Rivaroxaban: A New Treatment Paradigm in the Setting of Vascular Protection?

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Abstract

The pathophysiology of atherosclerosis involves a diseased endothelium, lipid accumulation and low-grade inflammation. In later stages of coronary artery disease (CAD) and peripheral arterial disease (PAD), plaque rupture may induce atherothrombosis caused by fibrin formation and platelet activation, leading to vessel occlusion with subsequent organ damage such as myocardial infarction, stroke or limb ischaemia. Because of the high disease burden associated with CAD and PAD, there is a need for continuous vascular protection beyond currently available treatments including antiplatelet agents. Due to its central role in the coagulation cascade, inhibition of factor Xa, with the subsequent reduced thrombin formation that impacts not only fibrin but also platelets, may provide additional benefit over using antiplatelets alone. Evidence from Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis In Myocardial Infarction-51 (ATLAS-ACS 2-TIMI 51) supports the use of the direct, oral, factor Xa inhibitor rivaroxaban (2.5 mg twice-daily [bid] and 5 mg bid) in reducing mortality and morbidity in patients with acute coronary syndrome, when combined with antiplatelets. Here, we review the role of rivaroxaban in three clinical trials of CAD and/or PAD: Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS), Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for PAD (VOYAGER PAD) and Cardiovascular Outcome Modification, Measurement AND Evaluation of Rivaroxaban in patients with Heart Failure (COMMANDER HF).

Keywords
► coronary artery disease
► heart failure
► peripheral arterial disease
► rivaroxaban
► thrombosis

Introduction

Coronary artery disease (CAD) includes the clinical consequences of coronary artery atherothrombosis, including angina pectoris and myocardial infarction (MI). CAD is the most common single cause of death worldwide.[1,2] In 2015, the Global Burden of Disease collaboration highlighted the increasing incidence of mortality from the effects of CAD, due to the increasing age of the global population.[3] The American Heart Association (AHA) updated its Heart Disease and Stroke Statistics in 2017, which showed that 16.5 million U.S. adults aged ≥20 years have CAD and its prevalence increases with age in women and in men.[4]

In 2013, a total of 202 million people were estimated to be living with peripheral arterial disease (PAD) and the prevalence of PAD was approximately 5% in patients aged 45 to 49 years, rising to approximately 18% in those aged 85 to 89 years.[5] PAD is an atherosclerotic process that leads to

stenosis and occlusion of non-cerebral and non-coronary arteries. These are typically arteries of the lower extremities —the resulting limb ischaemia can lead to amputation.[6] PAD of the lower extremity is recognized as the third leading cause of atherosclerotic cardiovascular (CV) morbidity, after CAD and stroke.[5,7] The risk of CV death is increased 5-fold in patients with asymptomatic PAD and 11-fold in patients with symptomatic PAD, compared with patients without PAD.[8]

Evidence surrounding the real-world risk and clinical consequences of atherothrombosis is also available. The REACH registry is a global observational study of around 68,000 patients in 44 countries who are at high risk of atherothrombosis.[9] Findings from the REACH registry show that a significant proportion (15.9%) of the symptomatic population has polyvascular disease, encompassing CAD, PAD and/or cerebrovascular disease, and it was generally concluded that, despite the associated risks, CV disease is not being optimally managed.[9] Patients with CAD and/or PAD have an unmet need for effective prevention of atherothrombotic events. The risk of atherothrombotic events in these patients remains high, as often aggressive antiplatelet-only treatment has not conferred sufficient protection benefits.[10–13]

Atherothrombosis, induced by ruptured atherosclerotic plaques, occupies a central role in the pathogenesis of CAD and PAD. Rupture of the plaque is thought to be similar to acute coronary syndrome (ACS) in pathogenic terms, and this event causes the thrombogenic subendothelial matrix to become exposed, in turn activating both circulating platelets and the coagulation cascade.[14,15] Platelet agonists released by circulating platelets recruit and activate further platelets, while tissue factor is locally released and catalyses factor X conversion into factor Xa, leading to thrombin formation. Thrombin facilitates fibrin formation, crosslinking platelets and stabilizing the thrombus, suggesting a relationship between the two processes.[15] Clots forming at the vascular wall have similar levels of contribution from both fibrin and platelets, and thrombin appears to play a pivotal role in myocardial necrosis, vascular inflammation and endothelial dysfunction.[16] Antiplatelet therapy inhibits the aggregation of platelets activated through contact with collagen in the exposed vessel wall. Anticoagulation reduces the risk of clot formation by suppressing the direct activation of platelets and the generation of fibrin via the coagulation cascade.[14,15]

Factor Xa has a dual-pathway function by reducing thrombin generation and potentially showing complementary favourable activity, such as anti-inflammatory effects and endothelial protection (►Fig. 1). There is recognized therapeutic potential in targeting this dual pathway to reduce the risk of atherothrombotic events, through combining antiplatelet therapy with anticoagulation. Preclinical data have shown that the combination of rivaroxaban (at a dose equivalent to the trough plasma concentration after rivaroxaban 2.5 mg bid in humans) with single- or dual-antiplatelet therapy (DAPT) resulted in improved antithrombotic activity compared with rivaroxaban or antiplatelet therapy alone.[17] The effects of rivaroxaban were strongest on the dynamics of thrombin generation. The combination of rivaroxaban and ticagrelor further reduced thrombin C_{max} and mean velocity, and prolonged thrombin T_{max}, compared with either agent alone. The combination of rivaroxaban, ticagrelor and acetylsalicylic acid (ASA) showed another slight improvement in the effects compared with the rivaroxaban and ticagrelor combination. Similar synergistic effects were also seen with rivaroxaban and ticagrelor for the inhibition of tissue factor-induced platelet aggregation.[17]

