 are still in preclinical or clinical studies. 82D6A3 is a mAb against vWF A3 domain [15]. Preclinical study showed that 82D6A3 completely inhibited the binding between vWF and collagen in baboon stent implantation [16]. ARC15105 is a chemically advanced aptamer. Ex vivo trials demonstrated it had less inhibition effect on platelet aggregation than ARC1779 [17]. ALX-0081 and ALX-0681 are humanized nanobody against vWF A1 domain which inhibits binding of vWF to GP Ib. Currently, Phase II clinical study of ALX-0081 in percutaneous coronary intervention (PCI) patients is ongoing [18].

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Agents Targeting GPIb Receptor

The h6B4 is a fully recombinant and humanized Fab fragment against GPIbα [19]. It inhibits platelet adhesion by competing with vWF for binding to GPIbα under high-shear condition. In vivo in baboons, thrombus formation was induced at an injured and stenosed site of the femoral artery, resulting in cyclic flow reduction (CFRs). Injection of h6B4-Fab dose-dependently reduced the CFRs without significant increase in bleeding time. This antibody is a useful tool to study the role of GPIb in human thrombotic diseases.

GPG 290 is a chimeric recombinant protein from Chinese hamster ovary (CHO) cell culture that contains the amino-terminal 290 amino acid of GPIbα linked to the human IgG1. Preliminary data show GPG 290 has prolonged bleeding time in dogs; despite it provides protection against coronary artery thrombosis [20].

SZ2 is a mAb against GPIbα. In vitro, it inhibits both ristocetin- and botrocetin-induced platelet aggregations [21]. The in vivo efficacy of SZ2 is still under investigation.

Anti-platelet Agents Targeting Platelet Activation

Agents targeting platelet receptors and signaling molecules are the potential therapeutic targets. As listed in Table 2, seven of these agents have been approved by FDA, and thirteen of these agents are currently under investigation.

Agents Targeting GPVI Receptor

PR-15 (Revacept; ABX-CRO/Medifacts) is a dimeric glycoprotein (GPVI)-Fc. PR-15 has been reported to inhibit collagen-induced platelet adhesion without affecting general hemostasis in humans [22,23], and abolished platelets stable arrest and aggregation following vessel injury in mice [24]. A Phase I clinical trial demonstrated that PR-15 injection was safe and capable of reducing bleeding events compared with P2Y12 antagonist clodipogrel treatment [26].

Agents Targeting ADP Receptor

Adenosine diphosphate (ADP), an important platelet agonist in vivo, has two types of membrane receptors named P2Y1 and P2Y12 [27]. P2Y1 is a Gq linked 7-transmembrane G-protein-coupled-receptor (GPCR), while P2Y12 is coupled to Gi protein. Activation of the P2Y1 receptor leads to calcium mobilization, a rapid platelet shape change and reversible aggregation. However, activation of P2Y12 allows for a
induced platelet aggregation by blocking P2Y12 receptors [27,28].

cytochrome P450 metabolism prior to irreversibly inhibit ADP-second generation discovered oral thienopyridine class that requires thrombocytopenic purpura (TTP) [29,30].

substituted by clopidogrel, owing to its delayed onset and obvious parent molecule [27,28]. In clinical practice, ticlopidine has been largely in the liver, is a first-generation discovered thienopyridine class that

P2Y12 antagonists (Ticlopidine, Clopidogrel, Prasugrel, and Ticagrelor) slow yet progressive platelet aggregation and secretion. Currently, four potent and stable drugs. Currently, clopidogrel has been approved by FDA, and three of these agents (Elinogrel, Cangrelor and BX667) are under development.

Ticlopidine (Ticlid; Roche) metabolized by cytochrome P450 in the liver, is a first-generation discovered thienopyridine class that irreversibly antagonizes P2Y12 by an active metabolite rather than the parent molecule [27,28]. In clinical practice, ticlopidine has been largely substituted by clopidogrel, owing to its delayed onset and obvious hematologic side effects, including neutropenia and thrombotic thrombocytopenic purpura (TTP) [29,30].

