Dual pathway inhibition for atherosclerotic cardiovascular disease: Recent advances

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ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD), which includes coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD) is associated with significant morbidity, mortality, and healthcare costs. Antiplatelet therapy has long been the mainstay of antithrombotic therapy for the prevention of first-ever and recurrent ASCVD events. More recently, however, randomized trials have demonstrated the benefits and cost-effectiveness of a dual pathway inhibition (DPI) strategy in acute and chronic ASCVD. When used in combination, aspirin and low-dose rivaroxaban work synergistically to inhibit platelet activation and thrombin generation, thereby preventing thrombus formation. Among patients with recent acute coronary syndrome (ACS), those with positive cardiac biomarkers or ST-segment elevation myocardial infarction, or a history of heart failure derive the greatest absolute benefits. Among patients with chronic ASCVD, those with involvement of two or more vascular beds, heart failure, chronic kidney disease, or diabetes derive the greatest absolute benefits. Additional trials are underway to assess the impact of DPI therapy in other populations of interest, including patients with ACS at high risk of left ventricular thrombus formation, intracranial atherosclerotic disease with recent transient ischemic attack or stroke, peripheral arterial disease with limiting claudication or post lower extremity revascularization, and advanced chronic kidney disease with ASCVD or risk factors for ASCVD. Further work is required to assess the possible added benefit of combining rivaroxaban with clopidogrel or ticagrelor instead of aspirin.

Key words: atherosclerosis, cerebrovascular disease, coronary artery disease, peripheral arterial disease, rivaroxaban

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), which includes coronary artery disease (CAD), cerebrovascular disease, and peripheral arterial disease (PAD), is the leading cause of morbidity and mortality worldwide and is associated with major and rising healthcare costs. Worldwide cardiovascular deaths increased from 12.1 million in 1990 to 18.6 million in 2019, while years lived with disability increased from 17.7 million to 34.4 million over the same time [1]. Most patients with ASCVD present with disease in a single vascular bed, but one in six have clinical evidence of involvement of more than one vascular bed [2]. Despite lifestyle modification, cardiovascular (CV) risk factor modification, and revascularization procedures to treat severe or symptomatic manifestations of atherosclerotic disease, the burden of CV disease continues to rise, particularly in low- and middle-income countries. Additional effective therapies that are widely applicable and affordable could help to reduce the growing burden of disease.

This review summarizes the rationale and evidence for the use of dual pathway inhibition (DPI), in particular the combination

of aspirin and rivaroxaban, for the acute and long-term management of patients with ASCVD.

PATHOPHYSIOLOGY OF ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

Atherosclerosis is an inflammatory disease resulting from injury to the blood vessel wall induced by smoking, hypertension, dysglycemia, dyslipidemia, and other injurious agents that leads to the accumulation of lipids, macrophages, and lymphocytes within the intima of large arteries. Plaque growth and fissuring or rupture with superimposed thrombus formation can impair blood flow leading to the clinical manifestations of acute or chronic tissue ischemia, including coronary, cerebral, or peripheral arterial events [3].

ROLE OF ANTIPLATELET THERAPY

Single-agent antiplatelet therapy is effective for prevention of recurrent cardiovascular events in patients with a recent acute atherothrombotic event and those with chronic disease [4]. Efforts to improve the efficacy of single-agent antiplatelet therapy for cardiovascular prevention have focused on intensified therapy with a combination of antiplatelet drugs, most commonly aspirin, and a P2Y12 inhibitor, and more recently with the combination of antiplatelet and anticoagulant therapy.

EVIDENCE FOR DUAL ANTIPLATELET THERAPY (DAPT)

Recent acute event

The CURE trial demonstrated in 12 562 patients with a recent acute coronary syndrome (ACS) that the combination of clopidogrel and aspirin, compared to aspirin alone, reduced the risk of CV death, myocardial infarction (MI), or stroke by 20% (relative risk [RR], 0.80; 95% confidence interval [CI], 0.72–0.90; P <0.001), at the cost of a 38% increase in the risk of major bleeding (3.7% vs. 2.7%; RR, 1.38; P = 0.001), but no significant increase in life-threatening bleeding or hemorrhagic stroke [5].

Two subsequent trials demonstrated that the replacement of clopidogrel by a more rapidly acting and potent P2Y12 receptor antagonist produced additional benefits in patients with recent ACS. The PLATO trial demonstrated in 18 624 patients with a recent ACS treated with aspirin that ticagrelor compared with clopidogrel reduced the risk of CV death, MI, or stroke by 16% (hazard ratio [HR], 0.84; 95% CI, 0.77–0.92; P <0.001) and also significantly reduced mortality with no overall increase in major bleeding. However, this benefit came at the cost of an increase in non-coronary artery bypass graft (CABG)-related major bleeding, as well as fatal intracranial hemorrhage [6]. The TRITON-TIMI 38 trial demonstrated in 13 608 patients with a recent ACS that prasugrel compared with clopidogrel reduced CV death, non-fatal MI, or stroke by 19% (HR, 0.81; 95% CI, 0.73–0.90; P <0.001) but did not reduce mortality and increased life-threatening and fatal bleeding [7].

DAPT has also been demonstrated to have benefits over single-agent antiplatelet therapy in acute settings following lower limb revascularization or stroke. In 851 patients with PAD undergoing infrainguinal bypass surgery, the CASPAR trial found that clopidogrel plus aspirin, as compared to aspirin alone, reduced major adverse limb events in a pre-specified subgroup who received prosthetic bypass grafts (HR, 0.65; 95% CI, 0.45–0.95; P = 0.03) although there was no benefit in the overall population [8]. The CHANCE (n = 5 170) and POINT (n = 4 881) trials investigated the use of DAPT with clopidogrel plus aspirin, as compared to aspirin alone, in patients with a high risk of transient ischemic attack (TIA) or minor stroke. The CHANCE trial found that 21 days of treatment with DAPT, compared with aspirin, followed by clopidogrel monotherapy reduced the risk of recurrent stroke (HR, 0.68; 95% CI, 0.57–0.81; P <0.001) [9]. The POINT trial found that 90 days of treatment with DAPT, compared with aspirin, reduced the composite of ischemic stroke, MI, or death from ischemic vascular causes (HR, 0.75; 95% CI, 0.59–0.95; P = 0.02) [10].

Chronic cardiovascular disease

The benefits of DAPT are less pronounced in the chronic phase. The CHARISMA trial demonstrated in 15 603 patients with clinically evident CV disease (n = 12 153) or multiple risk factors (n = 3284) that clopidogrel plus aspirin, compared with aspirin alone, did not reduce the risk of the primary efficacy endpoint of MI, stroke, or CV death (RR, 0.93; 95% CI, 0.83–1.05; P = 0.22 and there was no reduction in mortality [11]. In a subset of patients with prior MI, stroke, or symptomatic PAD (n = 9 478), the combination reduced the primary efficacy endpoint by 17% (HR, 0.83; 95% CI, 0.72–0.96; P = 0.01) and did not increase the risk of Global Use of Strategies to Open Occluded Arteries (GUSTO)-defined severe bleeding (HR, 1.12; 95% CI, 0.81–1.53; P = 0.50) [12].

