Vorapaxar expands antiplatelet options
Which patients may benefit from thrombin receptor antagonism?

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Vorapaxar, antiplatelet therapy, atherothrombosis

Summary
Vorapaxar is the first substance of a new class of antiplatelet drugs that has been tested in large clinical trials. The protease-activated receptor 1 (PAR-1) antagonist inhibits thrombin-induced platelet activation to prevent atherothrombosis. In the phase 3 trials TRACER (acute coronary syndrome) and TRA 2P-TIMI 50 (stable atherosclerosis) reducing ischemic events with vorapaxar came at the cost of bleeding.

TRACER compared vorapaxar to placebo in 12 944 patients who had non-ST-segment elevation acute coronary syndromes on top of contemporary treatment including dual antiplatelet therapy (aspirin and clopidogrel). Vorapaxar reduced ischemic events and increased bleeding both significantly. Recruitment of patients with prior stroke was stopped early. Net clinical outcome and subgroup analyses suggested that vorapaxar could be beneficial for patients with prior myocardial infarction – but no history of stroke.

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Vorapaxar erweitert die Möglichkeiten der Plättchenhemmung – Welche Patienten könnten von Thrombinrezeptor-Antagonisten profitieren?
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Coronary artery disease (CAD) is still a global killer and new treatment options are needed.

The critical event in CAD is atherothrombotic occlusion of a coronary artery after plaque rupture, which leads to acute coronary syndrome (ACS) and, if untreated, to the death of patients with unstable CAD (1).

Dual antiplatelet therapy (DAT) with an adenosine diphosphate (ADP) inhibitor in addition to lifelong administration of acetylsalicylic acid (ASA, aspirin) has become the guideline-recommended standard of care medical treatment for patients with ACS (2–4). Currently used ADP inhibitors block the P2Y₁₂ receptor on the platelet surface. The first-line P2Y₁₂ inhibitors for most ACS patients according to European guidelines are

- the cyclopentyl-triazolo-pyrimidine ticagrelor and
- the thienopyridine prasugrel, while
- clopidogrel remains an alternative.

American guidelines favour clopidogrel for ACS patients in general but consider all
Platelets drive thrombus formation in acute coronary syndrome and are the primary therapeutic target. A near-occlusive intracoronary plaque creates blood flow perturbations, inducing formation of discoid platelet aggregates in a von Willebrand factor (VWF)-dependent manner. Once a plaque ruptures or a stent is implanted, collagen from the extracellular matrix is exposed and binds unfolded plasma VWF. Circulating platelets adhere to collagen-bound VWF and get activated by binding to collagen, involving phosphodiesterase (PDE) activation. Activated platelets release the depicted autocrine agonists and promote the formation of thrombin, initiating a second wave of platelet activation. Stable platelet aggregation via activated glycoprotein (GP) IIb/IIIa requires adenosine diphosphate (ADP) binding to P2Y12, receptor. ASA: acetylsalicylic acid; 5HT2A: serotonin receptor; TP: thromboxane A2 receptor; see (11) for review.

Platelet activation in CAD

Coronary artery thrombus formation is primarily driven by platelets and coronary thrombi are rich in platelets and fibrin (8). Initially, circulating platelets adhere to the site of plaque rupture (or stent implantation), become activated, and secrete soluble agonists (9, 10). Only if these autocrine agonists – most notably ADP – amplify activation, platelets then recruit other platelets and promote thrombus growth and stabilization. These processes are the targets of antiplatelet therapy. Several pathways are investigated in order to expand the currently approved antiplatelet options with ASA, ADP antagonists, and glycoprotein (GP) Ib/IIa inhibitors (Fig. 1) (11–13).