Clopidogrel (Plavix; sanofi Aventis/Bristol-Myers Squibb) is a second-generation discovered oral thienopyridine class that requires cytochrome P450 metabolism prior to irreversibly inhibit ADP-induced platelet aggregation by blocking P2Y12 receptors [27,28]. Currently, clopidogrel has become a standard part of dual antiplatelet therapy with aspirin in patients with acute coronary syndromes (ACS), unstable angina, non-ST elevation myocardial infarction, or stroke [31]; however, the dual regimen was associated with an increased bleeding risk compared with placebo [32]. Moreover clopidogrel has modest platelet inhibition, delayed onset of action, and significant inter-individual variability [33,34]. These shortages appeal to more potent and stable drugs.

Prasugrel (Effient; Eli Lilly/Daiichi Sankyo) is a third-generation discovered thienopyridine class, which irreversibly inhibits the P2Y12 platelet receptor. It has an approximately 10-fold greater in vivo potency than clopidogrel [35]. Subjects who responded weakly to clopidogrel demonstrated better platelet-inhibited induction in response to prasugrel [36]. More importantly, TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38), a Phase III trial, demonstrated prasugrel significantly reduced incidences of cardiovascular death and stent thrombosis [37]. However, administration of Prasugrel increases bleeding risk, including fatal bleeding [38]. It is contraindicated in patients with a history of stroke or transient ischemic attacks.

Prasugrel is a direct rather than requiring cytochrome P-450 biotransformation, reversible, and orally active P2Y12 antagonist with a rapid onset of action, reversible binding, and a low affinity for the P2Y12 receptor [39]. The PLATO (Platelet inhibition and patient Outcomes) trial showed that ticagrelor was superior to clopidogrel in reducing the primary endpoints (a composite of death from vascular causes, myocardial infarction, or stroke) in ACS patients with or without ST-segment elevation [40–42]. However, in subjects enrolled in United States and Canada, ticagrelor showed no benefit compared with clopidogrel. The most common sides of ticagrelor are dyspnea and various nonfatal bleeding such as hematoma, nosebleed, gastrointestinal or dermal bleeding [42].
Elinogrel (PRT060128; Novartis) is a reversible P2Y₁₂ antagonist with a direct action and novel structure [27]. A Phase II Clinical trial (patients Undergoing Non-urgent Percutaneous Coronary Interventions, INNOVATE-PCI) showed that elinogrel administered orally or intravenously overcomes high platelet reactivity in patients undergoing PCI who had a weak response to clopidogrel [43]. It is currently in the planning stage of Phase III trial as a next generation P2Y₁₂ antagonist.

Cangrelor (analog of adenosine triphosphate) (The Medicines Company) is an intravenous reversible P2Y₁₂ antagonist with direct action. Unlike the other P2Y₁₂ antagonists discussed above, cangrelor is a stable analogue of adenosine triphosphate (ATP) administered parenterally, which results in a more rapid onset of action and greater degree of platelet inhibition than clopidogrel. However, Phase II (A Clinical Trial Comparing Cangrelor to Clopidogrel in Subjects who Requires PCI, CHAMPION-PCI) and Phase III (CHAMPION-PLATFORM) trials have been stopped recently due to its limited efficacy in reducing the primary endpoints in PCI patients and higher bleeding risk compared with clopidogrel [44,45].

BX667 is an orally active reversible P2Y₁₂ antagonist which inhibited ADP-induced platelet aggregation in vitro [46]. In vivo in rat arteriovenous-shunt model [47], oral BX667 administration results in a rapid and lasting thrombus inhibition. It has yet to be assessed in human volunteers.

Agents Targeting Thromboxane A₂ / Prostaglandin H₂ (TH) Receptor

Activation of platelet triggers cyclooxygenase 1 (COX-1) induced arachidonic acid (AA) metabolism, resulting in the conversion of AA to prostaglandin G₂/H₂, and the latter is subsequently converted to TXA₂, which is potent platelet activator [48]. Thromboxane receptor α (TPα), also known as the TH receptor, is a GPCR that coupled to Gq and G₁₂/₁₃. Binding of TPα with its agonist TXA₂ may result in platelet activation via a number of intracellular pathways which enhances primary platelet activation through thrombin or collagen [49]. TPα has been an attractive target for antiplatelet therapy.