Atherothrombosis is pathophysiologically characterized by a diseased endothelium with a low grade of inflammation, which needs continuous and lasting protection.[18,19] Reduction of long-term CV risk is achieved by a comprehensive
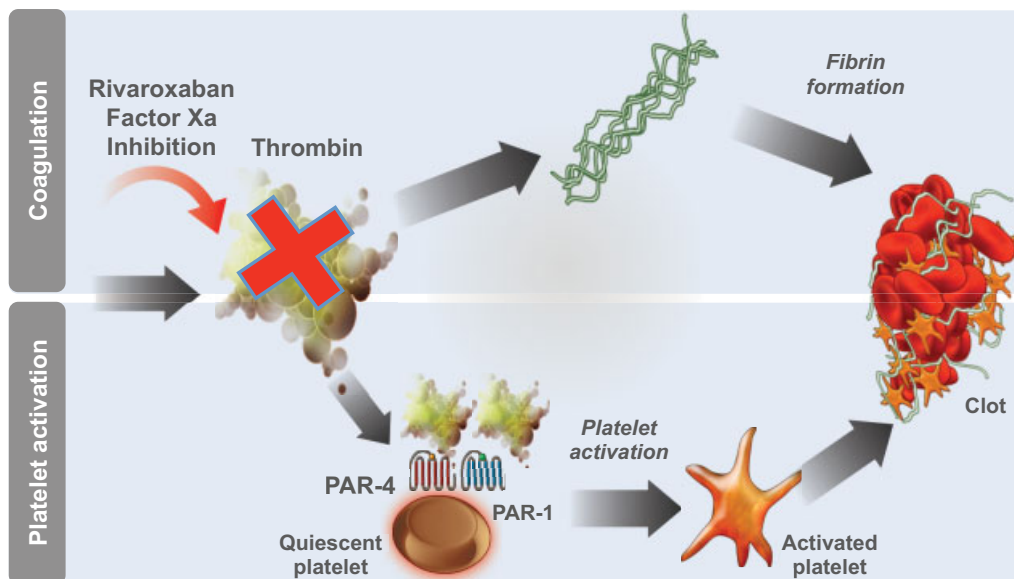

Fig. 1 Rivaroxaban targets essential components of atherothrombosis to provide vascular protection. Adapted with permission (Copyright© 2009 European Society of Cardiology. All rights reserved).[71] PAR, protease-activated receptor.

strategy, including the use of antithrombotics and lipid- or glucose-lowering drugs.[20] However, protection conferred with antiplatelets is likely to be limited and individual patient variability exists in response to these drugs.[21] On the other hand, rivaroxaban (2.5 mg twice-daily [bid] and 5 mg bid) has been shown to significantly reduce mortality and morbidity in patients with ACS, including those presenting with heart failure (HF).[22,23]

Targeted inhibition of thrombin generation with rivaroxaban in patients with CAD (with or without ischaemic HF) or PAD may stabilize multiple pathophysiological processes, i.e. reduce pro-inflammatory cytokines, reduce restenosis/narrowing of blood vessels and prevent atherosclerotic plaque progression/destabilization (via inhibition of protease-activated receptor [PAR]-1/2 by factor Xa or inhibition of PAR-1/4 by factor II),[24] thereby reducing mortality and morbidity. The development program of rivaroxaban in vascular protection aims to further evaluate the role of this factor Xa inhibitor in the prevention of atherothrombotic events (►Table 1). This article reviews the needs of specific groups of patients who have been included in three key randomized controlled trials (RCTs) involving rivaroxaban:

- Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial of patients with CAD and/ or PAD.
- Vascular Outcomes studY of ASA alonG with rivaroxaban in Endovascular or surgical limb Revascularization for PAD (VOYAGER PAD) trial of patients undergoing peripheral revascularization procedures.
- Cardiovascular Outcome Modification, Measurement AND Evaluation of Rivaroxaban in patients with Heart Failure (COMMANDER HF) trial of patients with HF and CAD.

Need for Vascular Protection in Patients with CAD

ACS, a key manifestation of CAD, describes a spectrum of clinical symptoms compatible with acute myocardial ischaemia and includes unstable angina, ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI). These manifestations of coronary artery atherosclerosis have a high clinical risk for the patient.[25,26]

Table 1 An overview of the rivaroxaban vascular protection program[23,50,51,67,70]

Patient population	Trial
Acute or unstable CAD	ATLAS ACS 2-TIMI 51 (complete) GEMINI-ACS-1 (complete)
Acute or unstable PAD	VOYAGER PAD (ongoing)
Acute heart failure and CAD	COMMANDER HF (ongoing)
Chronic or stable CAD/PAD	COMPASS (complete[a])

Abbreviations: CAD, coronary artery disease; PAD: peripheral arterial disease.
[a]Pantoprazole arm still ongoing.