A meta-analysis of trials evaluating the extended use of the combination of aspirin and a P2Y12 inhibitor as compared to aspirin alone beyond one year in patients with a history of MI (n = 33 435) found a reduction in major adverse cardiovascular events (RR, 0.78; 95% CI, 0.67–0.90; P = 0.001) and CV death (RR, 0.85; 95% CI, 0.74–0.98; P = 0.03) at the cost of an increased risk of major bleeding (RR, 1.73; 95% CI 1.19–2.50; P = 0.004) with no significant reduction in all-cause mortality [13].

More recently, the THEMIS RCT demonstrated in 19 220 patients with stable CAD and diabetes that ticagrelor plus aspirin, compared with aspirin alone, reduced ischemic CV events by 10% (HR, 0.90; 95% CI, 0.81–0.99; P = 0.04) at the cost of an increased risk of thrombolysis in myocardial infarction (TIMI) major and intracranial bleeding [14].

The MATCH trial conducted in 7599 patients with recent ischemic stroke or TIA with at least one additional risk factor

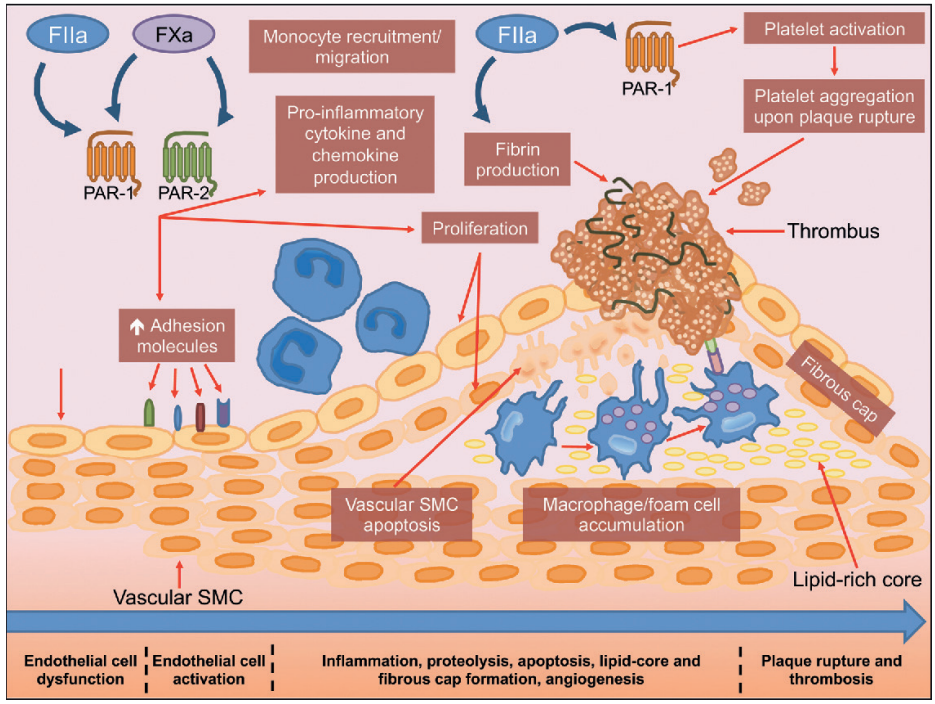

Figure 1. Pathophysiology of atherothrombosis and effect of dual pathway inhibition. Reproduced with permission, from: Esmon CT. Targeting factor Xa and thrombin: impact on coagulation and beyond. Thromb Haemost. 2014; 111(4): 625–633, doi: 10.1160/TH13-09-0730, indexed in Pubmed: 24336942

Abbreviations: F, factor; PAR, proteinase-activated receptor; SMC, smooth muscle cell

found no benefit of clopidogrel plus aspirin, compared with clopidogrel alone, for prevention of ischemic stroke, MI, CV death, or re-hospitalization for acute ischemia after a treatment duration of 18 months. There was, however, an increase in life-threatening bleeding (absolute risk increase [ARR], 1.3%; 95% CI, 0.6–1.9; P <0.001) [15].

GUIDELINE RECOMMENDATIONS FOR ANTIPLATELET THERAPY

Guidelines generally recommend combination antiplatelet therapy in patients with a recent acute atherothrombotic coronary, cerebral, or peripheral arterial event [16–18]. After the acute phase, they recommend re-evaluation of long-term risk to determine whether to continue intensified therapy with DAPT (or an alternative intensified antithrombotic regimen) or to de-escalate treatment to single-agent antiplatelet therapy.

DPI has now emerged as an alternative to long-term DAPT in the chronic phase in patients with ASCVD who remain at persistently high risk of recurrent ischemic events.

EVIDENCE FOR DUAL PATHWAY INHIBITION

Dual pathway inhibition (DPI) involves the use of an antiplatelet drug in combination with an anticoagulant, thereby targeting both platelets and coagulation. Aspirin inhibits platelets by blocking platelet cyclooxygenase-1 and preventing the formation of thromboxane A2, whereas clopidogrel, prasugrel, and ticagrelor inhibit platelets by binding to the membrane P2Y12 receptor and preventing ADP-induced platelet activation. Anticoagulants target one or more coagulation proteins, thereby inhibiting thrombin generation or activity. Thrombin formed on the surface of activated cells plays a pivotal role in fibrin clot formation and is also a potent platelet agonist (Figure 1). Accordingly, a strategy that targets both platelets and thrombin can be expected to act synergistically to reduce thrombus formation. By targeting platelets, antiplatelet drugs not only prevent platelet activation but may also reduce thrombin formation on the surface of activated platelets. By inhibiting thrombin generation or activity, anticoagulant drugs not only prevent fibrin formation but may also reduce platelet activation [19].

WARFARIN AND DIRECT THROMBIN INHIBITORS

The first DPI therapy tested was the combination of warfarin and aspirin. A meta-analysis of randomized trials including 25 307 patients with a recent ACS demonstrated that the combination of warfarin (targeting an international normalized ratio of 2–3) and aspirin, compared to aspirin alone, reduced the risk of all-cause death, non-fatal MI, and non-fatal thromboembolic stroke (OR, 0.73, 95% CI; 0.63–0.84; P <0.0001) at the cost of an increase in major bleeding (OR, 2.32; 95% CI, 1.63–3.29; P <0.001), but with no reduction in mortality [20]. The WAVE trial involving 2161 patients with stable PAD found no evidence of a benefit of adding warfarin to aspirin, compared to aspirin alone, for the prevention of MI, stroke, or death from CV causes

