Vorapaxar

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ABSTRACT

Antiplatelet drugs are the cornerstone of treatment for patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention. Clopidogrel and aspirin improve long-term vascular clinical outcomes in these patients and have become a standard of care. However, many patients still experience ischemic/thrombotic events, and it appears that insufficient response to both aspirin and clopidogrel contribute to this failure. Newer P2Y12 receptor blocker therapy resulted in only an approximately 2% reduction in absolute risk compared with clopidogrel. This indicates that residual ischemic events are mediated by other pathways that are unblocked by current dual antiplatelet therapy. Thrombin is the most potent platelet agonist (over 1000 times more than adenosine diphosphate on a molar basis). Thrombin-mediated platelet activation depends on protease-activated receptor (PAR) binding. PAR-1 is the main receptor for thrombin on human platelets; PAR-4 may contribute to platelet activation at much higher concentrations of thrombin. Inhibition of the PAR-1 may provide additional benefits over the standard dual antiplatelet therapy in attenuating ischemic event in patients with ACS. Vorapaxar is a new highly selective oral PAR-1 antagonist that inhibits thrombin-induced platelet activation. We review the pharmacokinetic, pharmacodynamic and clinical profile of vorapaxar. Although preliminary data indicated that vorapaxar may have the potential to improve ischemic outcomes without significantly increasing bleeding, more recent larger clinical trials seem to be less optimistic about both its effectiveness and safety. At this time, the role of vorapaxar in the settings of atherothrombotic disorders is not clear. Although it may be associated with less bleeding than P2Y12 receptor blockers, its antithrombotic effectiveness and side effects are major concerns.

Introduction

In the last decade, the antiplatelet inhibitors of P2Y12 receptor for adenosin-diphosphate (ADP) (ticagrelor and the thienopyridines ticlopidine, clopidogrel and prasugrel), used in combination with aspirin, have been established as the backbone of the anti-thrombotic treatment of acute coronary syndromes (ACS).[1,2] Compared to aspirin alone, the association of aspirin and clopidogrel reduces the frequency of ischemic complications in patients with non-ST ACS by 20%[1] and by 25-30% the frequency of acute cardiac events (acute myocardial infarction, urgent revascularization and cardiac death) at 30 days[3] and 12 months[4] after placement of a coronary stent. Furthermore, it reduces by 20% the risk of the composite end point of death, reinfarction and recurrent myocardial ischemia in patients with acute myocardial infarction (AMI) treated with thrombolysis, and by 7% the overall mortality of patients with AMI, even in old age (75-100 years).[5]

However, many patients treated with this dual antiplatelet regimen still develop thrombotic complications (early recurrence of myocardial ischemia, restenosis after coronary angioplasty, stent thrombosis, etc.), and many of them show a suboptimal response to aspirin (up to 70%)[6] and/or to thienopyridines[7-9] in laboratory platelet aggregation tests (*drug resistance*). The causes of failure of antithrombotic therapy have been the subject of intensive investigation in recent years and have mostly been attributed to pharmacokinetic and pharmacodynamic features in part related to individual factors that cannot be controlled. For example, the latency of the pharmacological effect of thienopyridines (on average more than 4 h to obtain the maximum platelet inhibition), has proved to be a limiting factor for the therapeutic efficacy in ACS (a clinical scenario in which an early and virtually complete inhibition of platelet activity is of utmost importance), and led to the development of treatment regimens based on starting *load doses* much higher than the ordinary *maintenance*