Current guidelines from the European Society of Cardiology (ESC) on the management of stable CAD recommend ASA as the cornerstone of pharmacological prevention of arterial thrombosis, with a dosage of 75 to 150 mg/day offering the best risk–benefit ratio.[27] ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines recommend that in patients with ACS, DAPT with a P2Y$_{12}$ inhibitor combined with ASA is recommended regardless of initial treatment strategy.[28] Specifically, for ACS in STEMI patients undergoing percutaneous coronary intervention (PCI), ESC/EACTS guidelines recommend DAPT for 1 to 6 month(s) depending on the bleeding risk; for patients in whom the ischaemic risk prevails over the risk of bleeding, a longer DAPT duration may be considered.[28] Meanwhile, for ACS in NSTEMI patients, DAPT for 12 months is recommended unless contraindicated (e.g. in those with excessive bleeding risk).[29] Triple therapy, combining ASA with a P2Y$_{12}$ inhibitor and an oral anticoagulant (OAC), is recommended in STEMI patients if there is a clear need for anticoagulation (e.g. atrial fibrillation [AF] and CHA$_2$DS$_2$-VASc score $\geq$2 or mechanical valve prosthesis); the duration of DAPT should be as short as possible to minimize bleeding risk.[30]

A large meta-analysis of more than 25,000 ACS patients previously underlined the increased bleeding risk resulting from ASA being combined with warfarin versus ASA alone, although there was a significant clinical benefit in terms of reducing major adverse events.[31] In the Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial of patients with clinically evident CV disease or who were at high risk of atherothrombotic events, addition of clopidogrel to ASA did not reduce the risk of stroke, MI or CV death.[32] Recent trials have studied the efficacy of new antiplatelet agents. The Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial showed that compared with placebo, vorapaxar did not significantly reduce the primary efficacy endpoint of CV death, MI, stroke, recurrent ischaemia with hospitalization or urgent coronary revascularization when used in combination with standard therapy in stable patients with a history of MI, and was also associated with a significant increase in major bleeding and intracranial haemorrhage (ICH).[11] While long-term therapy with ticagrelor plus ASA reduced the risk of CV death, MI or stroke in the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared with Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial of patients with prior MI, this was accompanied by an increased risk of major bleeding.[33]

Need for Vascular Protection in Patients with PAD

Recent ESC/European Society for Vascular Surgery (ESVS) guidelines on the diagnosis and treatment of PAD use this collective term to describe all vascular sites, including the vertebral, carotid, upper extremity, renal, mesenteric and lower extremity vessels, with the term lower extremity

arterial disease (LEAD) being used for peripheral artery disease specifically.[34] The American College of Cardiology (ACC) and AHA Practice Guidelines define four categories of PAD: asymptomatic, claudication, critical limb ischaemia (CLI) and acute limb ischaemia (ALI).[35–37] Patients who present later than 2 weeks following the onset of ALI have CLI.[38] When considering the spectrum of PAD, ALI is an acute thrombotically mediated event that may be modified by antithrombotic therapy, while CLI describes the long-term sequelae of progressive atherosclerosis in the limbs, which is less likely to be impacted by antithrombotic therapy.[39,40]

The 2012 American College of Chest Physicians (ACCP) guidelines for patients aged ≥ 50 years with asymptomatic PAD include ASA 75 to 100 mg/day over no therapy for primary prevention of thrombosis in PAD.[41] For secondary prevention in patients with symptomatic PAD, including before and after peripheral arterial bypass surgery or percutaneous transluminal angioplasty, long-term ASA 75 to 100 mg/day, or clopidogrel 75 mg/day, is endorsed.[41] These recommendations are supported in the 2016 ACC/AHA Task Force clinical practice guidelines and the 2017 ESC/ESVS guidelines.[34,35] The 2017 ESC/ESVS guidelines also include recommendations of DAPT with ASA and clopidogrel for the management of LEAD after infra-inguinal stent implantation and in below-the-knee bypass with a prosthetic graft.[34] According to the ESC/ESVS guidelines, OAC alone should be considered in patients with PAD who have an indication for OAC (e.g. AF or mechanical prosthetic valve). OAC is recommended when the CHA_2DS_2-VASc score is ≥ 2 and OAC should be considered in all other patients with PAD and AF. After endovascular revascularization, ASA or clopidogrel should be considered in addition to OAC for at least 1 month if the bleeding risk is low compared with the risk of stent/graft occlusion; if the bleeding risk is high compared with the risk of stent/graft occlusion, OACs alone should be considered.[34]

Even with currently available clinical management guidelines, the residual risk of atherothrombotic events in PAD remains high. Earlier trials suggest a role for low-dose ASA in PAD outpatients with stage I–II PAD,[42] while more recent findings failed to support ASA use in a variety of PAD populations, such as those with diabetes mellitus and asymptomatic PAD,[43] those with asymptomatic atherosclerosis[44] and 5,269 PAD patients identified in a meta-analysis of 18 trials.[45]

In a subgroup analysis of PAD patients ($n = 3,096$) in the CHARISMA trial, clopidogrel added to ASA reduced the risk of MI or hospitalization but did not reduce the risk of stroke, MI or CV death versus placebo + ASA; severe bleeding remained similar between groups.[12] The PAR-1 antagonist vorapaxar was shown to reduce the need for peripheral revascularization in patients with PAD in the Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischaemic Events-Thrombolysis in Myocardial Infarction 50 (TRA 2 P-TIMI 50) trial.[46] Vorapaxar did not reduce the risk of CV death, MI or stroke but did reduce ALI and peripheral artery revascularization; however, this was accompanied by an increased incidence of bleeding, including significantly higher moderate-to-severe bleeding events.[46]