Aspirin, the most widely-used antiplatelet agent, irreversibly inhibits platelet COX-1 activity, leading to reduced synthesis of prostaglandin and TXA₂. Long-term aspirin therapy brings about a 20%-25% reduction in the odds of subsequent MI, stroke, or vascular death among intermediate- or high-risk cardiovascular diseases (CVDs) patients [50]. However, some patients produce resistance to aspirin because it produces only a partial inhibition of platelet aggregation. Moreover, its gastrointestinal toxicity prompts the search for more specific agents.

S18886 (terutroban) is a novel oral TPα antagonist [51]. In preclinical studies, S18886 rapidly inhibits platelet-dependent thrombosis in vivo in dog, as well as platelet aggregation and stent-induced thrombosis ex vivo [52,53]. However, it had no effect on the myocardial infarct size in ischemia-perfusion model. A Phase II study in patients with peripheral artery disease showed that orally administration of S18886 resulted in a rapid inhibition of platelet aggregation without significant adverse events [54]. In the ongoing Phase III clinical trial, Prevention of Cerebrovascular and Cardiovascular Events of Ischemic Origin with Terutroban in Patients with a History of Ischemic Stroke or Transient Ischemic Attack (PERFORM), S18886 and aspirin had similar rates of protection without safety advantages for S18886 [55].

Z-335 is an oral TPα antagonist that is under investigation [56]. Preclinical data show Z-335 inhibited U46619-induced human platelet aggregation in vitro [56]. In vivo in rat arteriovenous-shunt model [47], oral Z-335 administration results in a rapid and lasting thrombus inhibition. It has yet to be assessed in human volunteers.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Half-life</th>
<th>Administration</th>
<th>Stage</th>
<th>Use and side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PR-15 (Rerasept)</td>
<td>Dimeric GPVI-Fc</td>
<td>GPVI</td>
<td>Inhibits binding to platelet GPVI receptor</td>
<td>—</td>
<td>IV</td>
<td>Phase I completed</td>
<td>—</td>
</tr>
<tr>
<td>DZ-6976</td>
<td>—</td>
<td>GPVI</td>
<td>collagen and ristocetin inhibitor</td>
<td>—</td>
<td>Oral</td>
<td>Phase I completed</td>
<td>—</td>
</tr>
<tr>
<td>Elinogrel (PRT060128; Novartis)</td>
<td>Thienopyridine</td>
<td>P2Y12</td>
<td>same as Ticlopidine</td>
<td>—</td>
<td>Oral or IV</td>
<td>—</td>
<td>Phase II</td>
</tr>
<tr>
<td>Cangrelor (The Medicines Company)</td>
<td>Thienopyridine</td>
<td>P2Y12</td>
<td>same as Ticlopidine</td>
<td>—</td>
<td>IV</td>
<td>—</td>
<td>Phase III</td>
</tr>
<tr>
<td>BX667</td>
<td>—</td>
<td>P2Y12</td>
<td>same as Ticlopidine</td>
<td>—</td>
<td>Oral</td>
<td>Preclinical</td>
<td>—</td>
</tr>
<tr>
<td>S18886 (Terutroban)</td>
<td>—</td>
<td>TPα</td>
<td>Antagonist of TPα</td>
<td>—</td>
<td>Oral</td>
<td>Phase III</td>
<td>—</td>
</tr>
<tr>
<td>Z-335</td>
<td>—</td>
<td>TPα</td>
<td>Antagonist of TPα</td>
<td>—</td>
<td>Oral</td>
<td>Phase I</td>
<td>—</td>
</tr>
<tr>
<td>BM-573</td>
<td>—</td>
<td>TPα</td>
<td>Antagonist of TPα</td>
<td>—</td>
<td>—</td>
<td>Preclinical</td>
<td>—</td>
</tr>
<tr>
<td>DG-041</td>
<td>—</td>
<td>PGE2</td>
<td>Inhibits binding to PGE2 receptor</td>
<td>—</td>
<td>—</td>
<td>Phase II</td>
<td>—</td>
</tr>
<tr>
<td>Vorapaxar (SCH 530345)</td>
<td>Tricyclic 3-phenylpyridine analog of himbacine</td>
<td>PAR1</td>
<td>Reversible inhibition of PAR1</td>
<td>—</td>
<td>Oral; daily</td>
<td>Phase III</td>
<td>—</td>
</tr>
<tr>
<td>Atofapaxar (E5555)</td>
<td>2-Iminopyrrolidine antagonist</td>
<td>PAR1</td>
<td>Reversible inhibition of PAR1</td>
<td>—</td>
<td>Oral; daily</td>
<td>Phase II</td>
<td>—</td>
</tr>
<tr>
<td>SCH205831</td>
<td>—</td>
<td>PAR1</td>
<td>Reversible inhibition of PAR1</td>
<td>—</td>
<td>—</td>
<td>Preclinical</td>
<td>—</td>
</tr>
<tr>
<td>SCH602539</td>
<td>—</td>
<td>PAR1</td>
<td>Reversible inhibition of PAR1</td>
<td>—</td>
<td>—</td>
<td>Preclinical</td>
<td>—</td>
</tr>
</tbody>
</table>