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doses, and to recommend, when possible, starting treatment well before the time when the peak of the pharmacological effect is required (*e.g.* hours or days before coronary angioplasty). Moreover, all the thienopyridines currently in use are themselves devoid of significant biological activity and require a preliminary biotransformation in the body into active metabolites to be able to exercise their pharmacological effect. The activation of clopidogrel and ticlopidine occurs almost entirely in the liver, primarily by cytochrome (CYP) 2C19, which form 2-oxo-derivatives, further converted into open-ring thiol compounds which are wholly responsible for the antiplatelet effect.[10] In subjects with defective CYP 2C19 phenotypes, a reduced production of active derivatives favors the alternative metabolism of the two compounds by carboxyesterase 1, mitigating the antiplatelet effect. The wide spread in every ethnic group of defective alleles of the *CYP2C19* gene (20-30% of Caucasians, 30-45% of African-Americans, 50-65% of Asians) results in a high prevalence in the population of individuals with enzyme functionality 25-35% lower than normal (*CYP2C19* phenotypes *slow* or *intermediate*). These patients have a reduced ability to activate clopidogrel (plasma exposure to the active metabolite is on average lower by 32.4% compared to subjects with the *regular* phenotype) and a significantly lower antiplatelet effect.[11] Furthermore, in clinical practice, exogenous factors may affect the activity of the thienopyridines, in addition to the genetic background. For example, subjects with *regular* CYP2C19 phenotype may develop an acquired resistance to clopidogrel in case of concomitant exposure to strong exogenous inhibitors of CYP 2C19 (*e.g.* drugs).[12] After oral intake, the newer thienopyridine prasugrel is almost fully converted by the intestinal wall in the corresponding active open-ring metabolite (R-138 727) through a non-CYP2C19-dependent transformation pathway.[13] However, hopes related to this new compound have been only partially fulfilled since in comparative clinical studies the drug has only shown a moderate superiority over clopidogrel in terms of clinical efficacy (cardiovascular death, AMI, revascularization and stent thrombosis), in the face of a higher incidence of serious or fatal bleeding (especially in subjects aged >75 years, body weight <60 kg or with a history of stroke or transitory ischemic attack) and no significant difference on overall mortality.

Compared to thienopyridines, ticagrelor does not require metabolic activation to exert its antiaggregatory effect. Thus, no latency of action or drug resistance (congenital or acquired) based on this mechanism can be anticipated.[14] In fact, in the *Platelet Inhibition and Patient Outcomes* (PLATO) study (18,624 patients with ACS with or without ST segment elevation),[15] the administration of ticagrelor for 12 months reduced the rate of the composite primary end point of cardiovascular death/AMI/stroke by 16% compared to clopidogrel, and the frequency of various secondary clinical outcomes, such as AMI, stent thrombosis, and death from any cause. This was in spite of the fact that, in the subgroup analysis, major bleeding events (not related to coronary artery bypass) were more frequent (4.5% *vs* 3.8% with clopidogrel, P=0.03).

Ticagrelor summarizes many of the pharmacological aspects that, in light of the scientific evidence accumulated over the past ten years, could be considered ideal for the treatment of ACS: i) the possibility of oral administration; ii) small latency of effect (almost maximal within 2 h); iii) deep inhibition of platelet ADP-mediated aggregation; iv) uniform effect in the population (almost 0 drug resistance); v) short-term antiplatelet effect. Nevertheless, among ACS patients treated with ticagrelor and optimal medical therapy (including aspirin, anticoagulants and GP-IIb/IIIa receptor inhibitors), 5.8% still develop an AMI, 4% die from vascular causes and 1.3% develops stent thrombosis.[15] It, therefore, seems likely that at least a part of the residual thrombotic risk is not inherent to the molecule used, but depends on the antithrombotic therapeutic strategy as originally conceived. In fact, platelet activation can be triggered and enhanced by the action of multiple factors released from the same adherent platelets (serotonin, epinephrine, ADP, thromboxane A2, thrombin) from the damaged endothelium (von Willebrand factor, collagen) and by the activated clotting factors (mainly thrombin). Acting on specific G-protein coupled receptors on the platelet surface,[16] all of these signals stimulate the production and release of inflammatory (P-selectin,[17] sCD40L[18]), prothrombotic (ADP, TXA2) and procoagulant (thrombin, etc.) molecules, which promote a change in platelet shape and in the exposure of the GPIIb/IIIa receptor in its active form.[19] The GPIIb/IIIa receptors of the activated platelets bind to fibrinogen (and von Willebrand factor) which *bridge* them together leading to the physical phenomenon of platelet aggregation.[20,21]

Antiplatelet therapies currently used in the ACS based on aspirin and P2Y12 inhibitors conceivably exert only partial inhibitory effects on platelet-mediated thrombosis since they target only two of the many possible signals of platelet activation (the production of TXA2, through the block of cyclooxygenase-1, and the binding of ADP to the P2Y12 receptor, respectively), leaving intact several others. Foremost among these, the thrombin-mediated activation, which is believed to be of central importance, given that thrombin is the most potent known platelet agonist (acting at subnanomolar concentrations,[22,23] against micromolar concentrations required, for example, by ADP) and that, among all the prothrombotic activities exerted by this serine protease, platelet aggregation is the fastest to appear and occurs at the lowest concentration (≈0.5 nMol).