Mechanistically, the exposed extracellular matrix protein collagen first induces platelet tethering, adhesion, and activation, followed by tissue factor-driven coagulation in flow niches downstream of platelet aggregates (14). Platelet GPIbα binding to collagen-bound von Willebrand factor (VWF) constitutes the primary adhesion mechanism for platelets under arterial shear conditions (10, 15). Subsequent binding of GPVI to collagen then initiates platelet activation (16). Activated platelets release serotonin, ADP, and thromboxane A2 and promote the formation of thrombin (factor IIa) as mediators of a second wave of platelet activation, i.e. an amplification of activation. Amplified platelet activation finally leads to the sustained activation and conformational change of the cell-adhesion molecule integrin αIIbβ3 (GPIIb/IIIa). Activated GPIIb/IIIa is the key molecule for platelet-platelet binding (via fibrinogen, VWF, and fibronectin) and stabilization of platelet aggregates (9).

At sites of high shear stress and blood flow perturbation, discoid, i.e. resting platelets can also form tethers and aggregate loosely (17, 18). This process is VWF/L50480 binds to receptors on the platelet surface, triggering platelet activation and aggregation.

Fig. 1 Platelets drive thrombus formation in acute coronary syndrome and are the primary therapeutic target. A near-occlusive intracoronary plaque creates blood flow perturbations, inducing formation of discoid platelet aggregates in a von Willebrand factor (VWF)-dependent manner. Once a plaque ruptures or a stent is implanted, collagen from the extracellular matrix is exposed and binds unfolded plasma VWF. Circulating platelets adhere to collagen-bound VWF and get activated by binding to collagen, involving phosphodiesterase (PDE) activation. Activated platelets release the depicted autocrine agonists and promote the formation of thrombin, initiating a second wave of platelet activation. Stable platelet aggregation via activated glycoprotein (GP) IIb/IIIa requires adenosine diphosphate (ADP) binding to P2Y12, receptor. ASA: acetylsalicylic acid; 5HT2A: serotonin receptor; TP: thromboxane A2 receptor; see (11) for review.

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three substances as equal after percutaneous coronary intervention (PCI) in ACS (2–4).

PCI is the key interventional treatment in ACS (ACS comprising the entities ST-elevation myocardial infarction – STEMI, Non-ST-elevation myocardial infarction – NSTEMI, and unstable angina – UA) and the majority of patients require implantation of a drug-eluting stent (DES) during PCI (2–4). Defining the optimal duration of DAT after stent implantation is not trivial. Especially ACS patients who received an bare-metal stent (BMS) and exposed stent struts can activate platelets resulting in stent thrombosis (5).

Novel antiplatelet strategies are under investigation to improve CAD patient care. The thrombin receptor antagonist vorapaxar (SCH 530348, Merck/MSD) was compared to placebo on top of DAT for non-ST-elevation ACS patients in a multinational, double-blind, randomized study: the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial (6). Vorapaxar was also tested in patients with stable atherosclerotic disease on top of standard of care treatment: the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events (TRA2P)-Thrombolysis in Myocardial Infarction (TIMI) 30 trial randomized 26,449 patients who had a history of myocardial infarction, ischaemic stroke, or peripheral arterial disease to vorapaxar or placebo for a median of 30 months (7).
Intracellular signaling in thrombin-induced platelet activation

Collagen- as well as thrombin-induced platelet activation involves intracellular signaling via two synergistic, but independent pathways: one pathway signals via Ca\(^{2+}\)- and diacylglycerol-regulated guanine nucleotide exchange factor I (CalDAG-GEFI) and a parallel pathway involves protein kinase C (PKC) activation (19–22). Orchestration of these pathways requires crosstalk between the small GTPases Rac1 and Rap1 (23). CalDAG-GEFI senses intracellular Ca\(^{2+}\) liberation and translates this signal into activation of Rap1. PKC activation induces dense and alpha granule release, initiating the second wave activation of Rap1 by ADP binding to the P2Y\(_{12}\) receptor. If P2Y\(_{12}\) is completely blocked, GPIIb/IIIa activation relies solely on signaling through CalDAG-GEFI – which is reversible and insufficient for stable thrombus formation under arterial flow (19). Therefore, sustained activation of GPIIb/IIIa requires PKC-mediated granule release and the subsequent feedback via ADP binding to P2Y\(_{12}\) receptors (24).