Table 1. Major trials of dual pathway inhibition with rivaroxaban

Clinical trial	Patient population	Intervention	Control	Dual pathway vs. control	
				Efficacy	Safety
ATLAS ACS-2 TIMI 51	ACS in previous 7 days (n = 15 526)	Rivaroxaban 2.5 mg twice daily or rivaroxaban 5 mg twice daily[a]	Placebo	2.5 mg dose: Composite of CV death, MI, or stroke: 9.1% vs. 10.7%; HR, 0.84; 95% CI, 0.72–0.97; *P* = 0.007 5 mg dose: Composite of CV death, MI, or stroke: 8.8% vs. 10.7%; HR, 0.85; 95% CI, 0.73–0.98; *P* = 0.01	2.5 mg dose: Non-CABG TIMI major bleeding: 1.8% vs. 0.6%; *P* <0.001. Intracranial hemorrhage: 0.4% vs. 0.2%; *P* = 0.04 5 mg dose: non-CABG TIMI major bleeding: 2.4% vs. 0.6%; *P* <0.001. Intracranial hemorrhage: 0.7% vs. 0.2%; *P* = 0.005
COMPASS	Chronic atherosclerotic vascular disease: CAD, PAD, or both (n = 27 395)	Rivaroxaban 2.5 mg twice daily + aspirin or rivaroxaban 5 mg twice daily	Aspirin 100 mg once daily	Composite of CV death, MI, or stroke: 4.1% vs. 5.4%; HR, 0.76; 95% CI, 0.66–0.86; *P* <0.001. Death from any cause: 3.4% vs. 4.1%; HR, 0.82; 95% CI, 0.71–0.96; *P* = 0.01	Major bleeding: 3.1% vs. 1.9%; HR, 1.70; 95% CI, 1.40–2.05; *P* <0.001
VOYAGER	Symptomatic PAD with recent lower extremity endovascular or surgical revascularization (n = 6 564)	Rivaroxaban 2.5 mg twice daily + aspirin[b]	Aspirin 100 mg once daily	Composite of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or CV death: 17.3% vs. 19.9%; HR, 0.85, 95% CI, 0.76–0.96; *P* = 0.009	TIMI major bleeding: 2.65% vs. 1.87%; HR, 1.43; 95% CI, 0.97–2.10; *P* = 0.07
COMMANDER-HF	Heart failure with LVEF of 40% or less with CAD and an episode of worsening heart failure within 21 days	Rivaroxaban 2.5 mg twice daily[c]	Placebo	Composite of death from any cause, MI, or stroke: 25.0% vs. 26.2%; HR, 0.94, 95% CI, 0.84–1.05; *P* = 0.27	Fatal bleeding or bleeding into a critical space with a potential for causing permanent disability: 0.7% vs. 0.9%, HR, 0.80; 95% CI, 0.43–1.49; *P* = 0.48

[a]99% of patients received aspirin and 93% received a thienopyridine; [b]51% of patients received clopidogrel; [c]93% of patients used aspirin alone or in combination with a thienopyridine, and 35% of patients were receiving dual antiplatelet therapy

Abbreviations: ACS, acute coronary syndrome; CV death, cardiovascular death; MI, myocardial infarction; HR, hazard ratio, non-CABG TIMI major bleeding, non-coronary artery bypass graft thrombolysis in myocardial infarction major bleeding; CAD, coronary artery disease; PAD, peripheral arterial disease; LVEF, left ventricular ejection fraction

Table 2. Guideline recommendations for dual pathway inhibition in patients with atherosclerotic cardiovascular disease

Patient population	Guideline	Statement	Recommendation class
Atherosclerotic cardiovascular disease	2021 European Society of Cardiology Guidelines on cardiovascular disease prevention in clinical practice [51]	Adding a second antithrombotic drug (a P2Y12 inhibitor or low-dose rivaroxaban) to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischemic events and without high bleeding risk	IIa
Acute coronary syndrome	2020 European Society of Cardiology Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation [52]	In acute coronary syndrome patients with no prior stroke/transient ischemic attack who are at high ischemic risk and low bleeding risk and are receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately 1 year) may be considered after discontinuation of parenteral anticoagulation	IIb
Peripheral arterial disease — chronic	2021 European Society of Cardiology Guidelines on cardiovascular disease prevention in clinical practice [51]	In patients with diabetes mellitus and chronic symptomatic lower extremity atherosclerotic disease without high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg twice daily) and aspirin (100 mg once daily) may be considered	IIa
	2022 Canadian Cardiovascular Society Guidelines for Peripheral Arterial Disease [53]	We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80-100 mg daily) for management of patients with symptomatic lower extremity peripheral arterial disease who are at high risk for ischemic events (high-risk comorbidities, such as polyvascular disease, diabetes, history of heart failure, or renal insufficiency) and/or high-risk limb presentation post peripheral revascularization (limb amputation, rest pain, ischemic ulcers) and at low bleeding risk	Strong recommendation
		We recommend combination treatment with rivaroxaban 2.5 mg twice daily and aspirin or single antiplatelet therapy for patients with symptomatic lower extremity peripheral arterial disease and low bleeding risk in the absence of high-risk limb presentation or high-risk comorbidities	Strong recommendation
Peripheral arterial disease — acute		We recommend rivaroxaban 2.5 mg twice daily in combination with aspirin (80–100 mg daily), with or without short-term clopidogrel use, for patients with lower extremity peripheral arterial disease after elective endovascular revascularization	Strong recommendation
		We recommend treatment with rivaroxaban 2.5 mg twice daily in combination with aspirin (80–100 mg daily) for patients with lower extremity peripheral arterial disease after elective open revascularization	Strong recommendation

Table 3. Atherosclerotic cardiovascular disease patients who may experience the greatest benefit of dual pathway inhibition

Trial/population	CV death, MI, and stroke per 1000 patients prevented with rivaroxaban twice daily + aspirin as compared to aspirin alone over 24 months	Non-CABG TIMI major bleeding events per 1000 patients caused by rivaroxaban twice daily + aspirin as compared to aspirin alone over 24 months	Net clinical benefit (non-bleeding CV death, MI, ischemic stroke, fatal bleeding, and intracranial hemorrhage) per 1000 patients with rivaroxaban twice daily + aspirin as compared to aspirin alone over 24 months
ATLAS ACS-2 TIMI 51 overall	18.0	15.0	9.3 [54]
Recent ACS with history of heart failure	64.0	2.0	Not reported
Recent ACS with no history of heart failure	6.5	Not reported	Not reported
Trial/population	**MACE, ALI, and total amputation per 1000 patients prevented with rivaroxaban 2.5 mg twice daily + aspirin as compared to aspirin alone over 30 months**	**Severe major bleeding events per 1000 patients caused by rivaroxaban 2.5 mg twice daily + aspirin as compared to aspirin alone over 30 months**	**Net clinical benefit (MACE, ALI, vascular amputation, and severe major bleeding) per 1000 patients with rivaroxaban 2.5 mg twice daily + aspirin as compared to aspirin alone over 30 months**
COMPASS overall	23.0	2.0	22.0
Polyvascular (involvement of ≥2 vascular beds)	60.0	0	58.6
No polyvascular involvement	14.0	3.0	12.4
History of mild or moderate heart failure	44.0	0	45.9
No history of heart failure	18.0	3.0	16.4
eGFR <60 ml/min/1.73 cm^2	36.0	5.0	33.6
eGFR ≥60 ml/min/1.73 cm^2	19.0	2.0	18.1
History of diabetes	31.0	4.0	31.0
No history of diabetes	19.0	2.0	16.5

Abbreviations: ACS, acute coronary syndrome; ALI, acute limb ischemia; CV death, cardiovascular death; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiac events; MI, myocardial infarction; non-CABG TIMI major bleeding, non-coronary artery bypass graft thrombolysis in myocardial infarction major bleeding

(RR, 0.92; 95% CI, 0.73–1.16; $P = 0.48$) but the combination increased the risk of life-threatening bleeding (RR, 3.41; 95% CI, 1.84–6.35; $P < 0.001$), most importantly intracranial hemorrhage [21].