COX1, cyclooxygenase1; PEG, prostaglandin; TPα, Thromboxane receptor α; PAR, protease-activated receptor 1.

Table 2.2: Under development.
DG-041 inhibited platelet aggregation by selectively blocking EP<sub>2</sub> stimulation [60]. DG-041 is still effective in the presence of a P<sub>2Y</sub><sub>12</sub> antagonist and aspirin [61]. It is currently being evaluated in Phase II clinical trials as a potential agent for the treatment of atherothrombosis.

**Agents Targeting Phosphodiesterase (PDE) Inhibitor**

PDE isoenzymes from platelet extracts can regulate the metabolism of 3',5'-cyclic adenosine monophosphate (cAMP) and 3',5'-cyclic guanosine monophosphate (cGMP) [62]. Elevated cytosol cAMP and cGMP level in the platelet may stimulate signaling pathways that inhibit platelet activation [63]. Currently, two PDE inhibitors (dipyridamole and cilostazol) have been approved by FDA.

Dipyridamole (Aggrenox; Boehringer Ingelheim) is a derivative of pyridopyrimidine, has both antiplatelet and vasodilator properties [64]. Its antiplatelet mechanism includes inhibition of cyclic PDE and blockade of adenosine uptake that results in increased intraplatelet cyclic adenosine monophosphate, thereby inhibiting signal transduction. In European Stroke Prevention Study 2 (ESP S-2) and European Stroke Prevention Reversible Ischemia (ESPRIT) trials, dual treatment of dipyridamole and aspirin reduced risk of stroke or death by 37% compared with aspirin alone [65]. However, it was not superior to clopidogrel in the treatment of recurrent stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial [66].

Cilostazol (Pletal; Otsuka) is an oral selective PDE3 inhibitor with antiplatelet mechanism, and antiangiogenic effects [68]. Cilostazol dilates blood vessels and hinders ADP-, collagen- and AA-induced platelet aggregation. It is currently used in the treatment of peripheral ischemia (e.g., intermittent claudication). Like aspirin and clopidogrel, cilostazol is safe and effective in reducing the risk of restenosis and repeated revascularization after PCI; however, a combination of cilostazol with aspirin and clopidogrel do not show superiority in reducing the primary composite endpoints of adverse cardiovascular events after drug-elution stent implantation [67].

**Agents Targeting Thrombin Receptor**

Thrombin is the most potent known platelet activator. Protease activated receptor 1 (PAR1) is the major human platelet receptor through which thrombin facilitates cellular effects of platelet activation without interfering with thrombin-induced cleavage of fibrinogen [68]. Currently, two of these agents (vorapaxar, atopaxar) are in Phase II or Phase III investigation.

Vorapaxar (SCH 530348; Schering-Plough), an analog of hibamicine, is an orally active, high-affinity reversible PAR1 antagonist. The Thrombin Receptor Antagonist-Percutaneous Coronary Intervention (TRA-PCI) study showed that addition of SCH 530348 to conventional antiplatelet therapy with aspirin and clopidogrel had no significant increase in thrombosis in MI (TIMI) or bleeding time. However, the Phase III trials (The Thrombin Receptor Antagonist for Clinical Events Reduction, TRACER; and The Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events, TRA2P-TIMI50) failed because of unforeseen intracranial bleeding [69].

