REVIEW ARTICLE

Who may benefit from low-dose rivaroxaban plus aspirin? Practical implications for outpatients with cardiovascular disease

Leonardo De Luca

Department of Cardio-Thoracic and Vascular Medicine and Surgery, Division of Cardiology, Azienda Ospedaliera San Camillo-Forlanini, Rome, Italy

KEY WORDS

COMPASS, coronary artery disease, peripheral artery disease, rivaroxaban, VOYAGER

ABSTRACT

Despite availability of effective preventive therapies based on guidelines, patients with vascular diseases continue to be at a high risk for recurrent ischemic events. Therefore, novel therapeutic strategies are required to further reduce the residual risk present in these patients. Platelet aggregation and fibrin organization are involved in arterial thrombosis. Rivaroxaban is capable of targeting both processes and has a synergistic effect when used in combination with acetylsalicylic acid (ASA), providing the so-called dual pathway inhibition (DPI). The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial showed that the DPI (a combination of rivaroxaban at 2.5 mg twice daily [vascular dose] and ASA at 100 mg once daily) reduced cardiovascular death, stroke, or myocardial infarction by 24% in patients with chronic coronary artery disease (CAD) and peripheral artery disease (PAD). Subsequently, the VOYAGER PAD (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) trial confirmed the effectiveness of the vascular dose of rivaroxaban in patients with PAD after lower-extremity revascularization, as compared with ASA alone. Therefore, DPI is recommended in the patients with CAD (+/– PAD) or symptomatic PAD at a high risk of ischemia. The purpose of this review is to examine the clinical benefits and practical implications of DPI in the CAD and PAD patients.

Correspondence to:
Leonardo De Luca, MD, PhD, Department of Cardio-Thoracic and Vascular Medicine and Surgery, Division of Cardiology, Azienda Ospedaliera, San Camillo-Forlanini Circonvallazione Gianicolense 87, 00152 Roma, Italy,
phone: +39 06 58704419,
email: leo.deluca@libero.it
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INTRODUCTION Vascular diseases, such as cerebrovascular disease, peripheral artery disease (PAD), and coronary artery disease (CAD), are a leading cause of morbidity and mortality on a global scale.[1] Despite availability of efficacious preventive therapies based on clinical practice guidelines, patients with vascular diseases are at a high risk for recurrent ischemic events.[1] The REACH (Reduction of Atherothrombosis for Continued Health) registry assessed long-term outcomes in 64 977 patients with vascular diseases or with 3 or more cardiovascular risk factors. Despite recommended therapies, the observed annual rate of cardiovascular mortality, myocardial infarction (MI), or stroke in the secondary prevention subgroup (n = 53 391) was 4.6%.[2] Considering the composite of cardiovascular mortality, MI, stroke, or hospitalization for unstable angina, transient ischemic attack, or worsening PAD,[2] this rate increased to 14.4%. Even with appropriate treatment, these results demonstrate that adverse cardiovascular events are common in patients with atherothrombosis. The picture is even more complex if the risk factors are not adequately controlled, and the recommended secondary prevention therapies are not adequately prescribed.[3,4]

The purpose of this review is to examine the potential mechanisms and clinical benefits of a new therapeutic option derived from a low dose of rivaroxaban combined with acetylsalicylic acid (ASA), known as dual pathway inhibition (DPI), in patients with vascular diseases.

Inhibition of factor Xa reduces protease-activated receptor-mediated inflammation Recent research evaluated the addition of factor Xa inhibitors to ASA in patients with vascular disorders. Notably, the coagulation system enhances the activation

and reactivity of platelets in multiple ways. Coagulation proteins, such as thrombin, fibrinogen, and the von Willebrand factor, play an important role in platelet activation or aggregation. The most potent endogenous platelet activator is thrombin, which binds to protease-activated receptors (PARs) on the platelet surface.[1]

PARs are highly expressed at the membrane surface of numerous inflammatory cells.[5] In response to the activation of PARs, an intracellular signal induces cell morphological alterations and modifies cell proliferation and motility,[6] therefore participating in the progression of atherosclerosis and the occurrence of atherothrombotic events.[7-9]

From ATLAS to COMPASS The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome--Thrombolysis in Myocardial Infarction 51) trial enrolled 15 526 stable patients with acute coronary syndrome.[10] The patients were randomized to receive 2.5 mg or 5 mg rivaroxaban twice daily together with ASA (+/– $P2Y_{12}$ receptor inhibitor) or placebo together with ASA +/– $P2Y_{12}$ receptor inhibitor. The primary efficacy end point was a composite of cardiovascular mortality, MI, and stroke. TIMI major hemorrhage unrelated to coronary artery bypass grafting served as the primary safety end point. At 13 months, adding rivaroxaban at 2.5 mg twice daily (vascular dose) to the standard therapy significantly reduced the primary efficacy end point, as compared with placebo (relative risk reduction [RRR], 16%; $P = 0.02$). These results were predominantly driven by a decrease in cardiovascular-related mortality (RRR, 34%; $P = 0.003$). In addition, this strategy reduced all-cause mortality (RRR, 32%; $P = 0.004$), and the benefits persisted after thienopyridines were discontinued (at a maximum follow-up of 31 months). Interestingly, rivaroxaban at the vascular dose reduced the incidence of stent thrombosis (probable or certain, as defined by the Academic Research Consortium[11]) in comparison with placebo (2.9% vs 4.5%; RRR, 39%; $P = 0.002$). As for the safety outcomes, even though rivaroxaban at the vascular dose significantly increased the risk of major bleeding, approximately tripling the risk of TIMI major bleeding and doubling the risk of intracranial hemorrhage,[10] the drug was found to be safe. The reason for the improvement in cardiovascular outcome is a proper dose with a targeted approach to the thrombotic process.