Several direct oral anticoagulants have been tested as part of a DPI strategy in phase II studies of patients with a recent ACS. The ESTEEM trial involving 1883 post-MI patients demonstrated that the combination of ximelagatran and aspirin reduced all-cause death, nonfatal MI, or severe recurrent ischemia (HR, 0.76; 95% CI, 0.59–0.98; $P = 0.04$) [22]. In a similar post-MI population (n = 1861), the REDEEM trial demonstrated that dabigatran compared with placebo on a background of dual antiplatelet therapy produced a dose-dependent decrease in D-dimer levels which was accompanied by a dose-dependent increase in major and clinically relevant non-major bleeding. The combination did not reduce recurrent ischemic events, but the trial was not powered for efficacy outcomes [23]. Neither of these agents has been evaluated in phase III trials.

FACTOR XA INHIBITORS

Recent acute event

Apixaban

APPRAISE-2 enrolled 7 392 patients with a recent MI before it was stopped because apixaban 5 mg twice daily versus placebo on a background of routine antiplatelet therapy (81% of patients were receiving DAPT) was associated with excess major bleeding, including additional intracranial and fatal bleeding, with no reduction in recurrent ischemic events [24].

Rivaroxaban

The combination of rivaroxaban and antiplatelet therapy has been tested in patients with a recent ACS, as well as in those with chronic ASCVD and incorporated into practice guidelines (Tables 1 and 2). Unlike apixaban, which was tested at the same dose and shown to be effective for stroke prevention in patients with AF, rivaroxaban was tested at a dose of 2.5 mg or 5 mg twice daily, which is one-quarter to one-half of the total daily dose routinely used for stroke prevention in AF and the treatment of venous thromboembolism.

ATLAS TIMI 46 was a phase II dose-finding trial in patients with recent ACS which compared rivaroxaban at total daily doses of 5-20 mg given in single or divided doses with placebo given on a background of single or dual antiplatelet therapy. Rivaroxaban reduced death, MI, or stroke with an overall risk reduction of 31% for the 2.5 and 5 mg doses combined (HR 0.69; CI; 0.50–0.96; $P = 0.03$) and increased bleeding in a dose-dependent manner [25].

Building on the results of the phase II trial, the phase III ATLAS ACS-2 TIMI 51 trial tested rivaroxaban at doses of 2.5 and 5 mg twice daily compared to placebo in 15 526 post-ACS patients receiving standard antiplatelet therapy (93% were receiving dual antiplatelet therapy). The combined doses of rivaroxaban reduced the risk of

CV death, MI, or stroke (8.9% vs. 10.7%; HR, 0.84; 95% CI, 0.74–0.96; *P* = 0.008), and the 2.5 mg twice daily dose also reduced stent thrombosis (HR, 0.65; 95% CI, 0.45–0.94; *P* = 0.02), CV death (HR, 0.66; 95% CI, 0.51–0.86; *P* = 0.002), and death from any cause (HR, 0.68; 95% CI, 0.53–0.87; *P* = 0.002), albeit at the cost of an increased risk of major and intracranial bleeding [26].

High-risk patients

Subgroup analyses of the ATLAS ACS-2 TIMI 51 and COMPASS trials were performed to identify patients at the highest risk of recurrent thromboembolic events who would be expected to derive the greatest benefits (Table 3).

In a subgroup analysis of the ATLAS ACS-2 TIMI 51 trial, patients with a history of heart failure appeared to experience greater benefit (HR, 0.60; 95% CI, 0.46–0.78) than those without heart failure (HR, 0.92; 95% CI, 0.79–1.06; *P* for interaction = 0.006) [27].

Additional analyses demonstrated benefits of rivaroxaban in patients with STEMI and in those with positive biomarkers (troponin and/or creatine-kinase myocardial band isoenzyme elevation); STEMI: HR, 0.85; 95% CI, 0.70–1.03; biomarker positive disease: HR, 0.81; 95% CI, 0.71–0.93 [28, 29]. Furthermore, among biomarker-positive patients, there appeared to be a significant interaction between treatment and past history of TIA or stroke (prior TIA or stroke: HR, 2.18; 95% CI, 0.82–5.77; no history of TIA or stroke: HR, 0.79; 95% CI, 0.69–0.91; *P* for interaction = 0.04) [29]. The latter results must, however, be cautiously interpreted because the analyses were performed post-hoc, are of borderline significance, and are inconsistent with external data from the COMPASS trial which demonstrated substantial benefits of DPI in patients with prior stroke.

The results of the ATLAS trial suggest that rivaroxaban provides clear benefits in the management of patients with recent ACS treated with routine antiplatelet therapy. However, regulators in the United States and Canada did not approve rivaroxaban for this indication because of methodological concerns (high rates of loss to follow-up) and the increase in serious bleeding. Outside of North America, rivaroxaban has been approved for this indication, but uptake has been limited, presumably because the combination of ticagrelor and aspirin appears to provide similar benefits to the combination of rivaroxaban 2.5 mg twice daily and DAPT.

Symptomatic PAD with recent revascularization

VOYAGER was a multinational randomized controlled trial (RCT) of 6564 patients post endovascular or surgical revascularization for lower extremity PAD that randomized patients to rivaroxaban 2.5 mg twice daily or placebo on a background of single-agent or dual antiplatelet therapy. Rivaroxaban, compared with placebo, was associated with a reduced risk of acute limb ischemia, major amputation for vascular causes, MI, ischemic stroke, or death from CV causes (17.3% vs. 19.9% (HR, 0.85; 95% CI, 0.76–0.96; *P* = 0.009) at the cost of an increase in major bleeding according to the score of the International Society of Thrombosis and Hemostasis [30].

Revascularization approach

A subgroup analysis of VOYAGER patients compared efficacy and safety outcomes in those who underwent surgical revascularization (33%) compared to those who underwent an endovascular approach (67%). The analysis demonstrated that regardless of revascularization strategy, effects on efficacy or safety endpoints were consistent (p for interaction 0.17 and 0.73 respectively) [31].

