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REVIEW

# Thrombin Receptor Antagonism in Antiplatelet Therapy

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## ABSTRACT

Activated platelets play a crucial role in the pathogenesis of atherothrombotic disease and its complications. Even under treatment of antiplatelet drugs, such as acetylsalicylic acid and P2Y12 antagonists, morbidity and mortality rates of thromboembolic complications remain high. Hence, the therapeutic inhibition of protease-activated receptor (PAR)-1, which is activated by thrombin, is a novel promising approach in antiplatelet therapy. Recent data suggest that PAR-1 is mainly involved in pathological thrombus formation, but not in physiological hemostasis. Therefore, PAR-1 inhibition offers the possibility to reduce atherothrombotic events without increasing bleeding risk. So far, two emerging PAR-1 antagonists have been tested in clinical trials: vorapaxar (SCH530349; Merck & Co., Whitehouse Station, NJ, USA) and atopaxar (E5555; Eisai, Tokyo, Japan). Although in TRACER vorapaxar showed an unfavorable profile for patients with acute coronary syndrome in addition to standard therapy, it revealed promising results for patients with prior myocardial infarction in TRA 2P-TIMI50. Depending on the status of clinical approval, vorapaxar might be an option for patients with peripheral arterial disease to reduce limb ischemia. The second PAR-I antagonist, atopaxar, tended towards reducing major cardiovascular adverse events in acute coronary syndrome patients in a phase II trial. However, although statistically not significant, bleeding events were numerically increased in atopaxar-treated patients compared with placebo. Furthermore, liver enzymes were elevated and the relative corrected QT interval was prolonged in atopaxar-treated patients. Currently, the development of atopaxar by Eisai is discontinued. The future of this novel class of antithrombotic drugs will depend on the identification of patient groups in which the risk–benefit ratio is favorable.

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## INTRODUCTION

Worldwide, clinical manifestations of cardiovascular diseases, such as acute coronary syndrome (ACS), coronary artery disease (CAD), and ischemic stroke, are among the leading causes of death [1]. The underlying pathogenetic mechanisms of ACS are multifactorial but finally lead via platelet activation to intravascular clot formation and vessel occlusion with ischemia of the downstream located tissue [2].

Platelet activation, which commonly occurs when platelets are exposed to subendothelial structures such as fibrinogen, is a physiological process of primary hemostasis. Activation of the glycoprotein (GP)Ib/V/IX, which is expressed on the surface of platelets, mediates the initial tethering of platelets to the vessel wall. Binding of the platelets to von Willebrand factor, which is exposed in subendothelial tissues following vascular injury, triggers an interaction between GPVI and collagen. Autocrine and paracrine stimulation of platelet receptors by potent platelet-aggregating agonists and vasoconstrictors, such as thromboxane A2 (TXA2), platelet-activating factor, and adenosine diphosphate (ADP), lead to activation of an integrin called GPIIb/IIIa, which is also expressed on the platelet surface. As a result, the soluble plasma coagulation factor, fibrinogen, binds to this receptor and mediates platelet-to-platelet aggregation, and consequently, a primary platelet plug, or thrombus, at the site of injury is formed. Another important platelet agonist is thrombin. It is generated in the coagulation cascade, a pathway of secondary hemostasis, which is activated simultaneously with primary hemostasis. A main function of thrombin is the conversion of fibrinogen to the insoluble protein fibrin, the major stabilizing component of the thrombus. Physiologic activation of these pathways contributes to the prevention and control of bleeding events.

Notably, pathological platelet activation causes thrombus formation in conditions other than after vascular injury, such as after plaque rupture [3]. The stationary or traveling thrombus (embolism) may cause the occlusion of arteries and subsequent ischemic cell death [3] resulting in ACS or a myocardial infarction (MI). Invasive treatment options in ACS include coronary revascularization with percutaneous coronary intervention (PCI) or in rare cases acute coronary artery bypass graft surgery.

## CURRENT ANTIPLATELET THERAPY

Enhanced platelet activation can be found in ACS patients and often leads to thrombus formation and cardiac ischemia. Hence, international cardiac societies recommend the use of antiplatelet drugs, e.g., acetylsalicylic acid (ASA) and P2Y12 antagonists for these patients in order to reduce ischemic complications [4–6].

