State-of-the-Art Mini Review: Dual-Pathway Inhibition to Reduce Arterial and Venous Thromboembolism

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Abstract

Venous thromboembolism (VTE) and arterial thromboembolism (ATE) are linked by the common mechanism of thrombin generation. Historically these entities have been treated as separate pathophysiologic processes requiring different treatments: VTE, as the formation of fibrin-/coagulation-factor-derived thrombus in low-flow vasculature, requiring anticoagulants; versus ATE, as largely platelet-derived thrombus in high-flow vasculature, requiring antiplatelet agents. Observational studies have elucidated shared risk factors and comorbidities predisposing individuals with VTE to ATE, and vice versa, and have bolstered the strategy of dual-pathway inhibition (DPI)—the combination of low-dose anticoagulants with antiplatelet agents—to reduce thrombotic outcomes on both sides of the vasculature. Randomized clinical trials have evaluated the efficacy and safety of such regimens—mostly rivaroxaban and aspirin—in high-risk groups of patients, including those with recent acute or chronic coronary syndrome, as well as those with peripheral artery disease with or without revascularization. Studies of extended VTE prophylaxis in acutely ill medical patients have also contributed to the evidence evaluating DPI. The totality of available data supports the concept that DPI can reduce major and fatal thromboembolic outcomes, including stroke, myocardial infarction, VTE, and cardiovascular death in key patient cohorts, with acceptable risk of bleeding. Further data are needed to refine which patients derive the best net clinical benefit from such an approach. At the same time, other novel agents such as contact pathway inhibitors that reduce thrombin generation without affecting hemostasis—and thus maximize safety—should be assessed in appropriate populations.

Keywords
► venous thromboembolism
► arterial thromboembolism
► direct oral anticoagulant
► anticoagulants
► antiplatelet agents
► dual-pathway inhibition

Introduction

Thrombosis is responsible for 1 in 4 deaths worldwide. Venous thromboembolism (VTE) and arterial thromboembolism (ATE) are often considered distinct entities, but there is mounting evidence of pathophysiologic linkages between them. Atherosclerotic disease and VTE share common risk factors such as advanced age,[1] obesity, cigarette smoking,[2,3] and metabolic syndrome.[4] Observational studies have shown associations between VTE and carotid or peripheral artery disease (PAD), hypertension, and dyslipidemia.[1,2,5–9] Moreover, a meta-analysis of 21 studies revealed an association between VTE and known cardiovascular risk factors including obesity, hypertension, diabetes mellitus, smoking, and hypercholesterolemia.[10] A seminal case–control study demonstrated a twofold higher risk of carotid plaque on screening ultrasound in patients with unprovoked deep venous thrombosis (DVT) compared with controls or those with provoked DVT, after adjustment for atherosclerosis risk factors and thrombophilia.[11] Because carotid plaque is a marker of systemic vascular disease,[12–14] the authors hypothesized that atherosclerosis was linked to, or could even induce VTE.[11] Subsequent prospective studies revealed an increased risk of arterial thromboembolic events, including myocardial infarction (MI), stroke, symptomatic PAD, cardiovascular death, and unexplained sudden death in patients with VTE, particularly those with unprovoked pulmonary embolism.[15–18] Considering that nearly one in six individuals with atherosclerosis has baseline polyvascular disease,[19] and risk of both nonfatal and fatal events increases in relation to the number of involved vascular beds,[20,21] experts in recent years have emphasized enhanced prevention strategies.[22] In particular, for patients with isolated venous or arterial disease, or shared risk factors for both, it has been suggested that comprehensive treatment might necessitate a pharmacologic strategy targeting pathogenesis of both the platelet-rich thrombi that can form on top of disrupted atherosclerotic plaques and the fibrin-rich thrombi that can originate in the valve cusps of the deep veins of the leg.