Concomitant clopidogrel use

Another subgroup analysis of VOYAGER patients demonstrated consistent efficacy and safety outcomes in patients treated with background DAPT with the combination of clopidogrel and aspirin (51%) and in those who received aspirin alone (*P* for interaction 0.92 and 0.71, respectively). However, rivaroxaban was associated with more major bleeding within 365 days in patients treated with clopidogrel for more than 30 days compared with those treated for shorter periods (clopidogrel >30 days: HR, 3.20; 95% CI, 1.44–7.13, clopidogrel ≤30 days: HR, 1.30; 95% CI, 0.68–2.47; *P* for interaction = 0.07) [32].

Chronic atherosclerotic vascular disease

The COMPASS trial, a large multinational RCT of 27 395 patients with chronic ASCVD, randomized participants to DPI with rivaroxaban 2.5 mg twice daily with aspirin, rivaroxaban 5 mg twice daily monotherapy, or aspirin monotherapy [33]. The combination of rivaroxaban and aspirin, compared with aspirin alone, reduced the primary composite endpoint of CV death, MI, or stroke (4.9% vs. 5.4%; HR, 0.76; 95% CI, 0.66–0.86; *P* <0.001), but there was no benefit of rivaroxaban 5 mg twice daily. DPI produced consistent benefits with respect to individual components of the primary composite endpoint, including CV death (HR, 0.78; 95% CI, 0.64–0.96; *P* = 0.02), MI (HR, 0.86; 95% CI, 0.70–1.05; *P* = 0.14) and stroke (HR, 0.58; 95% CI, 0.44–0.76; *P* <0.001). The study also found a reduction in the secondary endpoint of death from any cause (HR, 0.82; 95% CI, 0.71–0.96; *P* = 0.01). In addition, major adverse limb events were reduced with DPI therapy (HR, 0.54; 95% CI, 0.35–0.84; *P* = 0.005). These benefits came at the cost of an excess of major bleeding events (HR, 1.70; 95% CI, 1.40–2.05; *P* <0.001). Most of the excess major bleeding was in the gastrointestinal tract, and there were no significant differences between the groups with respect to fatal or intracranial bleeding or symptomatic bleeding into a critical organ. Overall, a composite net clinical benefit outcome of CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ was lower with rivaroxaban plus aspirin than with aspirin alone (HR, 0.80; 95% CI, 0.70–0.91; *P* <0.001).

High-risk patients

The Reduction of Atherothrombosis for Continued Health (REACH) registry risk score and Classification and Regression Trees (CART) survival analysis were used to identify patient populations at the highest risk of atherothrombotic events most likely to benefit from DPI therapy as tested in the COMPASS trial. Absolute net clinical benefit (composite of CV death, MI, stroke, acute limb ischemia, vascular amputation, fatal bleeding, or symptomatic bleeding into a critical organ) was greatest in patients with vascular disease involving two or more vascular beds and those with mild or moderate heart failure, kidney disease, or diabetes [36].

The relative net clinical benefits of DPI with rivaroxaban 2.5 mg twice daily and aspirin were consistent in patients regardless of the number of concomitant medical conditions, and absolute benefits were greatest in patients taking four or more concomitant cardiovascular medications [37].

Symptomatic lower extremity peripheral arterial disease

In patients with symptomatic PAD, DPI with rivaroxaban 2.5 mg twice daily and aspirin, as compared to aspirin alone, had consistent benefit with respect to the overall trial population and with respect to the primary composite endpoint (HR, 0.71; 95% CI, 0.53–0.97) with greater absolute benefit in this subpopulation owing to their higher baseline risk of atherothrombotic events [38].

Coronary artery bypass grafting (CABG)

The combination of rivaroxaban and aspirin, compared with aspirin, produced a consistent reduction in the primary outcome among 1448 patients who underwent CABG surgery 4–14 days before randomization (HR, 0.69; 95% CI, 0.33–1.47; $P = 0.34$) but did not reduce graft failure rates at one year [39].

Heart failure in patients with underlying coronary artery disease

The COMMANDER-HF trial involving 5 022 patients with CAD and recent heart-failure hospitalization (in the previous three weeks) receiving routine antiplatelet therapy (93%) found no benefit of rivaroxaban 2.5 mg twice, compared with placebo, for prevention of death from any cause, MI, or stroke [40]. This result appears to be inconsistent with the benefits of rivaroxaban 2.5 mg twice daily in patients with heart failure enrolled in the ATLAS ACS-2 TIMI 51 and COMPASS trials. However, deaths in the COMMANDER-HF trial were dominated by pump failure and sudden cardiac death which would not be expected to be favorably modified by antithrombotic treatment. Consistent with this conclusion, a post-hoc analysis that excluded heart failure and sudden cardiac deaths suggested that rivaroxaban 2.5 mg twice daily was effective in preventing thromboembolic events [41]. Taken together with the results of the COMPASS trial, these data suggest that DPI produces consistent reductions in thromboembolic events across the spectrum of severity of heart failure.

Table 4. Dual pathway inhibition-eligible patients who may warrant consideration of alternative antithrombotic therapy

Population	Recommended antithrombotic therapy
ACS receiving aspirin + ticagrelor	Aspirin + ticagrelor alone × 1 year; consider switching to DPI afterwards unless high risk of stent thrombosis[a]
ALI post revascularization	Consider full dose anticoagulation (warfarin or DOAC) + aspirin or DAPT × 3–6 months; switch to DPI afterwards[a]
Atrial fibrillation	Therapeutic dose anticoagulation
VTE (provoked)	Therapeutic dose anticoagulation × 3–6 months; consider switching to DPI afterwards[a]
VTE (unprovoked)	Therapeutic dose anticoagulation; consider switching to DPI 3–6 months after VTE event after individual benefit/risk assessment[a]
CKD with eGFR <15 ml/min/1.73 cm^2	Single antiplatelet[a]

[a]Unless additional comorbidities warrant more intensive antithrombotic therapy

Abbreviations: ACS, acute coronary syndrome; ALI, acute limb ischemia; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; DOAC, direct oral anticoagulant; DPI, dual pathway inhibition; eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism

Stroke reduction in post-stroke patients

In a separate analysis of 351 patients with previous stroke, DPI with rivaroxaban 2.5 mg twice daily and aspirin, as compared to aspirin alone, produced consistent benefits with respect to the primary composite endpoint (prior stroke: HR, 0.42; 95% CI, 0.19–0.92; no prior stroke: HR, 0.60; 95% CI, 0.45–0.80; P for interaction = 0.40) but greater absolute benefit owing to their higher baseline risk of thrombotic events [35].

Long-term and community patient benefit and safety of DPI

Of the 27 395 patients enrolled in COMPASS, 12 964 were enrolled in a long-term open-label evaluation of DPI continued for a median time of an additional 374 days (maximum 1 191 days). The study demonstrated an incident rate for the primary outcome per 100 patient years of 2.35, which is similar to that observed in the randomized evaluation. Major and minor bleeding rates were 1.01 and 2.49 events per 100 patient years which were lower than those observed in the main trial [42]. While these data appear to be reassuring, they should be cautiously interpreted because of potential selection and survival biases since only 47% of patients originally enrolled in COMPASS continued in LTOLE.