Robust evidence is still needed to inform PAD management. Adequate trials are lacking and the management of PAD is sometimes extrapolated from CAD data. Previously published clinical studies support a dual role for rivaroxaban in the activation of platelets and the coagulation pathway, indicating that rivaroxaban could have a synergistic effect when used in combination with antiplatelet agents, leading to the potentiation of antithrombotic efficacy. Following the Phase II dose-finding study Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in Subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 46 (ATLAS ACS-TIMI 46), the clinical benefits of rivaroxaban at doses of 2.5 and 5 mg bid were subsequently shown in the ATLAS ACS 2-TIMI 51 trial. Both doses significantly reduced the composite endpoint of death from CV causes, MI or stroke, when used on background therapy (ASA/clopidogrel) in patients with ACS.[23,47] In subsequent subanalyses, the rivaroxaban 2.5 mg bid dose was associated with reduced stent thrombosis and patient mortality in patients with ACS who received coronary artery stenting,[48] along with a reduction in CV deaths in patients with a recent STEMI,[22] while both rivaroxaban 2.5 and 5 mg bid reduced MIs, the majority of which were spontaneous.[49] The COMPASS and VOYAGER PAD studies aim to further elucidate the efficacy of rivaroxaban 2.5 and/or 5 mg bid: COMPASS, terminated early because of overwhelming efficacy, included patients with stable PAD (also including asymptomatic carotid artery stenosis of mild-to-moderate severity), while the ongoing study VOYAGER PAD includes those with highly symptomatic LEAD recently undergoing peripheral revascularization procedures, thus with critical or acute PAD.[50,51]

COMPASS: Rivaroxaban for the Prevention of Major CV Events in CAD or PAD

COMPASS is a Phase III trial, designed to determine the efficacy and safety of rivaroxaban, rivaroxaban plus ASA or ASA alone, for reducing the risk of MI, stroke and CV death in patients with CAD and/or PAD.[52,53]

COMPASS included 27,395 patients with CAD or PAD receiving a 1:1:1 ratio of rivaroxaban 2.5 mg bid + ASA 100 mg od; rivaroxaban 5 mg bid or ASA 100 mg od.[51] Another randomized comparison is still ongoing and is comparing pantoprazole with placebo in those patients not receiving a proton-pump inhibitor (the main outcome is upper gastrointestinal complications). The primary efficacy endpoint in the COMPASS primary analysis was the composite of MI, stroke or CV death. Secondary efficacy endpoints were the composite of ischaemic stroke, MI, ALI or death from coronary heart disease; the composite of ischaemic stroke, MI, ALI or CV death; and death from any cause. The primary safety outcome was based on a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria and included fatal bleeding, symptomatic bleeding in a critical organ or bleeding into a surgical site requiring reoperation, and bleeding leading to hospitalization (includes presentation to an acute care

facility without overnight stay). All bleeding that led to presentation at an acute care facility or hospitalization was regarded as major. The net clinical benefit outcome was the composite of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ.[51]

Patients included were those who met the criteria for CAD or PAD. Those with CAD needed to meet the following criteria: age ≥65 years, or age <65 years with documented atherosclerosis or revascularization in ≥2 vascular beds, or ≥2 additional risk factors. Key exclusion criteria included (but were not limited to) a high risk of bleeding; the requirement for DAPT, other non-ASA antiplatelet therapy or OAC therapy; stroke within 1 month or any history of haemorrhagic or lacunar stroke; severe HF with known left ventricular ejection fraction (LVEF) <30% or New York Heart Association class III or IV symptoms and an estimated glomerular filtration rate <15 mL/min.[51]

Recruitment for the COMPASS trial began in early 2013, with an original completion date expected in 2018. However, the rivaroxaban and ASA arm ceased in February 2017, a year ahead of time, on the recommendation of the Data Monitoring Committee, after reaching their pre-specified criteria for superiority.[51]

A total of 602 centres across 33 countries were included in the trial. A total of 9,152, 9,117 and 9,126 patients were included in the rivaroxaban 2.5 mg bid + ASA arm, rivaroxaban 5 mg bid alone arm and ASA alone arm, respectively. The mean age of participants was 68.2 years, and 22% were women. Lipid-lowering agents were used by 89.8%, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers by 71.2%. A total of 90.6% of the participants had a history of CAD, and 27.3% had a history of PAD.[51]