Atopaxar (E5555; Eisai) is an oral administration of the PAR1 antagonist. In preclinical studies, atopaxar inhibits thrombin-mediated platelet aggregation without significant bleeding risks [70]. The Phase II trial, performed in patients with coronary artery disease or non-ST-segment elevation acute coronary syndrome (NSTEMI-ACS), supports the efficacy of atopaxar. However, higher incidence of bleeding complications and the lack of a definite dose-related trend for bleeding risk and efficacy should be alert [71-73].

Currently, newer PAR-1 antagonists (e.g. SCH 205831 and SCH 602539) are still under investigation. Preclinical data show SCH 205831 inhibited platelet deposition in arteriovenous-shunt thrombosis model in baboons, and SCH 602539 dose-dependently inhibited thrombus formation in the Fols model of thrombosis in anesthetized cynomolgus monkeys [74].

**Anti-platelet Agents Targeting Platelet Aggregation**

The aggregation of platelet and formation of a thrombus requires functional integrin αIIβ3 (GPIIb/IIIa). As a final pathway of platelet activation, it has been a favored target for anti-platelet therapies [68]. As listed in Table 3, there are three FDA-approved GPIIb/IIIa antagonists (abciximab, eptifibatide, and tirofiban) and one investigational agent (ZAA5).

Abciximab (ReoPro; Lilly) is an anti-αIIβ3 monoclonal F(ab’), fragment which developed from the murine human chimera c7e3 Fab, preventing integrin binding to fibrinogen and vWF [75]. Abciximab cross-reacts with the αvβ3 integrin on endothelial cells and smooth muscle cells and with the αMβ2 integrin (CD11b/CD18) on granulocytes and monocytes [76], which is administered intravenously and is beneficial in preventing thrombosis in patients undergoing PCI including percutaneous transluminal angioplasty (PTA), atherectomy and carotid artery stenting (CAS) [77]. The dose required for anti-thrombotic effects is associated with bleeding risks [78].

Eptifibatide (Integrilin; Millennium Pharmaceuticals/Schering-Plough) is a cyclic heptapeptide that contains a KGD (lysine-glycine-aspartic acid) sequence as the active group which selectively recognizes αIIbβ3 and reversibly inhibits platelet aggregation. The Imaging for Myocardial Perfusion Assessment in Coronary artery disease (IMPACT-II) study showed that a single loading dose followed by continuous infusion for 20–24 hours only resulted in 50% αIIbβ3 receptor blockade; thus, limited benefits and efficacy through eptifibatide were observed [79]. Acute Catheterization and Urgent

<table>
<thead>
<tr>
<th>FDA-approved Agent</th>
<th>Type</th>
<th>Target</th>
<th>Mechanism of action</th>
<th>Half-life</th>
<th>Administration</th>
<th>Use and side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab (ReoPro; Lilly)</td>
<td>Murine human chimeric Fab fragment</td>
<td>GP IIb-IIIa</td>
<td>Preventing integrin binding to fibrinogen and vWF</td>
<td>&lt;10-30 minutes</td>
<td>IV only; Once</td>
<td>PCI; Bleeding, thrombocytopenia, EDTA-induced pseudothrombocytopenia</td>
</tr>
<tr>
<td>Eptifibatide (Integrilin; Millennium Pharmaceuticals/Schering-Plough)</td>
<td>KGD-containing cyclic heptapeptide</td>
<td>GP IIb-IIIa</td>
<td>Selectively recognizes integrin GP IIb-IIIa and reversibly inhibits platelet aggregation</td>
<td>~2.5 hours</td>
<td>IV only; Once</td>
<td>NSTEMI, PCI, Unstable angina; Bleeding, thrombocytopenia, EDTA-induced pseudothrombocytopenia</td>
</tr>
<tr>
<td>Tirofiban (Aggrastat; Merck)</td>
<td>Non-peptide mimetic based on RGD</td>
<td>GP IIb-IIIa</td>
<td>Competitively binds to integrin GP IIb-IIIa</td>
<td>2 hours</td>
<td>IV only; Once</td>
<td>Same as Eptifibatide</td>
</tr>
<tr>
<td>ZAAS (Preclinical)</td>
<td>—</td>
<td>GP IIb-IIIa</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

**Table 3: Agents targeting platelet aggregation.**
Intervention Triage strategy (ACUITY) trial showed an increase incidence of major bleeding in patients with ACS undergoing PCI [80].