The use of DPI therapy in community patients was further evaluated in the international XATOA registry. A total of 5808 patients with CAD, PAD, or both, receiving DPI were enrolled. As compared to the COMPASS trial where only 27% of patients had PAD, 59% of patients enrolled in XATOA had PAD (59%). The analysis found a similar incidence of major adverse cardiac events and lower rates of major bleeding as compared to the COMPASS trial. Rates of major adverse limb events were higher, which was

Table 5. Ongoing clinical trials of dual pathway inhibition therapy in patients with, or at risk of, atherosclerotic cardiovascular disease

Clinical trial	Population	Intervention	Control	Primary outcome
NCT05077683	Anterior STEMI or very high-risk NSTEMI patients with anterior wall motion abnormalities and culprit lesion of the proximal or mid portion of the left anterior descending artery (n = 560)[a]	Rivaroxaban 2.5 mg twice daily + DAPT	DAPT	Rate of left ventricular thrombus formation
NCT04838808	Type II MI patients (n = 100)[a]	Rivaroxaban 2.5 mg twice daily	Placebo	Feasibility
NCT04142125	ICAD with recent TIA or stroke (n = 100)	Rivaroxaban 2.5 mg twice daily + aspirin 81 mg daily	Aspirin 81 mg daily	Feasibility, rate of intracranial hemorrhage
NCT05047172	ICAD with recent stroke (n = 1683)[a]	Rivaroxaban 2.5 mg twice daily + aspirin 81 mg daily or ticagrelor 180 mg × 1, then 90 mg twice daily + aspirin 81 mg daily	Clopidogrel 600 mg × 1, then 75 mg daily + aspirin 81 mg daily	Composite of ischemic stroke, intracerebral hemorrhage, or vascular death
NCT04853719	PAD with limiting claudication (n = 88)[a]	Rivaroxaban 2.5 mg twice daily + aspirin 100 mg daily	Aspirin 100 mg daily	Claudication distance and quality of life walking impairment questionnaire
NCT03969953	CKD with high CV risk (n = 2000)[a]	Rivaroxaban 2.5 mg twice daily	Placebo	MACE
NCT04168398	PAD after lower extremity revascularization (n = 1536)	Apixaban 2.5 mg twice daily + aspirin 81 mg daily	Clopidogrel 75 mg daily + aspirin 81 mg daily	MALE
NCT04229264	PAD after infrapopliteal angioplasty for critical limb ischemia (n = 200)[a]	Apixaban 2.5 mg twice daily + aspirin 100 mg daily	Clopidogrel 75 mg twice daily + aspirin 100 mg daily	Restenosis of treated infrapopliteal artery, major amputation, clinical driven target lesion revascularization, MACE

[a]Estimated enrollment

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; DAPT, dual antiplatelet therapy; ICAD, intracranial atherosclerotic disease; MACE, major adverse cardiac events; MALE, major adverse limb events; NSTEMI; non-ST-segment elevation myocardial infarction; MI, myocardial infarction; PAD, peripheral arterial disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attack

consistent with the inclusion of a greater proportion of high-risk patients with PAD [43].

Cost-effectiveness of DPI therapy

Given the impressive patient-level benefits of DPI therapy, cost-effectiveness analyses have been performed to assess the value of this intervention from a systemic perspective. Incremental cost-effectiveness ratios (ICERs) of 1–3 times a country's gross domestic product are commonly used as a threshold; interventions below this threshold are considered an efficient use of healthcare dollars [44]. A Swedish cost-effectiveness study of the use of rivaroxaban 2.5 mg twice daily in addition to standard antiplatelet therapy, as compared to standard antiplatelet therapy alone, in patients with ACS with elevated cardiac biomarkers without a history of TIA or stroke found rivaroxaban to be a cost-effective treatment option with a gain of 0.14 quality-adjusted life years (QALY) with an incremental cost-effectiveness ratio (ICER) of 8073 USD/QALY [45]. More compellingly, over a lifetime, DPI therapy as tested in patients with chronic ASCVD enrolled in the COMPASS trial was associated with a gain of 1.17 QALY, with ICER ranging from 3946 USD/QALY in Canada to 10 254 USD/QALY in Germany [46]. Even lower ICERs in patients were calculated for patients with PAD and polyvascular disease although these patient groups often have low adherence to guideline-recommended therapies [47], and targeted initiatives to increase uptake of DPI in these populations would be required to realize full system benefits. The ICERs reported in both of these studies would be considered cost-effective in most middle- and high-income countries.

Antithrombotic therapy in patients ineligible for DPI

DPI therapy has proven to be effective, safe, and cost-effective in a wide variety of ASCVD populations. Some patient groups may, however, be better served by alternate antithrombotic regimens (Table 4).

Specifically to patients with recent ACS, those receiving DAPT with ticagrelor were not represented in the ATLAS ACS-2 TIMI 51 trial, and this regimen may be preferred over the combination of rivaroxaban, aspirin, and clopidogrel.

With respect to patients with PAD, those with acute limb ischemia in the previous two weeks were excluded from the VOYAGER trial and the optimal antithrombotic management strategy in this population is unknown. In a survey conducted by Canadian vascular surgeons, respondents indicated that they most commonly recommend full-dose anticoagulation (warfarin or direct oral anticoagulant) in combination with aspirin or dual antiplatelet therapy after urgent or emergent limb revascularization in patients at high risk of graft or stent thrombosis [48].

In terms of the broader ASCVD population, those with concomitant atrial fibrillation should continue to be treated with therapeutic anticoagulation for optimal stroke-reduction benefits. Likewise, patients with concomitant venous thromboembolism (VTE) should be treated with therapeutic doses of anticoagulant therapy for at least the first 3–6 months after a VTE event. Thereafter, patients with ASCVD and a provoked VTE event could be switched to DPI therapy. In patients with ASCVD and an unprovoked VTE, consideration could be given to using DPI therapy as an alternative to reduced-dose anticoagulant therapy for both ASCVD and extended VTE treatment after a careful individualized benefit-and-risk assessment. The COMPASS trial demonstrated efficacy of the combination of rivaroxaban and aspirin for VTE prevention. The trial also found similar rates of VTE in patients receiving DPI as compared to those receiving rivaroxaban 5 mg bid, but event rates were low, and the trial was likely underpowered to detect a difference with respect to this outcome. Finally, patients with severe renal dysfunction with an estimated glomerular filtration rate of less than 15 ml/min were excluded from COMPASS and VOYAGER and should be treated with single-agent antiplatelet therapy.

Unanswered questions and future directions

Additional studies are underway to assess the benefit of DPI in additional populations, including in type II MI (NCT04838808), prevention of left ventricular thrombus after MI (NCT05077683), intracranial atherosclerotic disease (NCT04142125 and NCT05047172), PAD with limiting claudication (NCT04853719), post lower extremity revascularization (NCT04168398 and NCT04229264), and advanced chronic kidney disease with ASCVD or risk factors for ASCVD (NCT03969953) (Table 5).