The study met its primary endpoint, as the primary outcome was significantly reduced: 4.1% of patients in the rivaroxaban + ASA group versus 5.4% in those who received ASA alone (hazard ratio [HR]: 0.76; 95% confidence interval [CI]: 0.66–0.86; $p < 0.001$; ►Fig. 2). The incidence of major bleeding was higher in the rivaroxaban + ASA group (3.1%) compared with 1.9% for ASA alone (HR: 1.70; 95% CI: 1.40–2.05; $p < 0.001$); importantly, however, there was no significant difference in intracranial, fatal or critical organ bleeding between these two groups. Secondary composite outcomes (composite of ischaemic stroke, MI, ALI or death from coronary heart disease; and the composite of ischaemic stroke, MI, ALI or CV death) were also significantly more favourable in the rivaroxaban + ASA group versus ASA alone ($p < 0.001$ for both). The number of overall deaths was reduced in the rivaroxaban + ASA arm versus the ASA alone arm (313 [3.4%] vs. 378 [4.1%]; HR: 0.82; 95% CI: 0.71–0.96; $p = 0.01$). While significant benefits were observed following the use of rivaroxaban 2.5 mg bid + ASA, the use of rivaroxaban 5 mg bid alone did not lead to a significant reduction in the primary outcome compared with ASA alone (4.9 vs. 5.4%; HR: 0.90; 95% CI: 0.79–1.03; $p = 0.12$), while major bleeding was significantly higher compared with ASA (2.8 vs. 1.9%; HR: 1.51; 95% CI: 1.25–1.84; $p < 0.001$). The risk of the composite net clinical benefit outcome of CV death, stroke, MI, fatal bleeding or symptomatic bleeding into a critical organ was lower with rivaroxaban + ASA than with ASA alone (431 patients [4.7%] vs. 534 patients [5.9%]; HR: 0.80; 95% CI: 0.70–0.91; $p < 0.001$); however, this was not the case for rivaroxaban alone versus ASA alone.[51]

Rivaroxaban + ASA versus ASA alone also showed consistent benefits across subgroups studied, including those
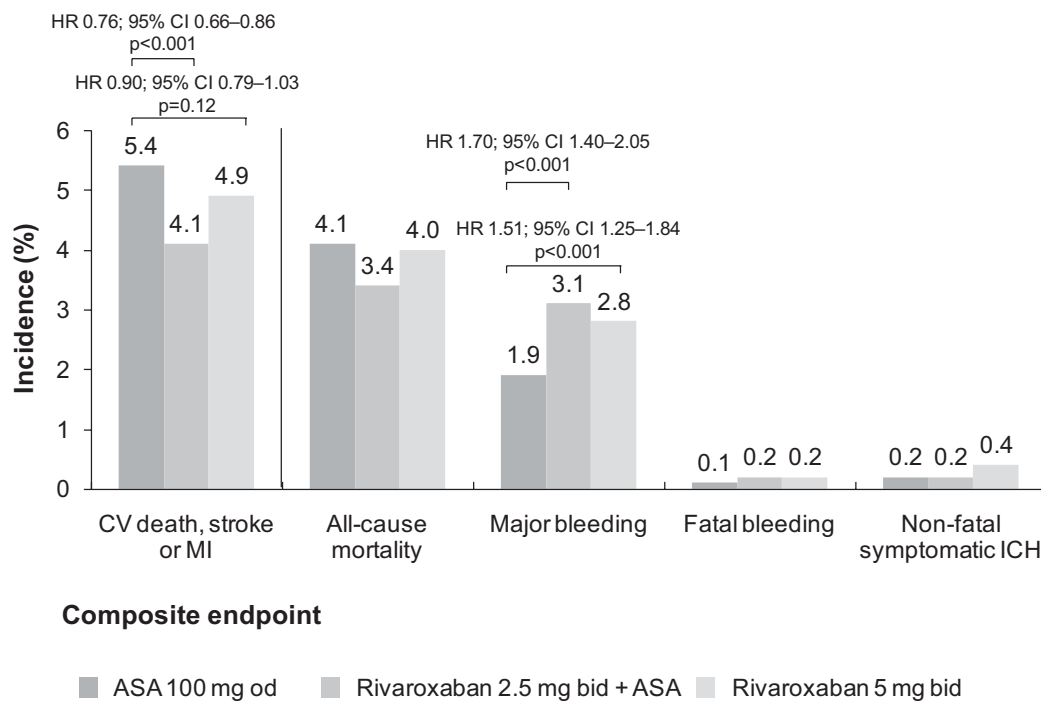

Fig. 2 Clinical outcomes from COMPASS primary analysis.[51] ASA, acetylsalicylic acid; bid, twice daily; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; ICH, intracranial bleeding; MI, myocardial infarction; od, once daily.

with either CAD or PAD. Of the PAD patients included in COMPASS ($n = 7,470$), similar outcomes were observed with regards to the clinical efficacy of rivaroxaban, where rivaroxaban 2.5 mg bid + ASA was significantly superior to ASA alone in reducing major adverse CV events (MACE) or major adverse limb events (MALE) or major amputation (HR: 0.69; 95% CI: 0.56–0.85; $p = 0.0003$).[54] While there was an increase in major bleeding with rivaroxaban + ASA, there was no significant increase in fatal or critical organ bleeding. MACE or MALE or major amputation outcomes were also consistent across PAD subgroups (symptomatic PAD, PAD lower extremities and carotid artery disease) where rivaroxaban 2.5 mg bid + ASA was favoured over ASA alone.[54] There were several limitations of COMPASS. Patients with a recent stroke or previous haemorrhagic or lacunar stroke were excluded; however, of those enrolled, 1,032 had a history of stroke, and the benefits of the rivaroxaban and ASA combination in preventing cardiovascular death, stroke or MI were consistent in these patients. Furthermore, the rivaroxaban and ASA combination resulted in a lower rate of ischaemic stroke than ASA alone. The investigators did not specifically record statin use or low-density lipoprotein cholesterol levels at baseline, and the trial protocol did not specifically emphasize aggressive use of secondary prevention therapies to lower blood pressure and cholesterol levels. However, the results supported the conclusion that the benefits of combination therapy were additive to those of other proven secondary preventive therapies. As the trial was stopped early, it could be suggested that the efficacy observed may overestimate the treatment effect. However, before the time of stopping, the data and safety monitoring board had observed a progressive increase in benefit of the rivaroxaban and ASA combination for more than 1 year.[51]

Data from COMPASS present substantial benefits with rivaroxaban 2.5 mg bid in combination with ASA in terms of improved survival and reductions in stroke and MI in patients with stable CAD or PAD. These landmark findings support the concept of combined antithrombotic therapy with an anticoagulant and an antiplatelet agent to ultimately provide long-lasting vascular protection.