Thrombin receptors

The serine protease thrombin activates its receptors indirectly by enzymatic cleavage of a silencing domain, which allows subsequent binding of its unmasked ligand site to the receptor body (autoactivation) (Fig. 2) (25, 26). Human platelets express the Gq protein-coupled protease-activated receptors (PAR)-1 and PAR-4 (murine platelets express PAR-3 and PAR-4). It was understood around the turn of the millennium that PAR-mediated platelet activation by thrombin – in particular via PAR-1 in human – is a central feature of haemostasis (27, 28). PAR-1 has since become a target for antiplatelet therapy development (29–32).

Interestingly, PAR-1 can be activated by 100-fold lower concentrations of thrombin than PAR-4 and is hence considered a more sensitive – albeit weaker – mediator of platelet activation (33, 34). PAR-1 signaling via Ca\(^{2+}\) and CalDAG-GEFI is transient and unable to induce sustained GPIIb/IIIa activation unless amplified by the ADP-feedback via the Gi-coupled P2Y\(_{12}\) receptor and PKC activation in the parallel pathway. One rationale for investigating PAR-1 antagonism was the hope that atherothrombotic events could be prevented without interfering with the haemostatic properties of thrombin, because high thrombin concentrations could still induce strong PAR-4 signaling (33). Moreover, it was reasoned that bleeding complications might not increase with concomitant P2Y\(_{12}\) inhibition because PAR-4 signaling after strong thrombin-induced aggregation was effectively inhibited (30). Several other preclinical and early clinical studies confirmed these findings (33). In two phase 2 trials with patients undergoing elective PCI and with patients with Non-ST-elevation ACS receiving DAT, vorapaxar did not increase the risk of bleeding significantly as compared to placebo (31, 32). Moreover, vorapaxar treatment was associated with a trend toward fewer myocardial infarctions in these studies.

Another PAR-1 antagonist, atopaxar (E5555) has been tested in two pase 2 clinical studies, the Lessons From Antagonizing the Cellular Effects of Thrombin-Acute Coronary Syndromes (LANCELOT-ACS) and ─Coronary Artery Disease (LANCELLOT-CAD) trials (35, 36). Atopaxar increased bleeding numerically but not significantly in patients with ACS or advanced but stable CAD. Atopaxar was generally considered safe enough to proceed to phase 3 clinical testing, but to date, there is no phase 3 trial investigating atopaxar efficacy and safety registered at clinicaltrials.gov.

Phase 3 trials with vorapaxar

Vorapaxar, a synthetic tricyclic 3-phenylpyridine analog of himbacine, is an orally administered, rapidly absorbed, high-affinity reversible PAR-1 blocker. Based on the preclinical and clinical safety data, two phase 3 trials were initiated with vorapaxar, TRACER (37) and TRA 2P-TIMI 50 (38).
TRACER did not achieve the primary end point

TRACER compared vorapaxar (2.5 mg daily for at least 1 year after a 40 mg loading dose) to placebo in patients with non-ST-elevation ACS (6, 37). To be enrolled, patients had to present with acute symptoms of coronary ischaemia and either elevation of cardiac necrosis markers (troponin I/T or creatine kinase MB) or significant ST segment changes (but not sustained ST elevation). A total of 6471 patients received placebo and 6473 received vorapaxar. More than 90% of patients were treated with DAT (with both, ASA and a P2Y12 blocker (almost exclusively clopidogrel). Approximately 21% of patients received a GPIIb/IIIa antagonist. PCI was performed in 57% of patients receiving placebo and 58% of patients receiving vorapaxar. Coronary artery bypass grafting (CABG) was performed in 10% of all subjects.

The primary end point (a composite of cardiovascular death, myocardial infarction, stroke, recurrent ischaemia with rehospitalization, or urgent coronary revascularization) occurred in 19.9% of patients receiving placebo and 18.5% of patients receiving vorapaxar (Kaplan-Meier event rates at 2 years) (Tab. 1). There was hence no significant difference between the study groups with respect to the primary end point (p = 0.07).