An outstanding question is the choice of antiplatelet agent to be used in combination with rivaroxaban. Previous studies have primarily used aspirin alone or in combination with clopidogrel. Given evidence of superior efficacy of P2Y12 inhibitors, as compared to aspirin, as demonstrated in the CAPRIE and HOST-EXAM trials [49, 50], there is a need for additional studies to evaluate the use of rivaroxaban in combination with clopidogrel or ticagrelor compared to aspirin.

CONCLUSIONS

Despite widely available lifestyle and medical interventions, ASCVD represents a growing worldwide burden of mortality, disability, and healthcare costs. DPI therapy, by synergistically targeting platelet activation and fibrin formation, has demonstrated substantial benefits in a broad range of patients with acute and chronic ASCVD and is now increasingly being incorporated into treatment guidelines. The challenge facing clinicians is to apply this therapy in patients at the highest risk of recurrent atherothrombotic vascular events who are expected to derive the greatest benefits, thereby helping further reduce morbidity and mortality of ASCVD.

Article information

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REFERENCES

1. Roth GA, Mensah GA, Johnson CO, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020; 76(25): 2982–3021, doi: 10.1016/j.jacc.2020.11.010, indexed in Pubmed: 33309175.
2. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006; 295(2): 180–189, doi: 10.1001/jama.295.2.180, indexed in Pubmed: 16403930.
3. Badimon L, Padró T, Vilahur G. Atherosclerosis, platelets and thrombosis in acute ischaemic heart disease. Eur Heart J Acute Cardiovasc Care. 2012; 1(1): 60–74, doi: 10.1177/2048872612441582, indexed in Pubmed: 24062891.
4. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009; 373(9678): 1849–1860, doi: 10.1016/S0140-6736(09)60503-1, indexed in Pubmed: 19482214.
5. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345(7): 494–502, doi: 10.1056/NEJMoa010746, indexed in Pubmed: 11519503.
6. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11): 1045–1057, doi: 10.1056/NEJMoa0904327, indexed in Pubmed: 19717846.
7. Roe MT, Armstrong PW, Fox KAA, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357(20): 2001–2015, doi: 10.1056/NEJMoa0706482, indexed in Pubmed: 17982182.
8. Belch J, Dormandy J. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (CASPAR) trial. J Vasc Surg. 2010; 52(4): 825–833.e2, doi: 10.1016/j.jvs.2010.04.027, indexed in Pubmed: 20678878.
9. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013; 369(1): 11–19, doi: 10.1056/NEJMoa1215340, indexed in Pubmed: 23803136.
10. Johnston SC, Easton JD, Farrant M, et al. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. N Engl J Med. 2018; 379(3): 215–225, doi: 10.1056/NEJMoa1800410, indexed in Pubmed: 29766750.

11. Bhatt DL, Fox KAA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006; 354(16): 1706–1717, doi: 10.1056/NEJMoa060989, indexed in Pubmed: 16531616.
12. Bhatt DL, Paré G, Eikelboom JW, et al. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. J Am Coll Cardiol. 2007; 49(19): 1982–1988, doi: 10.1016/j.jacc.2007.03.025, indexed in Pubmed: 17498584.
13. Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016; 37(4): 390–399, doi: 10.1093/eurheartj/ehv443, indexed in Pubmed: 26324537.
14. Steg PG, Bhatt DL, Simon T, et al. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med. 2019; 381(14): 1309–1320, doi: 10.1056/NEJMoa1908077, indexed in Pubmed: 31475798.
15. Diener HC, Bogousslavsky J, Brass L, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004; 364(9431): 331–337, doi: 10.1016/s0140-6736(04)16721-4, indexed in Pubmed: 15276392.
16. Collet JP, Thiele H. The 'Ten Commandments' for the 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2020; 41(37): 3495–3497, doi: 10.1093/eurheartj/ehaa624, indexed in Pubmed: 33085966.
17. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2021; 52(7): e364–e467, doi: 10.1161/STR.0000000000000375, indexed in Pubmed: 34024117.
18. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017; 135(12): e686–e725, doi: 10.1161/CIR.0000000000000470, indexed in Pubmed: 27840332.
19. Monroe D, Hoffman M, Roberts H. Platelets and thrombin generation. Arterioscler Thromb Vasc Biol. 2002; 22(9): 1381–1389, doi: 10.1161/01.atv.0000031340.68494.34, indexed in Pubmed: 12231555.
20. Andreotti F, Testa L, Biondi-Zoccai GGL, et al. Aspirin plus warfarin compared to aspirin alone after acute coronary syndromes: an updated and comprehensive meta-analysis of 25,307 patients. Eur Heart J. 2006; 27(5): 519–526, doi: 10.1093/eurheartj/ehi485, indexed in Pubmed: 16143706.
21. Anand S, Yusuf S, Xie C, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. N Engl J Med. 2007; 357(3): 217–227, doi: 10.1056/NEJMoa065959, indexed in Pubmed: 17634457.
22. Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet. 2003; 362(9386): 789–797, doi: 10.1016/S0140-6736(03)14287-0, indexed in Pubmed: 13678873.
23. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011; 32(22): 2781–2789, doi: 10.1093/eurheartj/ehr113, indexed in Pubmed: 21551462.
24. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011; 365(8): 699–708, doi: 10.1056/NEJMoa1105819, indexed in Pubmed: 21780946.
25. Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009; 374(9683): 29–38, doi: 10.1016/S0140-6736(09)60738-8, indexed in Pubmed: 19539361.
26. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012; 366(1): 9–19, doi: 10.1056/NEJMoa1112277, indexed in Pubmed: 22077192.
27. Korjian S, Braunwald E, Daaboul Y, et al. Usefulness of rivaroxaban for secondary prevention of acute coronary syndrome in patients with history of congestive heart failure (from the ATLAS-ACS-2 TIMI-51 trial). Am J Cardiol. 2018; 122(11): 1896–1901, doi: 10.1016/j.amjcard.2018.08.034, indexed in Pubmed: 30340765.
28. Mega JL, Braunwald E, Murphy SA, et al. Rivaroxaban in patients stabilized after a ST-segment elevation myocardial infarction: results from the ATLAS ACS-2-TIMI-51 trial (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction-51). J Am Coll Cardiol. 2013; 61(18): 1853–1859, doi: 10.1016/j.jacc.2013.01.066, indexed in Pubmed: 23500262.
29. Korjian S, Braunwald E, Daaboul Y, et al. Safety and efficacy of rivaroxaban for the secondary prevention following acute coronary syndromes among biomarker-positive patients: Insights from the ATLAS ACS 2-TIMI 51 trial. Eur Heart J Acute Cardiovasc Care. 2019; 8(2): 186–193, doi: 10.1177/2048872617745003, indexed in Pubmed: 29249166.
30. Bonaca MP, Bauersachs RM, Hiatt WR, et al. Rivaroxaban in peripheral artery disease after revascularization. N Engl J Med. 2020; 382(21): 1994–2004, doi: 10.1056/NEJMoa2000052, indexed in Pubmed: 32222135.
31. Debus ES, Nehler MR, Govsyeyev N, et al. Effect of rivaroxaban and aspirin in patients with peripheral artery disease undergoing surgical revascularization: insights from the VOYAGER PAD trial. Circulation. 2021; 144(14): 1104–1116, doi: 10.1161/CIRCULATIONAHA.121.054835, indexed in Pubmed: 34380322.
32. Hiatt WR, Bonaca MP, Patel MR, et al. Rivaroxaban and aspirin in peripheral artery disease lower extremity revascularization: impact of concomitant clopidogrel on efficacy and safety. Circulation. 2020; 142(23): 2219–2230, doi: 10.1161/CIRCULATIONAHA.120.050465, indexed in Pubmed: 33138628.
33. Eikelboom J, Connolly S, Bosch J, et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med. 2017; 377(14): 1319–1330, doi: 10.1056/nejmoa1709118, indexed in Pubmed: 28844192.
34. Perera KS, Ng KKH, Nayar S, et al. Association between low-dose rivaroxaban with or without aspirin and ischemic stroke subtypes: a secondary analysis of the COMPASS trial. JAMA Neurol. 2020; 77(1): 43–48, doi: 10.1001/jamaneurol.2019.2984, indexed in Pubmed: 31524941.
35. Sharma M, Hart RG, Connolly SJ, et al. Stroke Outcomes in the COMPASS Trial. Circulation. 2019; 139(9): 1134–1145, doi: 10.1161/CIRCULATIONAHA.118.035864, indexed in Pubmed: 30667279.
36. Anand SS, Eikelboom JW, Dyal L, et al. Rivaroxaban plus aspirin versus aspirin in relation to vascular risk in the COMPASS trial. J Am Coll Cardiol. 2019; 73(25): 3271–3280, doi: 10.1016/j.jacc.2019.02.079, indexed in Pubmed: 31248548.
37. Vanassche T, Verhamme P, Anand SS, et al. Low-dose rivaroxaban plus aspirin in patients with polypharmacy and multimorbidity: an analysis from the COMPASS trial. Eur Heart J Cardiovasc Pharmacother. 2022; 8(5): 462–473, doi: 10.1093/ehjcvp/pvab050, indexed in Pubmed: 34191011.
38. Kaplovitch E, Eikelboom JW, Dyal L, et al. Rivaroxaban and Aspirin in Patients With Symptomatic Lower Extremity Peripheral Artery Disease: A Subanalysis of the COMPASS Randomized Clinical Trial. JAMA Cardiol. 2021; 6(1): 21–29, doi: 10.1001/jamacardio.2020.4390, indexed in Pubmed: 32997098.
39. Lamy A, Eikelboom J, Tong W, et al. Rationale, design and baseline characteristics of participants in the cardiovascular outcomes for people using anticoagulation strategies (COMPASS) trial. Can J Cardiol. 2017; 33(8): 1027–1035, doi: 10.1016/j.cjca.2017.06.001, indexed in Pubmed: 28754388.
40. Zannad F, Anker SD, Byra WM, et al. Rivaroxaban in patients with heart failure, sinus rhythm, and coronary disease. N Engl J Med. 2018; 379(14): 1332–1342, doi: 10.1056/NEJMoa1808848, indexed in Pubmed: 30146935.
41. Greenberg B, Neaton JD, Anker SD, et al. Association of rivaroxaban with thromboembolic events in patients with heart failure, coronary disease, and sinus rhythm: a post hoc analysis of the COMMANDER HF trial. JAMA Cardiol. 2019; 4(6): 515–523, doi: 10.1001/jamacardio.2019.1049, indexed in Pubmed: 31017637.
42. Eikelboom JW, Bosch J, Connolly SJ, et al. Combination antiplatelet and oral anticoagulant therapy in patients with coronary and peripheral artery disease. Circulation. 2019; 139(18): 2170–2185, doi: 10.1161/CIRCULATIONAHA.118.033580, indexed in Pubmed: 31034291.
43. Fox KAA, Aboyans V, Debus ES, et al. Patients selected for dual pathway inhibition in clinical practice have similar characteristics and outcomes to those included in the COMPASS randomized trial: The XATOA Registry. Eur Heart J Cardiovasc Pharmacother. 2022; 8(8): 825–836, doi: 10.1093/ehjcvp/pvac028, indexed in Pubmed: 35594542.