In addition to the pathological thrombosis (formation of white multiple layer occlusive thrombi, rich in platelets), TXA2- and ADP-mediated platelet aggregation contributes to normal hemostasis (formation of monolayer platelet plugs in the seats of vascular damage) since activated platelets provide a substrate of anionic phospholipids (phosphatidylserine) considered essential for the assembly of the tenase and prothrombinase complex that support the clotting cascade and primitively stimulate thrombin generation.[24,25] It is likely that the profound inhibition of these mechanisms by the combined administration of aspirin and a thienopyridine (especially the most powerful, such as prasugrel) contributes substantially to the excess of bleeding complications encountered in clinical practice.

The search for new antiplatelet agents able to complement the antithrombotic effects of the drugs currently in use, with minimal effects on the physiological hemostasis, represents, therefore, the challenge in this research area for the years to come.

Vorapaxar (SCH 530348, Merck & Co., Inc., Whitehouse Station, NJ, USA) is a synthetic 3-fenylpiridine tricyclic molecule structurally derived from the natural compound imbacin (a natural alkaloid isolated from the bark of Australian Magnolia), compared to which, however, it is devoid of antagonistic activity on muscarinic M2 receptors. Vorapaxar is the first representative of a new class of orally active non-peptide platelet inhibitors of low molecular weight. Its mechanism of action [selective inhibition of platelet protease-activated-1 (PAR-1) receptor] differs from that of all drugs currently in use with respect to which it can, therefore, provide synergistic effects.

Mechanism of action

In vivo, vorapaxar behaves as a reversible (competitive), high affinity (IC 8.1 nMol) inhibitor of the PAR-1 receptor,[26] present on platelets, endothelial cells, some epithelial cells, fibroblasts, myocytes, neurons and astrocytes.[27] PAR-1 is an integral membrane protein classified in the family of the protease-activated receptor. Four types of PAR have been identified (PAR-1, -2, -3 and -4), of which three (types 1, 2 and 4) are activated by low concentrations of thrombin (which, therefore, acts as a natural ligand).[28] All the thrombin-sensitive PARs are distributed on endothelial cells, myocytes and astrocytes, while only PAR-1 and PAR-4 are present on platelets, where they mediate aggregation.[29] PAR-1 is considered functionally dominant in this respect, being activated by thrombin concentrations approximately 100 times lower than PAR-4 (50 *vs* 5 pmol nMol). Thrombin binds to PAR-1 via its fibrinogen site which recognizes the extracellular amino-terminal (hirudine-like) domain of the receptor. Once linked, thrombin cleaves the domain between Arg41 and Ser42, removing the extremity.[30] The new NH2-terminal portion (Ser42-Phe-Leu-Leu-Arg-Asn) folds inwards, binds the body of the molecule, and triggers the coupled G proteins (G families α12/13 and αq).[31,32] The activation of the G proteins inhibits platelet adenylate cyclase, leading to a rapid fall in cytoplasmic levels of cAMP, mobilization of calcium ions, and stimulation of CalDAG-GEFI that transiently activates the Rap1 inducing an unstable exposure of the active form of the GPIIb/IIIa fibrinogen receptor on the platelet surface. However, the G protein αq also stimulates protein kinase C (CPK), triggering platelet degranulation (extrusion of ADP-rich dense granules and α granules). The release of ADP stimulates the P2Y12 receptor, transmitting an activation signal to the associated αi/z G protein and to Rap1, which promotes a more stable surface exposure of the active form of GPIIb/IIIa receptor.[33-35] The activation of PAR-1, therefore, allows stable platelet aggregation through a dual chain of intracellular signals (Ca^{++}/CalDAG-GEFI and CPK), and with the crucial contribution of the ADP pathway.