VOYAGER PAD: Rivaroxaban in Patients with PAD Undergoing Peripheral Revascularization Procedures

VOYAGER PAD is a Phase III, randomized, double-blind, placebo-controlled trial, designed to determine the safety and efficacy of a dual-pathway approach versus standard of care (ASA alone) for the reduction of thrombotic vascular events in subjects after peripheral revascularization procedures (►Fig. 3).[50] The trial includes three strata of patients, all with infrainguinal procedures: angioplasty (with/without stent) receiving clopidogrel on top of ASA (DAPT); angioplasty (with/without stent) receiving no clopidogrel; and surgery, including bypass surgery or thromboendarterectomy. Approximately 6,500 patients will be randomized in a ratio of 1:1 to receive rivaroxaban 2.5 mg bid plus ASA 100 mg od, or ASA 100 mg od alone.[50] The primary efficacy outcome is the composite of MI, ischaemic stroke, CV death, ALI and major amputation due to PAD. The primary safety endpoint is major bleeding, as assessed by the Thrombolysis in Myocardial Infarction score.[50]
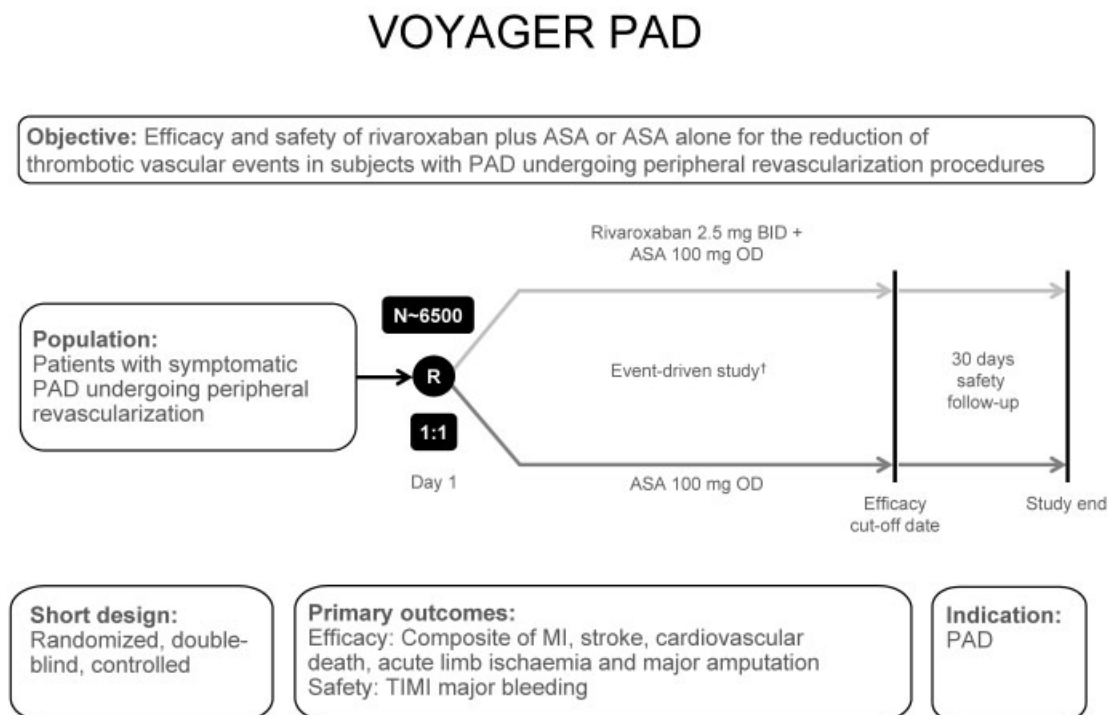

Fig. 3 VOYAGER PAD trial design.[50] †Mean treatment duration approximately 30 months. ASA, acetylsalicylic acid; bid, twice-daily; od, once daily; PAD, peripheral arterial disease; MI, myocardial infarction; R, randomized; TIMI, thrombolysis in myocardial infarction.

Key inclusion criteria for VOYAGER PAD are documented moderate-or-severe symptomatic lower limb PAD and recent successful peripheral infra-inguinal revascularization (within the last 10 days prior to revascularization), and age ≥50 years. Exclusion criteria include revascularization for asymptomatic PAD or mild claudication; revascularization to treat an asymptomatic restenosis of a bypass graft; prior revascularization on the index leg within 10 days of the qualifying revascularization planned use of additional antiplatelet agents other than clopidogrel and ASA following the revascularization procedure and planned dual-antiplatelet treatment beyond 6 months following the revascularization procedure.[50] VOYAGER PAD began enrolling in late 2015, with results expected in 2019.