ASA is an irreversible cyclooxygenase-1 inhibitor, and thereby reduces intraplatelet production of prothrombotic TXA2 with consecutive inhibited platelet aggregation. P2Y12 antagonists (clopidogrel, prasugrel, and ticagrelor) avoid ADP-mediated platelet activation and aggregation.

The benefit of ASA and P2Y12 antagonists in ACS patients has been shown in several large clinical studies [7]. However, the risk of further thrombotic events remains high [8]. An analysis

of the Global Registry of Acute Coronary Events (GRACE) registry demonstrated 5-year mortality rates in ACS patients under ASA and clopidogrel treatment of 19%, 22%, and 17% in patients with ST-elevation MI (STEMI), non-STEMI (NSTEMI), and unstable angina (UA), respectively [9]. The underlying phenomenon for this observation might be related to alternative platelet activation pathways, such as those mediated by thrombin [8].

Clinical trials have demonstrated that even a double antiplatelet therapy with ASA and clopidogrel is insufficient in about one-third of all treated patients resulting in recurrent atherothrombotic events [10, 11].

Several clinical trials were designed to compare treatment regimens of clopidogrel to prasugrel and ticagrelor, which are known to more effectively inhibit P2Y12 mediated platelet aggregation [12, 13]. In the trial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel (TRITON-TIMI 38), prasugrel had superior efficacy compared with clopidogrel [12]. The composite endpoint of death from cardiovascular causes, nonfatal MI, or nonfatal stroke was 9.9% for prasugrel compared with 12.1% for clopidogrel. However, the rate of thrombolysis in MI (TIMI) major bleeding was elevated in patients receiving prasugrel compared with patients receiving clopidogrel (2.4% vs. 1.8%, respectively) [12]. In the PLATelet inhibition and patient Outcomes trial (PLATO), ticagrelor also demonstrated superior efficacy compared with clopidogrel as only 9.0% of patients experienced the primary endpoint of cardiovascular death, MI, or stroke compared with 10.7% of patients taking clopidogrel [13]. Yet, similar to prasugrel, an increase in the rate of bleeding was observed with ticagrelor compared with clopidogrel [13].

Taken together, prasugrel and ticagrelor represent improved treatment options and reduce atherothrombosis. Nevertheless, inhibition of other pathways may provide a further opportunity to avoid ischemic events.

## PROTEASE-ACTIVATED RECEPTOR INHIBITORS

Targeting alternative pathways, which are not affected by ASA or P2Y12 antagonists, is one potential way to improve the treatment options. Protease-activated receptors (PAR-1, PAR-2, PAR-3, and PAR-4) are G-protein-coupled receptors expressed on platelets and other cells that are not involved in platelet activation (e.g., neurons, myocytes, fibroblasts, and endothelial cells) [8, 14]. Thrombin has the highest affinity for PAR-1, but also activates PAR-3 and PAR-4, whereas PAR-2 is activated by trypsin and other proteases, but not by thrombin. Only PAR-1 and PAR-4 are expressed on platelets.

The principle thrombin receptor, PAR-1, mediates platelet activation at subnanomolar concentrations, whereas the other thrombin receptor, PAR-4, requires higher thrombin concentrations for activation [14]. The inhibition of PAR-1 is a new approach in antiplatelet strategies. Mechanistically, PAR-1 activation is achieved when thrombin proteolytically cleaves a part of the extracellular loop of the receptor. The newly exposed N-terminus acts as a tethered ligand at a transmembrane loop of the receptor [2]. The effects of PAR-1 activation in endothelial and vascular smooth muscle cells (SMCs) are not fully established and are still controversial [15–17]. On platelets it has been shown that PAR-1 activation mediates calcium

mobilization, platelet shape change, and protein kinase C (PKC) activation finally resulting in activation of the platelet GPIIb/IIIa receptor [15, 16, 18]. Additionally, PAR-1 activation initiates intracellular signaling pathways that stimulate platelet procoagulant activities leading to enhanced thrombin formation [19].