Although antiplatelet agents are the mainstay for prevention of arterial thrombosis and anticoagulants are the cornerstone for prevention and treatment of venous thrombosis, studies in animal models of thrombosis have suggested that the combination of an antiplatelet agent with an anticoagulant attenuates thrombosis to a greater extent than either agent alone.[23] On its own, aspirin (ASA) is effective for VTE prevention. Thus, ASA and the direct oral anticoagulant (DOAC) rivaroxaban exhibit similar effectiveness for extended thromboprophylaxis after elective hip or knee arthroplasty when administered after an initial 5-day course of postoperative rivaroxaban.[24] Likewise, for secondary prevention in patients with unprovoked VTE, ASA reduces the risk of recurrence by approximately 32% compared with placebo. Therefore, ASA is effective for secondary VTE prevention, although less effective than rivaroxaban.[25,26] When ASA was given together with an anticoagulant for extended thromboprophylaxis in medically ill patients, there was a reduction in fatal and nonfatal arterial and venous thrombotic events; the same was seen on the arterial side when dual-pathway inhibition (DPI) was evaluated in patients with acute coronary syndrome (ACS) or with chronic coronary artery disease (CAD) or PAD.[27–30]

This state-of-the art review will (1) outline the rationale for DPI and describe the data supporting such therapy, (2) provide perspective on the opportunities and challenges of DPI, and (3) identify directions for future research.

Mechanism of Dual-Pathway Thrombin Inhibition

Although their pathogenesis differs, the formation of arterial and venous thrombi is dependent on simultaneous activation of the coagulation system and platelets. In most cases, arterial thrombosis is triggered by tissue factor exposure at sites of atherosclerotic plaque disruption. With venous thrombosis, the vein wall is usually intact. In response to reduced flow, hypoxia, and inflammatory mediators, however, endothelial cells lining the veins, particularly those in the valve cusps, become activated and express adhesion molecules that tether tissue factor-expressing leukocytes and microvesicles onto their surface. Neutrophil extracellular traps extruded from activated leukocytes provide a scaffold that traps and activates platelets and initiates clotting via the intrinsic pathway (►Fig. 1).

The critical nexus between the coagulation cascade and platelet activation is protease-activated receptors (PARs) PAR1/PAR4 on the surface of platelets, which serve as thrombin receptors. Vorapaxar, a selective PAR1 inhibitor, was shown to decrease ischemic events and cardiovascular death when given for secondary prevention in patients with CAD or PAD, but was associated with a risk of moderate or severe bleeding.[31] Inhibition of thrombin generation with DOACs such as rivaroxaban can reliably prevent venous thromboembolic events while attenuating platelet activation. This effect is enhanced with concomitant use of ASA, which dampens platelet activation by blocking thromboxane A2 production.[32]

More recent studies in mouse models support the notion that DPI is effective. Hanjaya-Putra et al studied SCE5-TAP, an engineered protein complex that fuses SCE5, an antibody against activated glycoprotein IIb/IIIa, with tick anticoagulant peptide (TAP), a potent direct inhibitor of factor (F) Xa.[33] SCE5-TAP was as effective as enoxaparin plus eptifibatide in models of arterial thrombosis and as effective as enoxaparin or rivaroxaban in venous thrombosis models, but was associated with less bleeding.[33] These findings and others provide a preclinical rationale for DPI.