Need for Vascular Protection in Patients with CAD and HF

The underlying cause of HF has changed from hypertension to CAD in recent decades.[55,56] Approximately 65% of patients admitted to hospital for HF have CAD as the underlying cause. CAD has also been shown to be independently associated with worsening long-term prognosis for patients with HF.[56] Coronary artery atherothrombosis, resulting in myocardial ischaemia, is a common cause of HF with a reduced ejection fraction (HFrEF, also known as systolic HF), where the heart muscle is not able to contract adequately. The pathogenesis of increased thrombosis in patients with HF may be due to reduced blood flow as a result of low cardiac output, decreased physical activity and a hypercoagulable state, as shown by an increase in platelet activation, plasma viscosity, fibrinogen, fibrin, D-dimer and von Willebrand factor.[57–59] Thrombin appears to play a pivotal role in fibrinolysis, inflammation and endothelial dysfunction in this setting[57] and, therefore, anticoagulants may be important in the prevention of CV events in HF for patients in sinus rhythm.

Guidance supporting the use of antiplatelets or anticoagulants other than ASA in the prevention of CV events in patients with HF is scarce. The 2013 American College of Cardiology Foundation (ACCF) and the AHA Task Force guidelines on the management of patients with HF recommend non-vitamin K antagonist oral anticoagulants (NOACs) in patients with HF and AF, and an additional risk factor for stroke.[26] NOACs are not recommended in patients with HFrEF without AF, a prior thromboembolic event or a known cardioembolic source.[26] The 2012 ESC guidelines do not recommend anticoagulation for patients with HFrEF, unless there is concomitant AF.[60] Although anticoagulants may have a role in preventing CV events in patients with HF in sinus rhythm, at present RCTs in this clinical setting have been inconclusive.[61]

As thrombotic events are more common in patients with HF, several studies have investigated oral anticoagulation treatment strategies. Analyses from the Warfarin/Aspirin Study in Heart failure (WASH) trial found that warfarin antithrombotic therapy does not modify mortality or vascular events in patients with HF in sinus rhythm,[62] while findings from the Heart failure Long-term Antithrombotic Study (HELAS) had inconclusive findings owing to the small

number of patients recruited.[63] These results were confirmed in a Cochrane review, which concluded that although OACs are indicated in certain groups of patients with HF, the available data do not support their routine use in patients with HF in sinus rhythm.[64] In another recent study of patients with HF in sinus rhythm, the Warfarin versus Aspirin Reduced Cardiac Ejection Fraction (WARCEF) trial showed no significant difference between warfarin and ASA in the primary composite outcome of ischaemic stroke, intracerebral haemorrhage or death from any cause. The reduced risk of ischaemic stroke observed with warfarin was accompanied by an increased risk in major bleeding.[61]

Subgroup analyses in ATLAS ACS 2-TIMI 51 showed consistent benefits of rivaroxaban 2.5 mg bid in those with congestive HF.[65] Rivaroxaban 2.5 mg bid is approved in Europe for the treatment of biomarker-positive patients after an ACS[66] and was chosen as the dose to investigate in the COMMANDER HF trial as the most likely to offer an optimal combination of safety and efficacy, by inclusion in a targeted antithrombotic strategy in patients with a recent exacerbation of HFrEF and concomitant CAD.

COMMANDER HF: Rivaroxaban in Patients with HF and Significant CAD following an Exacerbation of HF

COMMANDER HF is an international, Phase III, prospective, randomized, double-blind, placebo-controlled, event-driven, parallel-group comparison of the efficacy and safety of rivaroxaban with placebo and standard of care, to reduce the risk of MI, stroke or death in patients with documented symptomatic HF and evidence of significant CAD.[67] Approximately 5,000 patients will be randomized to receive rivaroxaban 2.5 mg bid plus standard of care versus placebo plus standard of care (►Fig. 4). Patients will take the study drug until the targeted number of events has been predicted to have occurred and will be followed up for 7 to 31 months.[67]

The inclusion criteria include a recent symptomatic exacerbation of HF, increased plasma concentrations of natriuretic peptides (N-terminal pro–B-type natriuretic peptide ≥800 pg/mL or B-type natriuretic peptide ≥200 pg/mL), with an LVEF ≤40% and significant CAD. The exclusion criteria include requirement of anticoagulation for AF or for other clinical conditions.[67]

Following an index event, such as a hospital admission, unscheduled outpatient treatment or worsening HF, patients will be randomized in a ratio of 1:1 to rivaroxaban or placebo (with standard of care). The primary efficacy outcome event is a composite of all-cause mortality, MI or stroke. The principal safety outcome event is the composite of fatal bleeding or bleeding into a critical space that has the potential for permanent disability, bleeding events requiring hospitalization and major bleeding events, according to ISTH criteria.[67]