Follow-up in TRACER was terminated early because of excessive bleeding

Bleeding complications were significantly more frequent in patients receiving vorapaxar. Moderate or severe bleeding according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) classification occurred in 5.2% of patients receiving placebo and 7.2% of patients receiving vorapaxar (p < 0.001) (Tab. 1). The Kaplan-Meier curves deviated from each other early in the first month and showed constant separation throughout the 2-year follow-up period. Similar results were seen for clinically significant bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) classification. Intracranial haemorrhage increased more than three-fold.

Due to this increase in vorapaxar-associated bleeding, follow-up was stopped 5 months early (after a safety review in January 2011). Median follow-up was therefore slightly shorter than envisioned (302 days) but the predefined number of primary and major secondary end points was accrued. Following the data and safety monitoring board’s recommendations, vorapaxar was also terminated in patients with prior stroke in TRA 2P-TIMI 50.

Secondary end point and subgroup analysis of TRACER

The key secondary end point (a composite of cardiovascular death, myocardial infarction, or stroke) occurred less frequently in vorapaxar-treated patients (relative risk reduction 11%, p = 0.02) (Tab. 1). According to a prespecified data analysis plan, this risk reduction in the key secondary end point did not translate into declaration of superiority because superiority with respect to the primary end point was not achieved. The risk reduction was mainly driven by a decrease in myocardial infarction in vorapaxar-treated patients. Death from any cause was not reduced. There was also no significant effect on stent thrombosis.

Results on the primary and key secondary efficacy end points were largely consistent across subgroups. Subgroup analysis showed a trend toward better efficacy with vorapaxar in patients who were not treated with a P2Y12 inhibitor at randomization while bleeding was not increased in these patients.

TRA 2P-TIMI 50 met the primary end point

TRA 2P-TIMI 50 was designed to examine the effects of vorapaxar (2.5 mg daily) in stable patients with a history of myocardial infarction, ischaemic stroke, or peripheral arterial disease (7, 38). In this very large trial, vorapaxar was administered to 13,224 patients with severe chronic, but stable atherosclerotic vascular disease on top of standard therapy and compared to placebo administered to an identical number of patients. The qualifying disease was defined as myocardial infarction or stroke within 3 weeks to 12 months before study inclusion or peripheral arterial disease either after revascularization or with an ankle-brachial index of less than 0.85. Almost all patients with prior myocardial infarction (67% of all included subjects had a history of myocardial infarction) were treated with ASA and more than 77% received DAT with a thienopyridine. The ADP receptor antagonist in TRA 2P-TIMI 50 was almost exclusively clopidogrel, only 0.7% of patients received prasugrel, and ticagrelor was not administered at all. More than 80% of patients with qualifying stroke (approximately 18% of all subjects had a history of stroke) received ASA and 24% a thienopyridine. Approximately 14% of all examined subjects had peripheral arterial disease and among these patients, about 88% were treated with ASA and 37% with a thienopyridine. No subject was reported to have received a GPIIb/IIIa antagonist in TRA 2P-TIMI 50. The original publications do not provide the numbers of patients undergoing PCI, but a footnote denotes that 201 patients in the placebo group and 175 patients in the vorapaxar group underwent CABG (7, 38).

The primary end point was a composite of cardiovascular death, myocardial infarction, and stroke. Vorapaxar significantly reduced the frequency of this end point from 10.5% of patients receiving placebo to 9.3% of patients receiving vorapaxar (3-year Kaplan-Meier event rates, relative risk reduction 13%, p < 0.001) (Tab. 1).