Clinical Trials of Dual-Pathway Inhibition

Recent clinical trials evaluating DPI are summarized in ►Table 1. The ATLAS ACS 2-TIMI 51 trial evaluated rivaroxaban (2.5 or 5 mg twice daily) versus placebo on top of background antiplatelet therapy with ASA with or without a thienopyridine in 15,526 stabilized ACS patients. Compared with placebo, rivaroxaban decreased major adverse cardiovascular events; the 2.5 mg twice-daily dose of
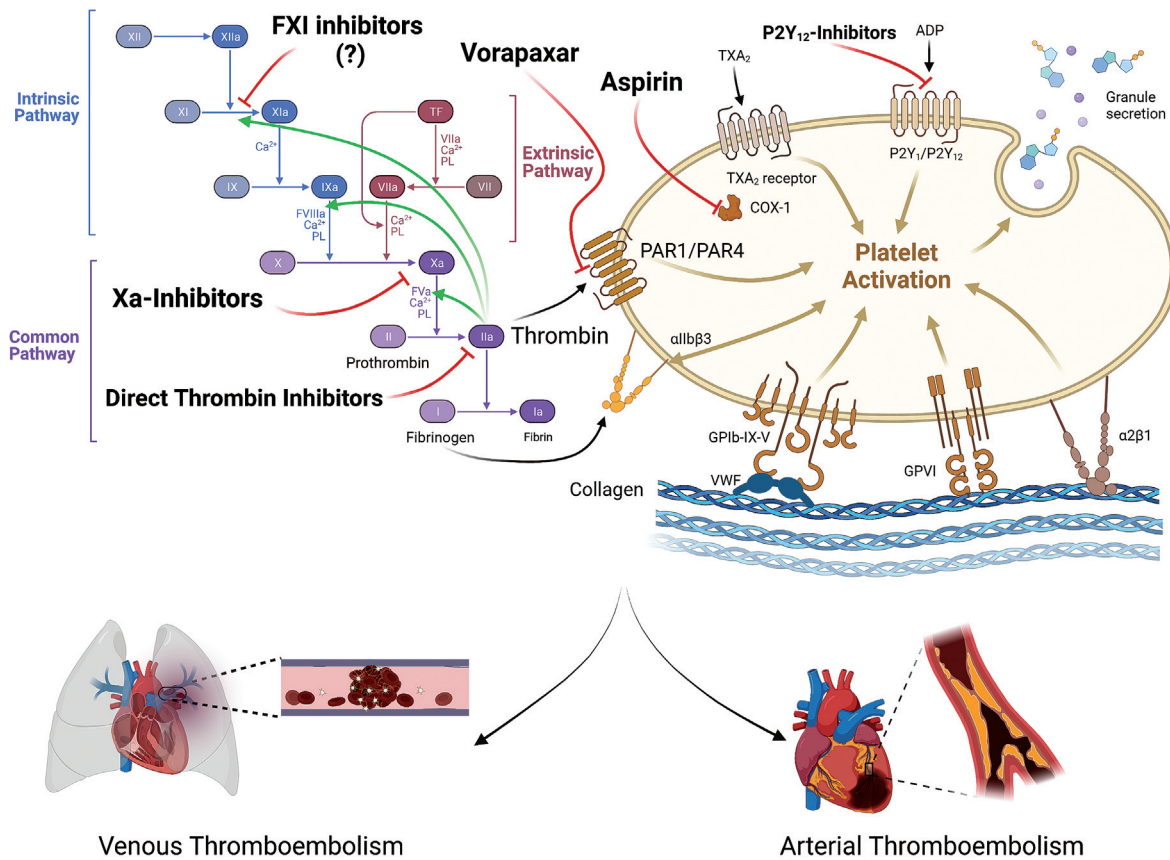
Fig. 1 Mechanisms of dual-pathway inhibition with anticoagulants and antiplatelet agents to reduce venous and arterial thromboembolic disease. The effects of antiplatelet therapy on the prevention of thrombotic events are enhanced by upstream inhibition of the coagulation cascade. Subsequently, the reduced production and release of thrombin leads to a decrease in platelet activation by reducing the binding of thrombin to PAR receptors on the surface of platelets. The targets of commonly used antiplatelets and direct anticoagulants are indicated by arrows as follows: *red arrow* = inhibition, *black arrow* = binding site, *green arrow* = positive feedback. ADP, adenosine diphosphate; PAR, protease-activated receptor; TXA2, thromboxane A2. (Adapted from "Platelet Activation" and "Coagulation Cascade" by BioRender.com [2021]. Retrieved from https://app.biorender.com/biorender-templates created with BioRender.com.)