Although, as seen, platelet aggregation plays a central role both in hemostasis and thrombosis, the selective inhibition of the PAR-1 at antithrombotic levels seems to have minimal impact on the efficiency of the clotting cascade, as suggested by some studies conducted *in vivo* and by the absence of any impact on laboratory clotting times (PT, aPTT, ACT).[36] In genetically modified mice that do not express PAR-4 (a receptor functionally similar to the human PAR-1), the juxtamural platelet accumulation immediately after laser injury is indistinguishable from genetically normal mice, while subsequent growth of platelet thrombi was markedly diminished in $Par4^{-/-}$ mice (more than 10 times at the peak of development).[37] These results suggest that platelet activation by thrombin is necessary for normal propagation of a platelet thrombus at a distance from the injured vessel wall (hence for normal thrombus growth), while it is not necessary for initial accumulation of platelets at the vessel wall. This apparent disjunction between antithrombotic and bleeding effects probably depends on the fact that the inhibition by the PAR-1 does not interfere with the mechanisms of platelet aggregation critical for hemostasis (TXA2, ADP, collagen).[36] Moreover, PAR-1-inhibited platelets remain responsive to thrombin, albeit at higher concentrations,[29] through the PAR-4, which may induce aggregation by ADP/P2Y12/G αi/z-independent mechanisms.[38,39]

Pharmacodynamics

As a superselective PAR-1 inhibitor, vorapaxar has shown potent inhibition of platelet aggregation by thrombin and thrombin receptor activating peptide

(TRAP) in pre-clinical functional assays, but was virtually inactive, at clinically relevant concentration, in functional assays with PAR-2, PAR-3, and PAR-4.[26] Furthermore, in assays performed on human platelet-rich plasma from healthy volunteers, vorapaxar inhibits thrombin-induced and TRAP-induced platelet aggregation at very low concentrations (IC50 nMol 47 and 25 nMol, respectively), without interfering with the aggregation induced by ADP, thromboxane A2 mimetic U46619, and collagen[26,40,41] or the coagulation parameters (*i.e.* prothrombin time and activated partial thromboplastin time). The powerful platelet inhibition exhibited by vorapaxar in *in vitro* experiments, in which platelets were exposed to the drug in the laboratory, demonstrates that, contrary to the thienopyridines, it does not require any preliminary biotransformation in the body to exert its pharmacological activity. Single doses of oral 5-40 mg vorapaxar administered to healthy volunteers inhibit TRAP-mediated platelet aggregation (PAI_{TRAP}) by over 90% for more than 72 h.[42] The full inhibitory effect (PAI_{TRAP} >80%) is established very quickly with loading doses of 20 or 40 mg (within 1 h after administration)[43] and more gradually in prolonged therapy with maintenance doses (within one day after the first administration of 5 mg/day; within a week with multiple doses of 1-3 mg/day). The antiplatelet effect of vorapaxar is dose-dependent, with limited inter-individual variability (no drug resistance) and inter-ethnic variability (in Caucasians and Japanese[44]). Two hours after a single loading dose of vorapaxar, PAI_{TRAP} rates of over 80% are found in 43% of patients with 10 mg, 53% with 20 mg, and 96.3% with 40 mg.[45] In prolonged, low-dose, maintenance therapies the antiplatelet effect of vorapaxar remains virtually unaltered over time (after 30-60 days of treatment at 0.5 mg or 2.5 mg/day, PAI_{TRAP} rates >80% were observed in 91% and 100% of cases, respectively), and disappears (PAI_{TRAP} <50%) approximately four weeks after stopping therapy.[41]

Pharmacokinetics

Vorapaxar administered as a bisulfate salt, is rapidly absorbed from the intestine, reaching the maximum plasma concentration (C_{max}) after 1-2 h in healthy volunteers (T_{max}, time to C_{max},).[46] The absolute oral bioavailability (>90% in humans) is not influenced by concomitant intake of food or antacids to a clinically significant extent.[47] Plasma levels are linearly dose-proportional for both single and multiple therapeutic doses. Following oral administration of multiple doses, steady-state plasma concentrations of vorapaxar are achieved after an average of approximately 21 days.[44,47]

Vorapaxar undergoes an extensive oxidative biotransformation by the liver, with production of two major metabolites: M19, a functionally inactive amine metabolite formed via carbamate cleavage mainly by CYP 3A4 (to a lesser extent by CYP 1A1 and 2C19), and M20 (monohydroxy-vorapaxar), produced by CYP 3A4 and CYP 2J2,[48] which has similar pharmacological potency to the parent drug. After a single oral dose, vorapaxar is essentially the only circulating drug-derived component in plasma (≈100%). However, after multiple dose administrations, the active M20 hydroxylated metabolite becomes more relevant, representing approximately 23% of the parent drug.[48] Vorapaxar is slowly eliminated from the body, with a mean terminal phase plasma half-life ($T_{1/2}$) of 129-311 h in patients with ischemic heart disease, and normal renal and hepatic function.[45] The parent drug is not eliminated in urine, and less than 2% of orally administered vorapaxar is eliminated unchanged in the feces. The drug is primarily eliminated as the amine metabolite (M19), with minor amounts of mono- and dihydroxy metabolites and glucuronide and sulfate conjugates.[48]