Several preclinical studies have indicated that PAR-1 might be involved mainly in pathological thromboembolic complications and might not be essential for physiological hemostasis [18–23]. Therefore, it was suggested PAR-1 inhibition may provide beneficial antithrombotic effects without inducing bleeding complications and thus might be a powerful alternative in antiplatelet treatment.

This review provides an overview of the two PAR-1 antagonists in the most advanced stages of development: vorapaxar [SCH530349; Merck & Co., Whitehouse Station, NJ, USA (following its merger with Schering-Plough)] and atopaxar (E5555; Eisai, Tokyo, Japan).

## Atopaxar (E5555)

Atopaxar is a low molecular weight (608 g/mol) reversible PAR-1 antagonist. It is metabolized by hepatic cytochrome CYP3A4 and eliminated through the gastrointestinal tract [24]. In preclinical studies, atopaxar demonstrated inhibition of thrombin receptor-activating peptides (TRAP)- and thrombin-induced platelet aggregation [25, 26]. Furthermore, atopaxar inhibited multiple other platelet activity biomarkers in plasma samples from healthy volunteers and patients with CAD [27]. A study evaluated the inhibitory effect of atopaxar on TRAP-induced platelet aggregation from healthy volunteers (ASA naive) and patients ($n = 10$ per group) with CAD who had been treated with ASA (81 mg/day) alone or combined with clopidogrel (75 mg/day) [27]. In plasma samples from healthy volunteers and patients, all concentrations of atopaxar significantly, and almost completely, inhibited TRAP-induced platelet aggregation compared with a vehicle control.

### *Phase I Studies*

The pharmacodynamics and safety properties of atopaxar were evaluated in two studies. In a randomized, double-blind, placebo-controlled, dose-ascending study, 40 healthy volunteers were randomized to receive 20, 50, 100, 200, or 400 mg atopaxar [28]. The 24 volunteers were randomized to three groups receiving 50, 100, or 200 mg atopaxar or placebo for 10 days. It was found that thrombin-induced platelet aggregation was inhibited in a dose-dependent manner, achieving the maximum effect 6 h after onset. Repeated administration inhibited thrombin-induced platelet aggregation almost completely, even 24 h after the last administration. At 7 days after the last medication, platelet function had returned to normal. Coagulation and bleeding times were not influenced demonstrating the specific effect of atopaxar [28].

At the time of publication, atopaxar had undergone phase II evaluation in a series of clinical trials cumulatively entitled Lesson from Antagonizing the Cellular Effect of Thrombin (LANCELOT) Trial that were undertaken in populations of patients with CAD and ACS in Japanese centers (NCT00540670 and NCT00619164) as well as in centers outside of Japan (NCT00312052 and NCT00548587) [29–31].

### *Phase II Studies*

To assess the safety of atopaxar, the Japanese Lessons from Antagonizing the Cellular Effect of Thrombin (J-LANCELOT) Trial [29]

consisting of two multicenter, randomized, double-blind, placebo-controlled phase II studies in Japanese patients with ACS or high-risk artery disease was conducted. In this trial 241 patients with NSTEMI or UA were randomized to 50, 100, or 200 mg atopaxar for 12 weeks including a 400 mg loading dose compared to placebo and placebo loading dose [29].