rivaroxaban significantly reduced the composite of cardiovascular death, MI, or stroke (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.74–0.96; $p = 0.02$), as well as cardiovascular death (HR: 0.66; 95% CI: 0.51–0.86; $p = 0.002$), and all-cause mortality (HR: 0.68; 95% CI: 0.53–0.87; $p = 0.002$).[27] Rivaroxaban (combined 5 and 2.5 mg twice-daily groups) significantly increased the rate of major bleeding not associated with coronary artery bypass graft surgery compared with placebo (HR: 3.96; 95% CI: 2.46–6.38; $p < 0.001$), as well as intracranial bleeding (HR: 3.28; 95% CI: 1.28–8.42; $p = 0.009$), but not fatal bleeding (HR: 1.19; 95% CI: 0.54–2.59; $p = 0.66$).[32–36]

The APPRAISE-2 trial compared apixaban (5 mg twice daily) with placebo on top of ASA or dual-antiplatelet therapy in 7,392 patients with ACS with at least two additional high-risk characteristics (age > 65 years, MI within the previous 5 years, cerebrovascular disease, PAD, diabetes mellitus, or clinical heart failure/reduced ejection fraction). Compared with placebo, there was no significant reduction in the composite of MI, ischemic stroke, or cardiovascular death with apixaban (HR: 0.95; 95% CI: 0.80–1.11; $p = 0.51$),

and apixaban was associated with a significant increase in Thrombolysis in Myocardial Infarction (TIMI) major bleeding (HR: 2.59; 95% CI: 1.50–4.46; $p = 0.001$), which prompted early trial termination.[37]

Longer term advantages of DPI were revealed by the COMPASS trial, which evaluated 27,395 patients with CAD, PAD, or both. Using a placebo-controlled design, patients were randomized to one of three treatment groups: rivaroxaban 2.5 mg twice daily plus ASA 100 mg once daily; rivaroxaban 5 mg twice daily alone; or ASA 100 mg once daily alone. Compared with ASA alone, rivaroxaban plus ASA significantly reduced the composite of stroke, MI, and cardiovascular death (HR: 0.76; 95% CI: 0.66–0.86; $p < 0.001$); this was driven by reductions in the incidences of stroke (HR: 0.58; 95% CI: 0.44–0.76; $p < 0.001$) and cardiovascular death (HR: 0.78; 95% CI: 0.64–0.96; $p = 0.02$). In contrast, rivaroxaban alone revealed no benefit over ASA. Compared with ASA alone, DPI with rivaroxaban plus ASA significantly increased major bleeding (HR: 1.70; 95% CI: 1.40–2.05; $p < 0.001$) driven mainly by increased gastrointestinal bleeding (HR: 2.15; 95% CI: 1.60–2.89; $p < 0.001$); however, there was no

Table 1 Randomized clinical trials evaluating dual-pathway inhibition (DPI) therapy in patients with cardiovascular disease