Bleeding complications more frequent with vorapaxar in TRA 2P-TIMI 50

Bleeding end points occurred more frequently with vorapaxar than with placebo. Moderate or severe GUSTO bleeding increased from 2.5% of patients receiving placebo to 4.2% of patients receiving vorapaxar (p < 0.001) (Tab. 1). The Kaplan-Meier curves deviated from each other early in the first month and showed constantly increasing separation throughout
Intracranial haemorrhage increased two-fold with vorapaxar, while fatal bleeding was rare without any significant difference between the groups. Following the data and safety monitoring board’s recommendation, vorapaxar was stopped in all patients with prior stroke or new stroke during the trial in January 2011. Indeed, bleeding was notably increased in patients with previous stroke (GUSTO moderate or severe bleeding hazard ratio 1.74, 95% confidence interval (CI) 1.26–2.39, p < 0.001) with an exceeding risk for intracranial haemorrhage (hazard ratio 2.55, 95% CI 1.52–4.28, p < 0.001). Bleeding was also especially increased in women, in patients with low body weight (<60 kg), and patients enrolled in North America, although none of these factors tested positive for a significant interaction.

Interestingly, consistent with platelet activation biology, concomitant treatment with a P2Y_{12} blocker did not further increase bleeding. On the contrary, ASA treatment strongly increased bleeding complications while ASA-naive patients showed no increased risk of bleeding (GUSTO moderate or severe bleeding hazard ratio in 1,703 ASA-naive patients 1.03, 95% CI 0.61–1.75).

### Secondary end point, subgroup, and net clinical benefit analysis in TRA 2P-TIMI 50

The key secondary end point (a composite of cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization) was also reduced by vorapaxar in the overall study population (Tab. 1). Death from any cause was not reduced significantly, but the trend was reversed as compared to TRACER. TRA 2P-TIMI did not report data on stent thrombosis. The effect on the primary end point was consistent among subgroups with the exception of patients with low body weight (<60 kg), in whom vorapaxar did not reduce ischaemic events (statistically significant interaction).

The design of TRA 2P-TIMI 50 allowed the pre-defined analysis of large subgroups, notably the three atherosclerotic patient groups. The close to 18,000 patients with qualifying myocardial infarction had a particularly large benefit: the primary end point was reduced by 20% (relative risk reduction, 95% CI 0.72–0.89, p < 0.001). GUSTO and TIMI bleeding remained sig-

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<th>vorapaxar</th>
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* composite of cardiovascular death, myocardial infarction, stroke, recurrent ischaemia with rehospitalization, or urgent coronary revascularization; ** composite of cardiovascular death, myocardial infarction, or stroke; # composite of cardiovascular death, myocardial infarction, or stroke; ## composite of cardiovascular death, myocardial infarction, stroke, or urgent coronary revascularization

Data are presented as cumulative Kaplan-Meier event rates unless otherwise indicated.

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The 3-year follow-up. Intracranial haemorrhage increased two-fold with vorapaxar, while fatal bleeding was rare without any significant difference between the groups.
significantly increased, but intracranial haemorrhage was not significantly increased in this subgroup (p = 0.076).

Net clinical outcome analysis yielded results in favor of vorapaxar particularly in patients with no history of stroke. In a composite of all-cause death, myocardial infarction, stroke, and GUSTO severe bleeding, vorapaxar was associated with a relative risk reduction of 11% in these patients (95% CI 0.82–0.97, p = 0.01). The primary end point was reduced by 16% (relative risk reduction) by vorapaxar in patients with no history of stroke (9.6% with placebo and 8.3% with vorapaxar, 95% CI 0.76–0.93, p < 0.001). Similarly to the overall study population these patients also showed increased GUSTO and TIMI bleeding rates, but notably, intracranial haemorrhage was only slightly increased (0.4% with placebo and 0.6% with vorapaxar, hazard ratio 1.55, 95% CI 1.00–2.41, p = 0.049).

Net clinical outcome was further improved in patients with no history of stroke or TIA and with a body weight above 60 kg (16% relative risk reduction in the combination of cardiovascular death, myocardial infarction, stroke, and GUSTO severe bleeding, p < 0.001). These data translated into six fewer cardiovascular deaths at the cost of two intracranial haemorrhages for every 1000 patients treated with vorapaxar in calculations that were not included in the original publication (39).