In the CAD study, 263 patients were randomized to receive the same doses of atopaxar as in the ACS study. In contrast, they did not receive a loading dose and were treated for 24 weeks [29]. The primary safety endpoint was the incidence of bleeding events adjudicated according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events CURE [32] and TIMI [33] definitions. The secondary endpoint was the incidence of major cardiovascular adverse events (MACE), defined as cardiovascular death, MI, stroke, or recurrent ischemia. Compared to placebo TIMI minor bleeding was not increased in atopaxar treated patients [ACS: 6.6% placebo vs. 5.0% atopaxar (all dose groups); CAD: 1.5% placebo vs. 1.5% atopaxar (all dose groups)] without the occurrence of any TIMI major bleeding [29]. A numerical increase in any TIMI bleeding with the dose of 200 mg atopaxar was observed (ACS: 16.4% placebo vs. 23.0% atopaxar, $P = 0.398$; CAD: 4.5% placebo vs. 13.2% atopaxar, $P = 0.081$) [29]. The rate of MACE in the combined atopaxar groups was not different from placebo [ACS: 6.6% placebo vs. 5.0% atopaxar (all dose groups), $P = 0.73$; CAD: 4.5% placebo vs. 1.0% atopaxar (all dose groups), $P = 0.066$] [29]. TRAP-induced platelet aggregation assessed in 42 ACS patients and 80 CAD patients showed inhibition by 20–60% with 50 mg atopaxar and by 90% with 100 and 200 mg atopaxar in agreement with the results of phase I studies [28, 29]. The most common adverse event (AE) was hepatic function disorder [ACS: 11.5% placebo vs. 23.3% atopaxar (all dose groups), $P = 0.064$; CAD: 1.5% placebo vs. 10.2% atopaxar (all dose groups), $P = 0.032$] [29]. In detail, in the ACS patients hepatic function disorder was seen in 9.3%, 29.2%, and 29.5% in the 50, 100, and 200 mg atopaxar groups, respectively (100 mg atopaxar vs. placebo, $P = 0.015$; 200 mg atopaxar vs. placebo, $P = 0.023$). The rate of hepatic function disorder in CAD patients was lower. It was observed in 3.2%, 7.6%, and 19.1% in the 50, 100, and 200 mg atopaxar groups, respectively (200 mg atopaxar vs. placebo, $P = 0.001$). Remarkably, a prolongation of QTc in the 100 mg ($P = 0.015$) and 200 mg ($P = 0.037$) groups in comparison with the placebo group was also observed.

Based on the same study design LANCELOT ACS and LANCELOT CAD studies have recently been completed to evaluate the safety of atopaxar outside of Japan in 603 and 720 patients, respectively [30, 31]. Although no difference in any TIMI bleeding was observed in LANCELOT ACS [ACS: 10.1% placebo vs. 9.3% atopaxar (all dose groups), $P = 0.77$], a trend towards increased TIMI bleeding in the atopaxar groups was seen in LANCELOT CAD [CAD: 6.8% placebo vs. 10.3% atopaxar (all dose groups), $P = 0.17$]. Differences in bleeding rates reached significant levels when analyzed according to the CURE criteria [CAD: 0.6% placebo vs. 3.9% atopaxar (all dose groups), $P = 0.03$]. TRAP-induced platelet aggregation was inhibited 74% at 1–3 h up to 92% at 3–6 h after loading dose corresponding to the results of J-LANCELOT and results of phase I studies [28, 29]. Similar to the results from the J-LANCELOT trial, a dose-dependent hepatic enzyme elevation and a prolongation of the QTc interval at higher doses were seen. In LANCELOT ACS atopaxar significantly reduced ischemia on continuous

electrocardiography (ECG) monitoring at 48 h compared with placebo [relative risk (RR) 0.67, $P = 0.02$] defined as horizontal or down-sloping ST-segment depression ≥0.1 mV or upward ST-segment elevation ≥0.1 mV [30]. The trial was not powered for differences in ischemic clinical endpoints.

The combined results of the phase II clinical trials would have been sufficiently positive to start phase III trials. However, the numerically greater incidence in safety endpoints and AE, such as QTc prolongation and liver enzyme elevation, as well as the lack of a convincing dose-related trend for safety and efficacy of atopaxar, limit the encouraging results of these clinical trials. Currently, the development of atopaxar by Eisai is discontinued.

## Vorapaxar (SCH530349)

Vorapaxar is an oral, low-molecular weight (492.58 g/mol), high-affinity, competitive PAR-1 antagonist, which has been shown in preclinical studies to inhibit thrombin and TRAP platelet aggregation without increased bleeding complications [34, 35]. In a phase II trial, vorapaxar administered in addition to standard ASA and clopidogrel to ACS patients was not associated with increased bleeding risks and was well tolerated [36]. The rate of AEs was comparable to the rate of AEs with standard therapy alone. Based on these results, two large, randomized, phase III trials [Thrombin Receptor Antagonist for Clinical Event Reduction in ACS (TRA-CER) and Thrombin Receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events (TRA-2P)] were initiated to evaluate the safety and efficacy of vorapaxar in combination with the standard-of-care therapy in patients who had NSTE-ACS or established atherosclerosis, respectively [37, 38]. An overview of the results is given in Table 1.