Clinical trial	Study population	Treatment	Endpoints	Primary efficacy endpoint	Primary safety endpoint
ATLAS ACS-2 TIMI 51 (n = 15,526)	Stabilized acute coronary syndrome	RIV (2.5 or 5 mg twice daily) vs. placebo (in combination with standard antiplatelet therapy)	Primary efficacy endpoint: cardiovascular death, MI, or stroke Primary safety endpoint: Non-CABG TIMI bleeding	2.5 mg RIV HR = 0.84 (95% CI: 0.72–0.97), p = 0.02; 5 mg RIV HR = 0.85 (95% CI: 0.73–0.98), p = 0.03	2.5 mg RIV vs. placebo: HR = 3.46 (95% CI: 2.08–5.77), p < 0.001; 5 mg RIV vs. placebo: HR = 4.47 (95% CI: 2.71–7.36), p < 0.001
COMPASS (n = 27,395)	Stable CAD and PAD, MI in the past 20 years	RIV 2.5 mg twice daily + ASA 100 mg once daily vs. RIV 5 mg twice daily vs. ASA 100 mg once daily	Primary efficacy endpoint: MI, stroke, or cardiovascular death Primary safety endpoint: major bleeding (fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization)	2.5 mg RIV+ASA vs. ASA alone: HR = 0.76 (95% CI: 0.66–0.86), p < 0.001; 5 mg RIV vs. ASA alone: HR = 0.90 (95% CI: 0.79–1.03), p = 0.12	2.5 mg RIV+ASA vs. ASA alone: HR = 1.70 (95% CI: 1.40–2.05), p < 0.001; 5 mg RIV vs. ASA alone: HR = 1.51 (95% CI: 1.25–1.84), p < 0.001
COMPASS-Stable CAD subgroup analysis (n = 24,824)	Stable CAD, MI in the past 20 years	Same as in the main COMPASS study	Same as in the main COMPASS study	2.5 mg RIV+ASA vs. ASA alone: HR = 0.74 (95% CI: 0.65–0.86), p < 0.0001; 5 mg RIV vs. ASA alone: HR = 0.89 (95% CI: 0.78–1.02), p = 0.094	2.5 mg RIV+ASA vs. ASA alone: HR = 1.66 (95% CI: 1.37–2.03), p < 0.0001; 5 mg RIV vs. ASA alone: HR = 1.51 (95% CI: 1.23–1.84), p < 0.0001
COMPASS-Stable PAD subgroup analysis (n = 7,470)	Stable PAD	Same as in the main COMPASS study	Same as in the main COMPASS study	2.5 mg RIV+ASA vs. ASA alone: HR = 0.72 (95% CI: 0.57–0.90), p = 0.0047; 5 mg RIV vs. ASA alone: HR = 0.86 (95% CI: 0.69–1.08), p = 0.19	2.5 mg RIV+ASA vs. ASA alone: HR = 1.61 (95% CI: 1.12–2.31), p = 0.0089; 5 mg RIV vs. ASA alone: HR = 1.68 (95% CI: 1.17–2.40), p = 0.0043
VOYAGER-PAD (n = 6,564)	PAD patients who had undergone revascularization	Aspirin 100 mg once daily + RIV 2.5 mg twice daily vs. aspirin 100 mg once daily + placebo	Primary efficacy endpoint: acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, and cardiovascular death at a follow-up period of 3 years Primary safety endpoint: TIMI major bleeding	DPI vs. aspirin only: HR = 0.85 (95% CI: 0.76–0.96), p = 0.009	DPI vs. aspirin: HR = 1.43 (95% CI: 0.97–2.10), p = 0.07
APPRAISE-2 (n = 7,392)	Patients with acute coronary syndrome within the previous 7 days receiving	Apixaban 5 mg twice daily + standard antiplatelet therapy	Primary efficacy endpoint: cardiovascular death, myocardial infarction, or	(Early termination) Apixaban vs. placebo: HR	Apixaban vs. placebo: HR = 2.59 (95% CI: 1.50–4.46), p = 0.001

Table 1 (Continued)

Clinical trial	Study population	Treatment	Endpoints	Primary efficacy endpoint	Primary safety endpoint
	antiplatelet therapy (either dual or monotherapy)	Vs. placebo + standard antiplatelet therapy	ischemic stroke Primary safety endpoint: major bleeding (TIMI)	= 0.95 (95% CI: 0.80–1.11), p = 0.51	
GEMINI-ACS-1 (n = 3,037)	Patients with acute coronary syndrome on antiplatelets	Clopidogrel or ticagrelor + RIV 2.5 mg twice daily vs. either clopidogrel or ticagrelor + aspirin 100 mg daily	Primary efficacy endpoint: composite of cardiovascular death, myocardial infarction, stroke, or definite stent thrombosis; all-cause death Primary safety endpoint: TIMI non-CABG clinically significant bleeding	RIV vs. aspirin: HR = 1.09 (95% CI: 0.80–1.50), p = 0.5840	RIV vs. aspirin: HR = 1.09 (95% CI: 0.80–1.50), p = 0.5840