Renal disease has no clinically relevant effect on the pharmacokinetics profile of vorapaxar or its ability to inhibit TRAP-induced platelet aggregation. In patients with end-stage renal disease on hemodialysis given a single oral 10 mg dose mean vorapaxar oral bioavailability was identical to healthy matched subjects, as well as T_{max} (2 h in both subject groups), and the observed means for elimination $T_{1/2}$ were (186 and 231 h in the patient and control groups).[49]

Similarly, hepatic dysfunction does not alter to a clinically relevant extent the kinetics of either vorapaxar or its monohydroxylated active metabolite. In a study with a single 40 mg oral dose of vorapaxar in 16 patients with hepatic impairment of varying degrees (from mild to severe) and 16 matched healthy subjects, there was no significant difference in mean values for vorapaxar $T_{1/2}$, area under the curve of plasma concentration over time (AUC), and $T_{1/2}$ (T_{max} 206 and 279 ng/mL; AUC 14.2 and 18.2 ng·h/mL, with the lowest values observed in patients with severe liver impairment, and $T_{1/2}$ 298 and 366 h, respectively). Furthermore, no apparent correlation was found between disease severity and vorapaxar or M20 AUC or $T_{1/2}$ values.[50]

Drug interactions

As a substrate of CYP3A4, vorapaxar can give rise to significant interactions with drugs that affect this enzyme system. For example, co-administration of ketoconazole (a potent CYP 3A4 inhibitor) for three weeks produced a 2-fold increase in vorapaxar exposure. Conversely, co-administration with rifampicin (a potent CYP 3A4 inducer) reduces vorapaxar exposure by 50%. Vorapaxar (2.5 mg/day or 40 mg) has no meaningful effect on the pharmacokinetics or pharmacodynamics (prothrombin time) of

warfarin (a CYP2C9 substrate)[51] suggesting that the co-administration of vorapaxar with other CYP2C9/CYP2C19 substrates is unlikely to cause a clinically significant pharmacokinetic drug interaction.

Dosage

Dose-response studies carried out *ex vivo* on platelets obtained from healthy volunteers examined one-time loading doses of 5, 10, 20, and 40 mg and maintenance doses of 0.5, 1.0, and 2.5 mg daily, given in the morning. It was shown that a satisfactory antiplatelet effect (PAI_{TRAP} >80%) after seven days may be obtained in the maximum number of patients with the administration of a loading dose of 40 mg and subsequent maintenance doses of 2.5 mg/day.[41] Furthermore, the 40 mg loading +2.5 mg/day dose maintenance dose was found to effectively inhibit platelets for up to 28 days. These doses were then adopted in most of the phase II and III clinical trials.[45,52]

Depending on the indication, two dosing regimens have been evaluated, with and without a loading dose. For non-ST elevation acute coronary syndrome (NSTE-ACS) patients with planned percutaneous coronary intervention (PCI), as well as those with high-risk features, a loading (40 mg)+maintenance dose (2.5 mg/day), has been shown to be safe and effective.[45,53] In patients with established coronary artery disease, a maintenance dose (2.5 mg/day) with no load has also been shown to be safe and effective for secondary prevention of ischemic events.[54]

Clinical trials

The *Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome* (TRACER) trial,[55] a phase III, prospective, randomized, double-blind, multicenter study, compared vorapaxar to placebo (in addition to standard care) in patients with high-risk non-ST-elevation ACS with acute symptoms of coronary ischemia within the 24 h before hospital presentation. A total of 12,994 high-risk patients were included in the study: age >55 years, previous AMI, PCI or coronary artery bypass grafting surgery (CABG), diabetes or peripheral arterial disease. Patients were randomly assigned in a 1:1 ratio to receive vorapaxar or matching placebo. Vorapaxar was administered at a loading dose of 40 mg immediately after being randomized and at least 1 h before any coronary revascularization procedure, and a daily maintenance dose of 2.5 mg thereafter until the end of the study or for at least one year. Patients were stratified according to the intention to use a glycoprotein IIb/IIIa inhibitor and the intention to use a parenteral direct thrombin inhibitor *versus* other antithrombin agents. Clopidogrel was administered in 91.8% of patients and cardiac catheterization was performed in 88.1% of patients, PCI in 57.8%, and CABG in 10.1%.

