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Safety and efficacy of vorapaxar in secondary prevention of atherosclerotic disease: A meta-analysis of randomized control trials

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ABSTRACT

Objective: To study the cumulative evidence for vorapaxar use in patients with atherosclerotic cardiovascular disease.

Methods: A systematic review of randomized control trials in MEDLINE, EMBASE, EBSCO, CINAHL, Web of Science and Cochrane databases comparing vorapaxar with placebo was performed. Pre-specified efficacy endpoints were all-cause mortality, CV mortality, myocardial infarction (MI), ischemic stroke and repeat revascularization. The pre-specified safety endpoint was intracranial hemorrhage (ICH) and a composite of TIMI major and minor bleeding. Risk ratios were used as the metric of choice by applying random effects models.

Results: Five randomized controlled trials with 40,630 patients were included in final analysis. Compared with placebo, vorapaxar led to a statistically non-significant reduction in risk of MI [RR 0.86; 95% CI 0.80–0.93, $p = 0.427$] and ischemic stroke [RR 0.84; 95% CI 0.72–0.97, $p = 0.920$]. No differences were observed between vorapaxar and placebo with respect to all-cause mortality [RR 0.99; 95% CI 0.90–1.08, $p = 0.620$], cardiovascular mortality [RR 0.94; 95% CI 0.83–1.06, $p = 0.351$], repeat revascularization [RR 0.97; 95% CI 0.82–1.15, $p = 0.236$], and TIMI bleeding [RR 1.29; 95% CI 0.98–1.69, $p = 0.126$]. Vorapaxar was associated with a statistically non-significant higher risk of ICH [RR 2.36; 95% CI 1.40–3.96, $p = 0.137$] compared with placebo.

Conclusion: Addition of Vorapaxar to standard medical therapy in patients with atherosclerotic disease led to a statistically non-significant reduction in the risk of MI and ischemic stroke at the cost of statistically non-significant increase in risk of ICH.

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1. Introduction

Atherothrombotic disease continues to be the leading cause of morbidity and mortality worldwide [1]. Major guidelines recommend dual anti-platelet therapy (DAPT) with aspirin and a P2Y12 inhibitor (thienopyridines or ticagrelor) for secondary prevention after an acute myocardial infarction (AMI) or percutaneous coronary intervention (PCI) with stent implantation [2,3]. However, a substantial residual

cardiovascular (CV) risk remains despite use of current evidence-based anti-thrombotic therapy, which has prompted investigators to explore additional mechanisms of platelet activation and thrombus formation [4,5].

Thrombin is a potent stimulator of platelet activation and aggregation, primarily acting via protease-activated receptor-1 (PAR-1) on human platelets [6,7]. Persistence of unsuppressed thrombin-mediated platelet activation after an index coronary event can therefore contribute to sustained thrombotic risk [8]. Vorapaxar (SCH 530348, Merck) is a novel orally active and selective PAR-1 antagonist that offers a new strategy to further mitigate residual CV risk by complementing currently used targeted-drug therapy (Thromboxane- and P2Y12-inhibitor) [9].

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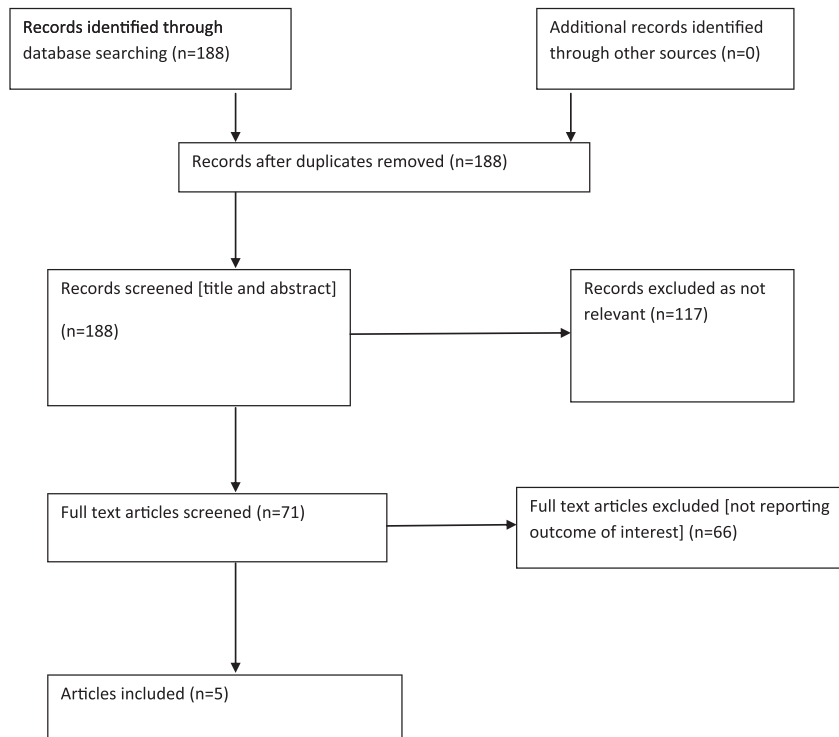