Abbreviations: 95% CI, 95% confidence interval; ASA, acetylsalicylic acid (Aspirin); BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass graft; CAD, coronary artery disease; DOAC, direct oral anticoagulant; DPI, dual-pathway inhibition; GUSTO, Global Use of Strategies to Open Occluded Arteries; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis; MI, myocardial infarction; NS, nonsignificant; PAD, peripheral artery disease; RIV, rivaroxaban; RR, relative risk; TIMI, Thrombolysis in Myocardial Infarction; VTE, venous thromboembolism.

significant difference in intracranial bleeding (HR: 1.16; 95% CI: 0.67–2.00; $p = 0.60$) or fatal bleeding (HR: 1.49; 95% CI: 0.67–3.33; $p = 0.32$).[29,38] Of note, rivaroxaban alone was associated with more major bleeding than ASA alone (HR: 1.51; 95% CI: 1.25–1.84; $p < 0.001$). Perhaps the most impressive finding was that reduction in the primary composite endpoint was driven by a 50% relative risk reduction in the incidence of stroke in the stable CAD subgroup.[29]

DPI with rivaroxaban and ASA was also studied in the VOYAGER PAD trial among 6,564 PAD patients who had undergone peripheral artery revascularization.[30] Compared with ASA alone, DPI significantly reduced the composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, and cardiovascular death (HR: 0.85; 95% CI: 0.86–0.96; $p = 0.009$). The benefits were seen across risk factor subgroups, qualifying symptoms, or types of vascular intervention. Kaplan–Meier curves separated at 3 months and continued to diverge over time, suggesting an early and lasting efficacy advantage to DPI. The principal safety outcome of TIMI major bleeding did not differ significantly between the ASA alone and rivaroxaban plus ASA groups (HR: 1.43; 95% CI: 0.97–2.10; $p = 0.07$). However, rivaroxaban plus ASA was associated with more ISTH (International Society on Thrombosis and Haemostasis)[39] major bleeding (HR: 1.42; 95% CI: 1.10–1.84; $p = 0.007$), although there was no increase in intracranial or fatal bleeding.[30]

Data from Studies of Extended VTE Thromboprophylaxis

Trials of extended VTE prophylaxis have also helped to identify populations at risk for venous thrombotic disease that may derive a net clinical benefit from DPI (►**Table 2**). The APEX trial[40] demonstrated the benefit of betrixaban for postdischarge VTE prophylaxis in 7,513 acutely ill medical patients, including those with cardiopulmonary or inflammatory disease or stroke. Approximately 49% of APEX subjects were prescribed antiplatelet therapy at baseline, mainly ASA.[41] The use of DPI may have contributed to the reduction in major and fatal venous and arterial cardiovascular events observed with betrixaban. Betrixaban was associated with a reduced incidence of ischemic stroke (HR: 0.53; 95% CI: 0.30–0.94; $p = 0.026$).[42] An additional analysis revealed associated reductions in fatal or irreversible thromboembolic events among the full APEX population at 35 to 42 days (HR: 0.71; 95% CI: 0.55–0.90; $p = 0.006$) and 77 days (HR: 0.70; 95% CI: 0.57–0.88; $p = 0.002$), particularly in patients with elevated D-dimer levels (at 35–42 days, HR: 0.73; 95% CI: 0.55–0.98; $p = 0.033$; at 77 days, HR: 0.70; 95% CI: 0.54–0.90; $p = 0.005$).[43]

The MARINER trial demonstrated the benefit of rivaroxaban (10 mg daily; 7.5 mg for those with a creatinine clearance less than 50 mL/min) compared with placebo for postdischarge thromboprophylaxis in 12,019 acutely ill medical subjects with congestive heart failure, stroke, or inflammatory diseases.[44] More than 50% of the MARINER population reported baseline ASA use.[28] A prespecified analysis showed a reduction in the composite of