### *TRA-CER*

Thrombin Receptor Antagonist for Clinical Event Reduction in ACS was designed as a multinational, double-blind, randomized trial to compare vorapaxar (2.5 mg per day for at least 1 year) with placebo in 12,944 ACS patients that did not show any ST-segment elevations [37]. The primary endpoint was a composite of cardiovascular death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. After a median follow-up time of 502 days, no significant difference in the primary endpoint was observed (18.5% vs. 19.9%; hazard ratio [HR] 0.92; 95% confidence interval [CI] 0.85–1.01; $P = 0.07$), but it was found that vorapaxar-treated patients had enhanced bleeding complications in comparison to placebo. Moderate and severe bleeding according to the Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries (GUSTO) definition [39] were 7.2% in the vorapaxar group and 5.2% in the placebo group (HR 1.35; 95% CI 1.16–1.58; $P < 0.001$). According to TIMI bleeding criteria [40], major or minor bleeding occurred in 6.5% of the cases in the vorapaxar group compared to 4.0% in the placebo group (HR 1.56; 95% CI 1.32–1.85; $P < 0.001$). Additionally, an increase in intracranial hemorrhage (ICH) in the vorapaxar group (1.1% vs. 0.2%; HR 3.39; 95% CI 1.78–6.45; $P < 0.001$) was observed. Due to these elevated bleeding rates, the data and safety monitoring board (DSMB) of the TRA-CER trial recommended after a safety review on January 8, 2011 that the trial should stopped rather than continued until June 4, 2011 as planned. The protocol-defined target number of primary efficacy endpoints had been reached. Following the recommendation of the DSMB, the study drug was discontinued and the follow-up in the

**Table 1** TRA-CER and TRA 2P-TIMI50: efficacy, bleeding, and net clinical outcome

| Endpoint | Vorapaxar | Placebo | Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| TRA-CER [37] | | | | |
| *n* | 6,473 | 6,471 | | |
| Cardiovascular death, myocardial infarction, stroke, recurrent ischemia with hospitalization or urgent coronary revascularization | 18.5 | 19.9 | 0.92 (0.85–1.01) | 0.07 |
| Cardiovascular death, myocardial infarction or stroke | 14.7 | 16.4 | 0.89 (0.81–0.98) | 0.02 |
| Myocardial infarction | 11.1 | 12.5 | 0.88 (0.79–0.98) | 0.02 |
| Death from any cause | 6.5 | 6.1 | 1.05 (0.90–1.23) | 0.52 |
| GUSTO moderate or severe bleeding | 7.2 | 5.2 | 1.35 (1.16–1.58) | <0.001 |
| TIMI major or minor bleeding | 6.5 | 4.0 | 1.56 (1.32–1.85) | <0.001 |
| Intracranial hemorrhage | 1.1 | 0.2 | 3.39 (1.78–6.45) | <0.001 |
| TRA 2P-TIMI50 [38] | | | | |
| *n* | 13,225 | 13,224 | | |
| Cardiovascular death, myocardial infarction or stroke | 9.3 | 10.5 | 0.87 (0.80–0.94) | <0.001 |
| Cardiovascular death, myocardial infarction, stroke or urgent coronary revascularization | 11.2 | 12.4 | 0.88 (0.82–0.95) | 0.001 |
| Myocardial infarction | 5.2 | 6.1 | 0.83 (0.74–0.93) | 0.001 |
| Death from any cause | 5.0 | 5.3 | 0.95 (0.85–1.07) | 0.41 |
| GUSTO moderate or severe bleeding | 4.2 | 2.5 | 1.66 (1.43–1.93) | <0.001 |
| Intracranial hemorrhage | 1.0 | 0.5 | 1.94 (1.39–2.70) | <0.001 |
| Cardiovascular death, myocardial infarction, stroke or GUSTO moderate or severe bleeding | 11.7 | 12.1 | 0.97 (0.90–1.04) | 0.40 |