Fig. 1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart for the trial selection process.

Table 1
Characteristics of the studies included in the analysis.

Study	Design	Inclusion criteria	Exclusion criteria	Primary efficacy end-point	Primary safety end-point
TRA 2P-TIMI 50 (2012)	Phase 3, Randomized, Multicentre Double-blind, Placebo-controlled	History of atherosclerosis, including spontaneous myocardial infarction or ischemic stroke within the previous 2 weeks to 12 months or peripheral arterial disease associated with a history of intermittent claudication	Planned to undergo a revascularization procedure, history of bleeding diathesis, recent active abnormal bleeding, ongoing treatment with warfarin, or active hepatobiliary disease.	Composite of cardiovascular death, myocardial infarction, stroke	GUSTO moderate or severe bleeding
TRACER (2012)	Phase 3, Randomized, Multicentre Double-blind, Placebo-controlled	Acute coronary syndrome defined by symptoms within 24 h, and with either cardiac troponin/CK MB > ULN or new ST-segment depression or transient ST-segment elevation (<30 min) in at least two contiguous leads; Plus one of following: Age > 55 y; Prior MI, PCI or CABG; DM; PAD	Treatment with warfarin or inhibitor of CYP3A4 isoenzymes, bleeding diathesis, active abnormal bleeding within 30 days, history of ICH, major surgery within prior 2 weeks, Known active hepatobiliary disease	Composite of cardiovascular mortality, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization.	GUSTO moderate or severe bleeding
TRA-PCI (2009)	Phase 2, Randomized, Multicentre Double-blind, Placebo-controlled	Symptoms of coronary artery disease, and scheduled to undergo non-urgent PCI or non-urgent coronary angiography with the intention to undergo PCI.	Pregnancy, serious illness, urgent PCI, bleeding diathesis, active bleeding within 30 days, history of hemorrhagic stroke, stroke or TIA within 30 d, thrombocytopenia, active or chronic hepatic disease, major surgery within 6 weeks, severe HTN.	Composite of cardiovascular death, non-fatal myocardial infarction, and stroke	TIMI major or minor bleeding
Goto et al. (2010)	Phase 2, Randomized, Multicentre Double-blind, Placebo-controlled	Age > 18 y with chest pain > 10 min within 24 h plus CK-MB or Trop I > ULN or ECG changes, and planned for PCI	Pregnancy, severe illness, use of investigational drug within 30 d, bleeding diathesis, severe hypertension, major surgery within 2 weeks, platelet count < 100,000, and impaired renal or hepatic function	All cause death and MACE (non-fatal MI, non-fatal stroke, hospitalization for recurrent ischemia, or urgent coronary revascularization)	TIMI major, minor, or Non-TIMI bleeding
Shinohara et al. (2010)	Phase 2, Randomized, Multicentre Double-blind, Placebo-controlled	Age > 18 y with stable ischemic stroke within 14 d to 1 y with stable neurologic symptoms for at least 24 h.	Cardiogenic cerebral embolism, bleeding diathesis, abnormal bleeding episode within 30 days, platelet count < 100,000/mm ³ , major surgery within 2 weeks, severe hypertension, history of ICH, pregnancy, hepatic or renal impairment.	Cardiovascular death and MACE (Nonfatal myocardial infarction, nonfatal stroke, acute hospitalization related to cardiac ischemia, any revascularization)	Non-MACE adverse events

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