Tirofiban (Aggrastat; Merck) is a tyrosine-derived nonpeptide mimetic reversible inhibitor of αIIbβ3 that specifically and competitively binds to the receptor with the features of short half-life period, no antigenicity and little adverse reaction. Treatment with tirofiban in combination with aspirin and heparin in patients with ACS significantly reduced the 30-day post-treatment incidence of death, MI, or recurrent ischemia [81]. Like epifibatide, tirofiban has a common feature of bleeding complications thus unsuitable for prophylaxis [82].

ZA45 is a novel αIIbβ3 peptide antagonist. In the rabbit arteriovenous shunt thrombosis model, ZA45 demonstrated effective antithrombotic effect when administered with aspirin [83]. Its effect in human subjects is currently under investigation.

Conclusion

Platelets play a central role in the pathogenesis of thrombosis, antiplatelet therapy is therefore crucial for patients with thrombotic disorders (e.g. ACS or stroke). The current antiplatelet drugs (e.g. the COX-1 inhibitor aspirin, the P2Y12 receptor antagonist clopidogrel and GPIIb/IIIa antagonists) and the newer agents under development demonstrate definite protection against thrombotic events.

Each category of antiplatelet agents has their advantages and limitations. COX-1 inhibitor aspirin and the P2Y12 receptor antagonist clopidogrel have been used as gold standards in the prevention of arterial thrombotic events; however, unforeseen bleeding risk, limited efficacy, significant inter-individual variability in response and extended duration of action that cannot be reversed in emergency surgery are still the main limitation of these agents. Novel P2Y12 receptor antagonist (prasugrel, ticagrelor, elinogrel and cangrelor) have advantages over clopidogrel, including more rapid, more complete inhibition of platelet function and less variable. Recent clinical studies for ticagrelor demonstrate that these new P2Y12 receptor antagonists have more rapid antithrombotic effects than clopidogrel, without an unacceptable bleeding risk or other side effects [42]. Further clinical studies are still ongoing. GPIIb/IIIa antagonists, such as abciximab, are mainly used in high-risk patients before PCI; however, it is associated with bleeding risks in dose-dependent manner. Many other novel antiplatelet agents (e.g. antagonists of vWF, PAR-1, GPVI, and novel integrin αIIbβ3 epitopes) are in development as antithrombotic agents. Among them, blocking the interaction between vWF and GPIb, which mainly occurs under high shear stress in arterioles, is recently suggested to be an alternative promising target due to fewer bleeding complications. Here, we highlight that the future goal for antiplatelet therapy should try to achieve an optimal balance between antithrombotic efficacy and bleeding risk.

Another fundamental question is so far known antiplatelet mechanisms aim at preventing platelet adhesion, activation and aggregation rather than the more clinically relevant issue of resolution of an existing thrombus, highlighting a pressing clinical need for better therapeutic approaches. Interestingly, recent studies pointed to an additional mechanism via platelet GPIIIa49-66 ligands that binds to platelet GPIIIa49-66 epitope that is aimed at disintegrating already formed platelet aggregates [84,85]. These agents are unique in that it has no effect on platelet function and minimal effect on platelet count (<15%) [85]. They dissolve already-formed platelet thrombi by binding to activated platelets within the platelet thrombus as well as to activated early platelet deposition on post ischemic endothelial cells[86]. These therapeutic agents are, therefore, safer as well more efficient than conventional antiplatelet agent that block platelet function and induce thrombocytopenia and mortality. Thus, GPIIIa49-66 ligand-induced platelet fragmentation may represent a new direction for thrombosis therapy.

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