The primary efficacy end point was a composite of cardiovascular death, MI, stroke, recurrent ischemia with re-hospitalization, and urgent coronary revascularization. The key secondary end point was a composite of cardiovascular death, MI and stroke. Safety was assessed by a composite of moderate and severe [according to the *Global Use of Strategies to Open Occluded Coronary Arteries* (GUSTO) classification system] and clinically significant (according to the *Thrombolysis in Myocardial Infarction* (TIMI) classification system) bleeding. After a median follow up of 502 days (349-667) the primary end point was seen in 19.9% of patients receiving placebo and 18.5% of patients receiving vorapaxar [Kaplan-Meier event rates at 2 years; hazard ratio (HR) 0.92; 95% confidence interval (CI): 0.85-1.01; P=0.07]. The key secondary end point occurred less frequently in patients treated with vorapaxar (14.7% *vs* 16.4%; HR 0.89; 95% CI: 0.81-0.98; P=0.02). The safety end point occurred in 7.2% of patients receiving placebo and 5.2% of patients receiving placebo (HR 1.35; 95% CI: 1.16-1.58; P=<0.001). Intracranial hemorrhage rates were 1.1% and 0.2%, respectively (HR 3.39; 95% CI: 1.78-6.45; P<0.001). Rates of non-hemorrhagic adverse events were similar in the two groups.

In the TRACER trial there was no significant difference between the study groups in the occurrence of the primary end point, whereas the secondary end point was significantly less frequent in patients treated with vorapaxar (relative risk reduction 11%). The risk reduction was mainly due to a decrease in MI [particularly spontaneous (type 1) MI]. There was no reduction in rates of death from any cause, and there was also no significant effect on stent thrombosis. Furthermore, a significantly higher risk of moderate to severe bleeding (including intracranial bleeding) was shown when vorapaxar is added to standard antiplatelet therapy (aspirin and clopidogrel).

Pre-clinical and phase II data did not raise suspicions about an increased risk of bleeding over that with aspirin and clopidogrel.[36,45,52,55] It is not clear whether the increase in the rate of intracranial hemorrhage was related to intensive antithrombotic therapy or whether there is a specific link between PAR-1 inhibition and intracranial vascular hemostasis. In the subgroup of patients who were not receiving clopidogrel at randomization, vorapaxar efficacy tended to be more pronounced and no increase in the bleeding risk was shown. Future studies will have to compare the efficacy of vorapaxar *versus* clopidogrel among patients taking aspirin. The duration of vorapaxar therapy in conjunction with dual antiplatelet therapy may have influenced the risk-benefit profile, since the rate

of bleeding continued to increase over time. TRACER studied patients for a much longer period than in several previous dual antiplatelet trials.[17,56] Recent trials have shown a lack of benefit and excessive bleeding with prolonged dual antiplatelet therapy.[57,58]

The *Thrombin-Receptor Antagonist in the Secondary Prevention of Atherothrombotic Ischemic Events* (TRA 2°P-TIMI 50)[54] trial was designed to evaluate the long-term efficacy and safety of vorapaxar in patients with established atherosclerosis receiving standard therapy. Over 26,000 patients with documented, stable, atherosclerotic disease (ischemic stroke or spontaneous MI within 2 weeks to 12 months before enrolment, or peripheral artery disease (defined as intermittent claudication in conjunction with an ankle-brachial index <0.85 or previous revascularization for limb ischemia) were randomly enrolled to receive vorapaxar for at least one year (administered as a 2.5 mg once-daily maintenance dose) or placebo, in addition to aspirin alone, clopidogrel alone or aspirin plus clopidogrel. Randomization was stratified by type of disease: coronary artery disease, cerebrovascular disease, or peripheral vascular disease. Patients with previous revascularization, or with a history of bleeding diathesis, active hepatobiliary disease, recent bleeding events, or taking oral anticoagulants were excluded.

The primary efficacy end point was a composite of cardiovascular death, MI, stroke, and urgent coronary revascularization; the major secondary efficacy end point was the composite of cardiovascular death, MI or stroke. The safety of vorapaxar was determined by assessing the incidence of bleeding according to the TIMI, GUSTO, and International Society of Thrombosis and Hemostasis (ISTH) classification systems.