44. Kazibwe J, Gheorghe A, Wilson D, et al. The use of cost-effectiveness thresholds for evaluating health interventions in low- and middle-income countries from 2015 to 2020: a review. Value Health. 2022; 25(3): 385–389, doi: 10.1016/j.jval.2021.08.014, indexed in Pubmed: 35227450.
45. Begum N, Stephens S, Schoeman O, et al. Cost-effectiveness analysis of rivaroxaban in the secondary prevention of acute coronary syndromes in sweden. Cardiol Ther. 2015; 4(2): 131–153, doi: 10.1007/s40119-015-0041-3, indexed in Pubmed: 26099515.
46. Lamy A, Eikelboom J, Tong W, et al. The cost-effectiveness of Rivaroxaban with or without aspirin in the COMPASS trial. Eur Heart J Qual Care Clin Outcomes. 2022 [Epub ahead of print], doi: 10.1093/ehjqcco/qcac054, indexed in Pubmed: 36001989.
47. Armstrong EJ, Chen DC, Westin GG, et al. Adherence to guideline-recommended therapy is associated with decreased major adverse cardiovascular events and major adverse limb events among patients with peripheral arterial disease. J Am Heart Assoc. 2014; 3(2): e000697, doi: 10.1161/JAHA.113.000697, indexed in Pubmed: 24721799.
48. McClure GR, Kaplovitch E, Chan N, et al. A national canadian survey of antithrombotic therapy after urgent and emergent limb revascularization. Can J Cardiol. 2021; 37(3): 504–507, doi: 10.1016/j.cjca.2020.06.008, indexed in Pubmed: 32585326.
49. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). The Lancet. 1996; 348(9038): 1329–1339, doi: 10.1016/s0140-6736(96)09457-3.
50. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet. 2021; 397(10293): 2487–2496, doi: 10.1016/S0140-6736(21)01063-1, indexed in Pubmed: 34010616.
51. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Eur J Prev Cardiol. 2022; 29(1): 5–115, doi: 10.1093/eurheartj/ehab484, indexed in Pubmed: 34458905.
52. Collet JP, Thiele H, Barbato E, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. Eur Heart J. 2021; 42(14): 1289–1367, doi: 10.1093/eurheartj/ehaa575, indexed in Pubmed: 32860058.
53. Abramson BL, Al-Omran M, Anand SS, et al. Canadian Cardiovascular Society 2022 Guidelines for Peripheral Arterial Disease. Can J Cardiol. 2022; 38(5): 560–587, doi: 10.1016/j.cjca.2022.02.029, indexed in Pubmed: 35537813.
54. Gibson CM, Levitan B, Gibson WJ, et al. Fatal or irreversible bleeding and ischemic events with rivaroxaban in acute coronary syndrome. J Am Coll Cardiol. 2018; 72(2): 129–136, doi: 10.1016/j.jacc.2018.04.055, indexed in Pubmed: 29976285.