Cumulative Kaplan–Meier event rates at 3 years

*GUSTO* Global Utilization of Streptokinase and t-PA for Occluded Coronary Arteries, *n* number of patients, *TIMI* thrombolysis in myocardial infarction, *TRA 2P-TIMI50* Thrombin Receptor Antagonist in Secondary Prevention of atherothrombotic ischemic events, *TRA-CER* Thrombin Receptor Antagonist for Clinical Event Reduction in ACS Trial

TRA-CER trial was terminated. In addition, the DSMB recommended the termination of the study drug in patients with a history of stroke in the TRA-2P trial.

The key secondary endpoint (a composite of death from cardiovascular causes, MI, or stroke) occurred in 822 patients in the vorapaxar group and 910 patients in the placebo group (14.7% vs. 16.4%, respectively; HR 0.89, 95% CI 0.81–0.98; $P = 0.02$) [37]. The reduction in the rate of MI was the main effect observed in the vorapaxar group, compared with the placebo group (11.1% vs. 12.5%; HR 0.88, 95% CI 0.79–0.98; $P = 0.02$) [37]. However, the rates of death from any cause did not vary significantly (6.5% vs. 6.1%; HR 1.05, 95% CI 0.90–1.23; $P = 0.52$).

The authors conclude that in patients with ACS, the addition of vorapaxar to standard therapy did not significantly reduce the primary composite endpoint but significantly increased the risk of major bleeding, including ICH [37].

### *TRA 2P-TIMI50*

The TRA 2P-TIMI50 trial evaluated the effect of vorapaxar on patients with a history of atherosclerosis, defined as a spontaneous MI or ischemic stroke within the previous 2 weeks to 12 months or peripheral arterial disease associated with a history of intermittent claudication in conjunction with either an ankle brachial index of less than 0.85 or previous revascularization for limb ischemia [38, 41]. In this study 13,225 patients were randomly assigned to receive vorapaxar (2.5 mg daily) and 13,224 patients to receive placebo. The median follow-up time was 30 months. As mentioned earlier, the DSMB recommended discontinuing the study treatment in patients with a history of stroke due to an increased risk of ICH in January 2011. Initially, the primary efficacy endpoint consisted of the composite of cardiovascular death, MI, stroke, or recurrent ischemia leading to urgent coronary revascularization. The secondary endpoint was defined as the composite of cardiovascular death, MI, or stroke. However, due to the results of the TRA-CER trial, the steering committee amended the main data-analysis plan to reorder the hierarchy of efficacy analyses, defining as the primary endpoint the composite of cardiovascular death, MI, or stroke. At 3 years, the primary endpoint had occurred less frequently in patients receiving vorapaxar compared to patients receiving placebo (9.3% vs. 10.5%; HR 0.87; 95% CI 0.80–0.94; $P < 0.001$). The secondary endpoint occurred in 11.2% of the patients in the vorapaxar group and 12.4% in the placebo group (HR 0.88; 95% CI 0.82–0.95; $P = 0.001$). In contrast, bleeding complications were increased in patients receiving vorapaxar. Moderate and severe GUSTO bleedings occurred in 4.2% in the vorapaxar group and in 2.5% in the placebo group (HR 1.66; 95% CI 1.43–1.93; $P < 0.001$) [38]. ICH occurred in significantly more patients in the vorapaxar group than in the placebo group (1.0% vs. 0.5%; HR 1.94; 95% CI 1.39–2.70; $P < 0.001$). Whereas no significant difference was observed in net clinical outcome, defined as the composite of cardiovascular death, MI, stroke, or GUSTO moderate or severe bleeding (11.7% in the vorapaxar group and 12.1% in the placebo group; HR 0.97; 95% CI 0.90–1.04; $P = 0.40$) [38].