Discussion

PAR-1 inhibition with vorapaxar on top of contemporary treatment (including DAT with ASA and a P2Y12 antagonist) for patients with non-ST-elevation ACS increased bleeding but did not significantly improve ischaemic outcome. This result of the well-designed and well-powered TRACER trial shows impressively that long-term triple antiplatelet therapy with inhibition of cyclooxygenase, P2Y12, and PAR-1 offers no net clinical benefit for patients with NSTEMI or UA. If a different primary end point comprising cardiovascular death, myocardial infarction, and stroke (such as in the key secondary end point) had been chosen, superiority of vorapaxar over placebo may have been declared. Still, even in that case, bleeding complications would be unacceptably high with an event rate for intracranial haemorrhage of 1.1%.

Therefore, DAT with ASA and a P2Y12 antagonist is an effective strategy for silencing platelet reactivity in non-ST-elevation ACS, that to date cannot be significantly improved by even stronger platelet inhibition. As was seen with oral GPIIb/IIIa antagonists, very strong platelet inhibition increases bleeding to a point where it outweighs any positive effect on ischaemic events (40). Adding a plasmatic anticoagulant at a low-dose to DAT however, has recently proven beneficial in ACS patients. In the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome—Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) trial rivaroxaban (2.5 mg twice daily) increased bleeding, too, but it improved ischaemic outcome significantly (41). This translated into a significant reduction of death from any cause from 4.5% events in patients receiving placebo to 2.9% events in patients receiving rivaroxaban (hazard ratio 0.83, 95% CI 0.72–0.97, p = 0.02) – while the event rate for intracranial haemorrhage did not exceed 0.4% with rivaroxaban (0.2% with placebo, p = 0.04).

Whether triple antiplatelet therapy with vorapaxar may improve the management of patients with STEMI remains to be shown. No trial investigating the effects of a PAR-1 inhibitor in patients with STEMI is currently registered at clinicaltrials.gov. Moreover, the optimal duration of DAT after PCI is not yet known and much less is known about the optimal duration of triple or dual antiplatelet therapy with a PAR-1 antagonist. The median follow-up in TRACER was 502 days and most patients received vorapaxar for much longer than 1 year. Although deviation of the Kaplan-Meier curves was evident within the first month, it is possible that shorter treatment courses allow fine-tuning of patient management after PCI.

While TRACER likely put an end to the concept of triple antiplatelet therapy with PAR-1 blockers in ACS, TRA 2P-TIMI 50 may have identified patient groups that benefit from PAR-1 blockade. Thanks to its special design, TRA 2P-TIMI 50 highlighted the exceeding risk of intracranial haemorrhage in patients with prior stroke. Patients with no history of stroke still had an increased risk of intracranial haemorrhage, but it was in a range that appears acceptable in the light of an improved net clinical outcome (0.6% with vorapaxar, compared to 0.4% with placebo). Patients with prior myocardial infarction in particular seemed to benefit from treatment with vorapaxar, which was associated with an up to 20% relative risk reduction of ischaemic events in these patients. It is unknown however, how vorapaxar would perform in addition to ticagrelor or prasugrel, because almost all patients evaluated in the vorapaxar trials receiving an APD blocker were treated with clopidogrel.

Conclusion

Vorapaxar in addition to standard treatment appears to be beneficial in the secondary prevention of patients with stable CAD who experienced myocardial infarction in the past. Certainly, patients with prior stroke should not be treated with vorapaxar. Caution is also warranted in other patient groups with increased risk for bleeding, such as patients with:
- low body weight or
- advanced age.

It is not clear however, whether these data will be sufficient for approval of vorapaxar.

Acknowledgement

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Conflict of interest

D.D. was investigator in the TRACER Ocular Safety substudy. C.B. received speaker’s honoraries from Merck, Astra-Zeneca, and Sanofi.

D. Duerschmied; C. Bode: Vorapaxar
References


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