COMMANDER HF began enrolling patients in Q3 2013, with results expected in 2018. It is the first prospective study of an NOAC in HF and will provide important information on the use of rivaroxaban following an HF event in an HFrEF patient population with CAD.[67,68]
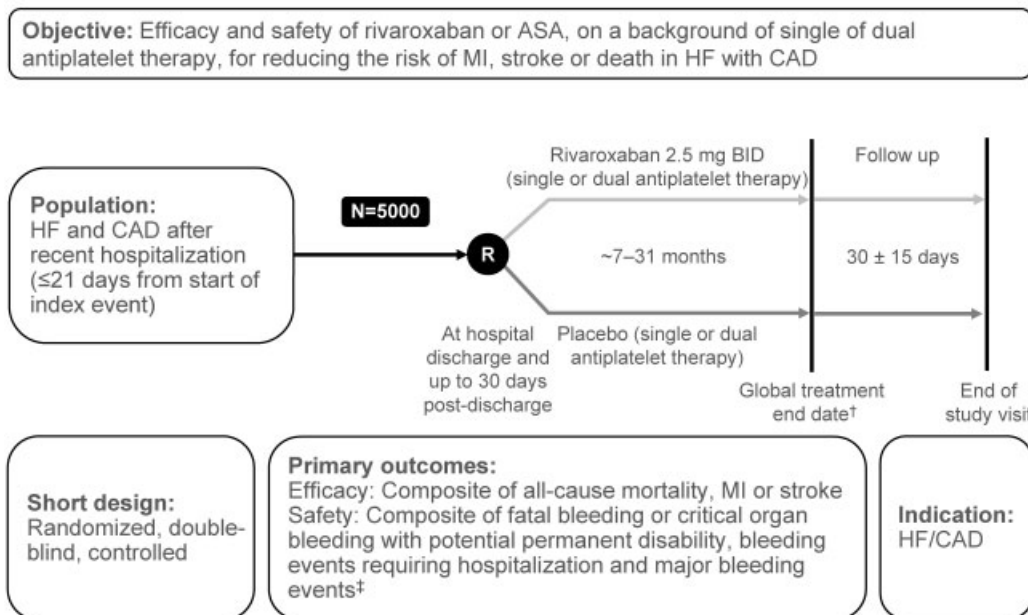
COMMANDER HF

Objective: Efficacy and safety of rivaroxaban or ASA, on a background of single of dual antiplatelet therapy, for reducing the risk of MI, stroke or death in HF with CAD

Population:
HF and CAD after recent hospitalization (≤21 days from start of index event)

N=5000

R

Rivaroxaban 2.5 mg BID (single or dual antiplatelet therapy)

Follow up

~7–31 months

30 ± 15 days

At hospital discharge and up to 30 days post-discharge

Placebo (single or dual antiplatelet therapy)

Global treatment end date†

End of study visit

Short design:
Randomized, double-blind, controlled

Primary outcomes:
Efficacy: Composite of all-cause mortality, MI or stroke
Safety: Composite of fatal bleeding or critical organ bleeding with potential permanent disability, bleeding events requiring hospitalization and major bleeding events‡

Indication:
HF/CAD

Fig. 4 COMMANDER HF trial design.[67,68] †The date when 984 primary efficacy outcome events are predicted to have occurred. ‡According to the International Society on Thrombosis and Haemostasis (ISTH) bleeding criteria. ASA, acetylsalicylic acid; bid, twice daily; CAD, coronary artery disease; HF, heart failure; MI, myocardial infarction; R, randomized.

Conclusion

Despite advances in medicine, the burden of CV disease continues to increase because of the aging population. A significant proportion of patients with CV disease have polyvascular disease or HF, which exacerbates their risk even further. Despite intensive antiplatelet therapy, which has been traditionally accepted as the standard of care in this setting, patients with CAD and PAD exhibit a high residual risk of atherothrombotic events. Antithrombotic therapy composed of anticoagulants in addition to antiplatelets may present an alternative approach. Importantly, the net clinical benefit of rivaroxaban 2.5 mg bid combined with ASA has been clearly shown in the landmark COMPASS trial. In November 2017, rivaroxaban in combination with ASA was filed for approval by the European Medicines Agency (EMA) for the treatment of patients with CAD or PAD.[69] While the benefits of this new approach are clear, integration into daily practice may be slowed down by barriers such as bleeding concerns, cost and identification of appropriate patients for treatment. Importantly, substantial changes will need to be implemented into practice to make way for the new treatment amongst many other existing antithrombotic options. Developing tools to individualize treatment decisions will be important in terms of implementation in an effort to balance thrombotic and bleeding risks in routine clinical practice. Other contemporary trials of rivaroxaban are ongoing in patients with HF and those undergoing peripheral revascularization procedures—while these findings are still awaited, we must anticipate that redefining the standard of care for CAD patients with a high need for improved CV protection will be a huge barrier to overcome—yet will also carry significant benefits for many.

What is known about this topic?

- With the ageing population, the burden of cardiovascular disease continues to increase.
- A significant proportion of patients with cardiovascular disease have polyvascular disease or HF, which further exacerbates their risk.
- Despite intensive antiplatelet therapy, patients with CAD and PAD exhibit a high residual risk of atherothrombotic events.
- Clinical trials support the efficacy of rivaroxaban following ACS events.

What does this paper add?

- This paper reviews ongoing and completed clinical trials from the development programme of rivaroxaban in vascular protection, which hypothesize that antithrombotic therapy comprising NOACs with or without antiplatelet therapy may present therapeutic potential in further reducing the risk of atherothrombotic events.
- Key findings from the Phase III COMPASS trial are discussed, which support the benefits of rivaroxaban 2.5 mg bid in combination with ASA in terms of improved survival and reductions in stroke and MI in patients with stable CAD or PAD.

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