Median follow up of the study was 30 months. However, after reviewing the safety and efficacy findings at two years, the study's *Data and Safety Monitoring Board* recommended that vorapaxar be immediately discontinued in patients with history of stroke or in those who experienced a stroke during the study period (about 25% of the patients) because of a potential for increased intracranial bleeding. After three years, the primary efficacy end point occurred in 1208 patients (9.3%) receiving vorapaxar and 1176 patients (10%) receiving placebo (HR 0.87; 95% CI: 0.80-0.94; P<0.001). The composite of cardiovascular death, MI, stroke, or recurrent ischemia was seen in 1259 patients (11.2%) treated with vorapaxar and 1417 patients (12.4%) with placebo (HR 0.88; 95% CI: 0.82-0.95; P=0.001), and MI alone was less frequent with vorapaxar (5.2%) than with placebo (6.1%) (HR 0.83; 95% CI: 0.74-0.93; P=0.001). However, the bleeding end points occurred more frequently with vorapaxar than with placebo. Moderate or severe (GUSTO classification) bleeding occurred in 4.2% of patients receiving vorapaxar and 2.5% of patients receiving placebo (HR 1.66; 95% CI: 1.43-1.93; P<0.001). Clinically significant (TIMI) bleeding occurred in 15.8% of patients in the vorapaxar group and in 11.1% of patients in the placebo group (HR 1.46; 95% CI: 1.36-1.57; P<0.001); intracranial hemorrhage was 2-fold more frequent with vorapaxar (1.0% *vs* 0.5%; HR 1.94; 95% CI: 1.39-2.70; P<0.001), especially in patients with previous ischemic stroke (HR 2.55, 95% CI: 1.52-4.28, P<0.001), while fatal bleeding was rare in both the groups (0.2% *vs* 0.3%; HR 1.46; 95% CI: 0.82-2.58; P=0.19).

The TRA 2°P-TIMI 50 study shows that, in the secondary prevention of atherosclerotic vascular accidents, the inhibition of alternative pathways of platelet aggregation, in addition to the TXA2- and ADP-mediated pathways, may reduce the risk of recurrence of thrombotic events. Patients with previous MI may obtain the greatest benefit from vorapaxar. In fact, the primary end point was reduced by 20% in this subgroup of patients (95% CI: 0.72-0.89; P<0.001) and the frequency of intracranial hemorrhage was not significantly higher than placebo (P=0.076), although GUSTO and TIMI bleeding remained significantly increased, similarly to the overall study population. Notably, concomitant treatment with a P2Y 12 blocker did not further increase bleeding in the vorapaxar group.

In a placebo-controlled trial of secondary prevention in patients with stable atherothrombotic disease or at high risk of vascular disease, clopidogrel plus aspirin did not prove better than aspirin alone in the whole cohort.[59] However, in a preliminary analysis of 3846 patients with a history of MI, adding clopidogrel to aspirin decreased the risk of recurrent stroke by 23%.[60] The reduction in thrombotic events associated with vorapaxar, however, may be offset by a significant increase in bleeding. Therefore, any benefit coming from the reduction of atherothrombotic events should be accurately evaluated in the light of the increased risk of bleeding: in the TRA 2°P-TIMI 50 study, net clinical outcome analysis favored vorapaxar in patients with no history of stroke. In this subgroup, the relative risk of the composite of all-cause death, MI, stroke, and GUSTO severe bleeding, was 11% lower with vorapaxar than with placebo (95% CI: 0.82-0.97; P=0.01). Again in the same subgroup, the relative risk of the primary end point was reduced by 16% (9.6% with placebo, 8.3% with vorapaxar, 95% CI: 0.76-0.93; P<0.001); although GUSTO and TIMI bleeding rates were higher with vorapaxar, intracranial hemorrhage was only slightly increased (0.4% with placebo 0.6% with vorapaxar, HR 1.55; 95% CI: 1.00-2.41; P=0.049).

Conclusions

For the moment, the role of vorapaxar in the settings of atherothrombotic disorders is still not clear. Although it may be associated with less bleeding than

P2Y12 receptor blockers, its antithrombotic effectiveness and side effects in association with other antiplatelet agents remain major concerns.

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