Table 2 Posthoc and pre-specified analyses of randomized trial studies of baseline aspirin use in extended thromboprophylaxis of medically ill patients

Study	Study population	Treatment	Endpoints	Primary efficacy endpoint	Primary safety endpoints
APEX substudy for the evaluation of stroke prevention ($n = 7,513$) (49% of subjects received low-dose DOAC + ASA)	Same as in main APEX study: Cohort 1: D-dimer at least two times the upper limit of normal Cohort 2: cohort 1 plus subjects 75 years of age or older	Same as in main APEX study: postdischarge subcutaneous enoxaparin (40 mg once daily) for 10 ± 4 days + oral betrixaban placebo once daily for 35–42 days vs. subcutaneous enoxaparin placebo once daily for 10 ± 4 days + oral betrixaban 80 mg once daily (with 160 mg loading dose) for 35–42 days	Primary efficacy endpoint: all-cause stroke, TIA	For betrixaban vs. enoxaparin in the overall population: all-cause stroke or TIA: RR = 0.59 (95% CI: 0.35–0.97), $p = 0.034$	Reported in the primary study
APEX substudy of all fatal or irreversible safety and efficacy events, time-to-event	Same as in main APEX study	Same as in main the APEX study	Primary efficacy endpoint: ischemic cardiopulmonary death, nonfatal ischemic stroke, MI, nonfatal pulmonary embolism) Primary safety endpoint: fatal bleeding or intracranial hemorrhage	First fatal or irreversible event betrixaban vs. enoxaparin in the all randomized population: HR = 0.70 (95% CI: 0.57–0.88)	Enoxaparin group: 0.19% Betrixaban group: 0.06%
Mariner substudy ($n = 9,822$): prespecified subgroup analysis for fatal and major thromboembolic events	Medically ill hospitalized patients at high risk for thrombosis postdischarge, with a baseline creatinine clearance ≥ 50 mL/min	RIV 10 mg vs. placebo daily at hospital discharge for 45 days	Primary efficacy endpoint: symptomatic VTE (DVT and nonfatal PE), MI, nonhemorrhagic stroke, CV death Primary safety endpoint: ISTH major bleeding	RIV vs. placebo: HR = 0.72 (95% CI: 0.52–1.00), $p = 0.049$	RIV vs. placebo: HR = 1.44 (95% CI: 0.62–3.37), $p = 0.398$
MARINER ($n = 12,019$) posthoc analysis of DPI	Medically ill hospitalized patients at high risk for thrombosis postdischarge	4 subgroups: (1) RIV alone (10 mg: creatinine clearance ≥ 50 mL/min; 7.5 mg: 30–49 mL/min); (2) ASA (≤ 162 mg daily) alone; (3) RIV plus ASA; (4) neither RIV nor ASA	Primary efficacy endpoint: symptomatic VTE and VTE-related death Primary safety endpoint: ISTH major bleeding	Event rates: RIV alone: 0.91% ASA alone: 0.92% RIV + ASA: 0.76% Neither RIV nor ASA: 1.28% (p-value for rivaroxaban $p = 0.042$ (p-value for rivaroxaban RIV + ASA vs. neither RIV nor ASA)	RIV alone: 0.28% ASA alone: 0.20% RIV +ASA: 0.29% Neither RIV nor ASA: 0.10%, $p = 0.105$ (p-value for RIV + ASA vs. neither RIV nor ASA)

Abbreviations: 95% CI, confidence intervals; ASA, acetylsalicylic acid (aspirin); CV, cardiovascular; DOAC, direct oral anticoagulant; DPI, dual-pathway inhibition; HR, hazard ratio; ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction; RIV, rivaroxaban; RR, relative risk; TIA, transient ischemic attack; VTE, venous thromboembolism.