Taking these data together, looking at the total patient populations vorapaxar reduces the rate of cardiovascular death, MI, or stroke in patients with a history of atherothrombosis who were receiving standard therapy at the cost of increased bleeding, including ICH [38]. To identify patients in which the benefit-risk ratio can be optimized prespecified subanalysis

were performed. In the subgroup of patients with a qualifying MI within the previous 2 weeks to 12 months (8,898 patients receiving vorapaxar and 8,881 receiving placebo) the primary endpoint occurred less frequently in vorapaxar-treated patients than in placebo-treated patients (8.1% vs. 9.7% in the placebo group; HR 0.80, 95% CI 0.72–0.89; $P < 0.0001$) [42]. Conversely, GUSTO moderate or severe bleeding occurred more frequently in the vorapaxar group than in the placebo group (3.4% vs. 2.1%, respectively; HR 1.61, 95% CI 1.31–1.97; $P < 0.0001$). Moreover, a numerical increase in ICH in the vorapaxar group compared to the placebo group was observed (0.6% vs. 0.4%, respectively; $P = 0.076$) [42].

In another subanalysis including the 3,787 patients with peripheral arterial disease, hospitalizations for acute limb ischemia (2.3% vs. 3.9%; HR 0.58; 95% CI 0.39–0.86; $P = 0.006$) and peripheral arterial revascularization (18.4% vs. 22.2%; HR 0.84; 95% CI 0.73–0.97; $P = 0.017$) were lower in the vorapaxar group. Nonetheless, moderate or severe bleeding was increased with vorapaxar (7.4% vs. 4.5%; HR 1.62; 95% CI 1.21–2.18; $P = 0.001$) including ICH (0.9% vs. 0.4%; HR 2.03; 95% CI 0.82–5.02; $P = 0.13$) [43].

Taken together, vorapaxar in addition to standard treatment may be beneficial in the secondary prevention of patients with established atherosclerosis who have a history of MI [44]. For patients with peripheral arterial disease, vorapaxar might be an option to reduce limb ischemia at the risk of increased bleeding.

### New Experimental Par-1 Inhibitors

There are several new experimental PAR-1 inhibitors with different pharmacodynamic profiles and slightly different mechanisms of action, which are currently in preclinical trials [45]. To date, PZ-128 is the furthest along in preclinical trials [46].

## CURRENT OPINION

Although antiplatelet agents such as ASA and P2Y12 antagonists are well established for patients with atherothrombotic complications, the risk of thrombotic and ischemic events still remains considerably high. A suboptimal inhibition of platelet aggregation might explain the residual mortality and underscores the need for novel antiplatelet agents to optimize the balance between antithrombotic efficacy and bleeding risk. Inhibition of additional pathways not affected by ASA or P2Y12 antagonists could offer more effective inhibition of platelet aggregation and avoid platelet-mediated thrombosis. A promising candidate is the PAR-1 receptor, which is activated by thrombin and represents a validated therapeutic target mediating thrombosis without being critical for hemostasis in preclinical models. Vorapaxar and atopaxar are new PAR-1 receptor antagonists tested in clinical trials.

Atopaxar, although well tolerated in initial clinical trials, was accompanied by a higher incidence of safety endpoints, such as QTc prolongations. Therefore, in the presence of a lack of convincing dose-related trend for efficacy its further clinical development is currently halted.

Vorapaxar has passed a clinical phase III program and demonstrated in the TRA-CER study that triple antiplatelet therapy including aspirin, clopidogrel, and vorapaxar is accompanied by increased bleeding rates without a significant benefit in terms of

ischemic events. However, specific subgroups, such as patients with previous MI or peripheral artery disease, may still take advantage of additional inhibition of the PAR-1 receptor.

In a recently published meta-analysis on PAR-1 antagonists, Chatterjee et al. [47] found that PAR-1 antagonists in addition to standard medical therapy may reduce the risk of cardiovascular mortality and recurrent MI but also enhances bleeding.

Until now no clinical approval has been granted for PAR-1 antagonists. The future of this novel class of antithrombotic drugs will depend on the identification of patient groups in which the risk–benefit ratio is favorable. Moreover, it is not known how PAR-1 blockers interfere with the new P2Y12 antagonists, prasugrel and ticagrelor.

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