symptomatic VTE, MI, nonhemorrhagic stroke, and cardio-vascular death with 10 mg rivaroxaban compared with placebo (HR: 0.72; 95% CI: 0.52–1.00; $p = 0.049$) with a nonsignificant increase in major bleeding (HR: 1.44; 95% CI: 0.62–3.37; $p = 0.398$).[28] A posthoc analysis[45] compared outcomes in four subgroups of the MARINER population: those receiving rivaroxaban plus ASA, rivaroxaban alone, ASA alone, or no prophylaxis. Compared with no prophylaxis, DPI with rivaroxaban and ASA was associated with a significant reduction in symptomatic VTE and VTE-related death (0.76 vs. 1.28%; $p = 0.042$) as well as all-cause mortality. There was no significant increase in major bleeding with DPI compared with rivaroxaban alone (0.29 vs. 0.28%), suggesting a favorable trade-off between reduction in major and fatal cardiovascular events versus bleeding.[45]

Current Knowledge Applications and Future Considerations

The totality of clinical data supports the concept that DPI improves efficacy in patients with both arterial and venous disease. Net clinical benefit analyses suggest that in selected patients with CAD or PAD, DPI would prevent 181 major and fatal cardiovascular events at a cost of 29 principal safety events such as major and fatal bleeds.[30] Extended thromboprophylaxis with a low-dose DOAC in medically ill patients (approximately half of whom were on baseline ASA therapy) would prevent 21 major and fatal thromboembolic events per 10,000 patients treated at the expense of 9 critical site or fatal bleeds.[44] Lastly, a recent benefit/risk analysis of major and irreversible thromboembolic events in hospitalized medical patients revealed that extended thromboprophylaxis with rivaroxaban against a background of antiplatelet therapy has an approximately 10:1 ratio in preventing thromboembolic events (number needed to treat = 197) to incurring major bleed events (number needed to harm = 2,045).[46]

In terms how to apply these clinical data, enrichment criteria using scored risk stratification tools and other analytics may help identify patients with vascular disease or medically ill patients who may benefit most from DPI. For patients with CAD or PAD, enrichment criteria include advanced age, impaired renal function, multibed vascular disease, and biomarkers such as C-reactive protein.[47] More recently, the REACH atherothrombosis risk score defined high-risk vascular patients as those with two or more affected vascular beds, history of heart failure, and history of renal insufficiency, with a score of 13+ defining high-risk groups.[48] Classification and regression tree analysis defined high-risk vascular patients as those with two or more vascular bed involvement, history of heart failure, and history of diabetes.[48] Both risk stratification schemes were able to identify high-risk vascular patients with a net clinical benefit from long-term DPI.[48] For medically ill patients, a validated, weighted, and scored risk assessment model—the IMPROVE VTE score—or its derivative, the IMPROVE-DD VTE score which incorporated elevated D-dimer (>2 times the upper limit of normal), was able to identify a high thrombotic risk

hospitalized medically ill population with a score of 4 or more.[49,50] The IMPROVE or IMPROVE-DD VTE risk score showed net clinical benefit using extended thromboprophylaxis in high-risk medically ill patients after hospital discharge, and as such may potentially select a high VTE risk population in a future trial of DPI. Lastly a careful bleed risk assessment in these populations also is important.

What does the future hold for a dual-pathway inhibitor strategy? For medically ill patients, a prospective randomized trial comparing no treatment or extended thromboprophylaxis with a low-dose DOAC with or without an antiplatelet arm such as ASA should be conducted, using appropriate venous and arterial thromboembolic outcomes. For patients with CAD or PAD, further refinement as to defining high thrombotic risk and low bleed risk subgroups should be analyzed from existing data. Lastly, the advent of FXI inhibitors, which have the potential to attenuate thrombosis with little or no disruption of hemostasis, may provide a safer anticoagulant platform for DPI.[51]

Conclusion

Thrombin generation results in fibrin formation and platelet activation and aggregation in both ATE and VTE. DPI is of proven benefit for secondary prevention in selected patients with ATE and may be of benefit for medically ill patients requiring extended VTE prevention as well.

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