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial randomized 27 395 individuals with stable atherosclerotic vascular disease to receive the DPI with rivaroxaban at the vascular dose (2.5 mg twice daily) plus ASA (100 mg once daily), rivaroxaban (5 mg twice daily), or ASA (100 mg once daily).[12] The primary outcome was a composite of cardiovascular mortality, stroke, and MI. The primary safety outcome was a modified version of the International Society on Thrombosis and Hemostasis (ISTH) criteria for major bleeding[13], which included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that resulted in hospitalization (including presentation at an acute care facility without an overnight stay). In contrast to the ISTH criteria, all significant bleedings leading to presentation at an acute care facility or hospitalization were evaluated. After an average of 23 months of follow-up, the study was terminated due to the superiority of the DPI group over ASA alone at the first formal interim analysis for efficacy (50% of the planned events). The patients were eligible if they met the criteria for CAD, PAD, or both conditions.[12] The patients with CAD younger than 65 years were also required to have documented atherosclerosis involving at least 2 vascular beds or to have at least 2 additional risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] below 60 ml/min/1.73 m^2, heart failure, or nonlacunar ischemic stroke more than 1 month earlier). The exclusion criteria included a high risk of bleeding, recent stroke or previous hemorrhagic or lacunar stroke, severe heart failure, advanced stable kidney disease (eGFR below 15 ml/min/1.73 m^2), the use of dual antiplatelet therapy (DAPT), anticoagulation, or other antithrombotic therapy, and noncardiovascular conditions deemed by the investigator to be associated with a poor prognosis.

The incidence of the primary outcome event was 4.1% for DPI and 5.4% for ASA alone (hazard ratio [HR], 0.76; 95% CI, 0.66–0.8; $P = 0.001$). The secondary composite outcome of ischemic stroke, MI, acute limb ischemia, or mortality from coronary heart disease occurred in fewer patients in the DPI group than in the ASA-alone group (3.6% vs 4.9%; HR, 0.72; 95% CI, 0.63–0.83; $P < 0.001$). The secondary outcome of ischemic stroke, MI, acute limb ischemia, or cardiovascular mortality occurred in fewer patients in the DPI group than in the ASA-alone group (4.3% vs 5.7%; HR, 0.74; 95% CI, 0.65–0.9; $P = 0.001$). At the conclusion of the follow-up period, 313 patients (3.4%) assigned to the DPI group and 378 patients (4%) assigned to the ASA-alone group had died (HR, 0.82; 95% CI, 0.7–0.96; $P = 0.01$).[12] The combination therapy reduced cardiovascular mortality in comparison with ASA alone (1.7% vs 2.2%; HR, 0.78; 95% CI, 0.64–0.96; $P = 0.02$).[14] There were also fewer fatalities following MI, stroke, and cardiovascular procedures, as well as fewer deaths from sudden cardiac, other, and unidentified causes of cardiovascular and coronary heart disease in the patients on DPI.

Major bleeding events, according to the modified ISTH classification, occurred in more patients in the DPI group than in the ASA-alone group (3.1% vs 1.9%; HR, 1.7; 95% CI, 1.4–2.1; $P = 0.001$), primarily because of a difference in bleeding that resulted in presentation at an acute care facility or hospitalization. The majority of excess major bleeding events occurred in the gastrointestinal

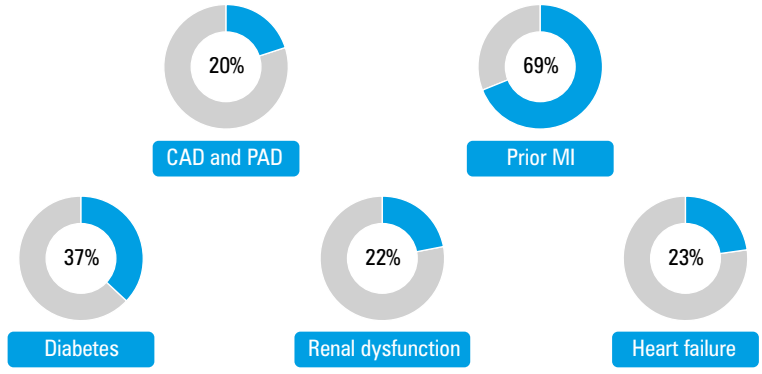

FIGURE 1 Proportion of patients with high-risk comorbidities represented in the COMPASS trial
Abbreviations: CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral artery disease

tract, and there was no significant difference between the groups in the incidence of fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ.[15] At the landmark analysis, the majority of bleeding events occurred in the first year of DPI treatment, whereas the benefits in terms of ischemic events remained consistent throughout the duration of the trial.

The risk of cardiovascular mortality, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ was lower with DPI than with ASA alone (4.7% vs 5.9%; HR, 0.8; 95% CI, 0.7–0.9; $P = 0.001$).[12,16]

Effects of low-dose rivaroxaban in various populations participating in the COMPASS trial The proportion of patients with the most common comorbidities enrolled in the COMPASS trial is represented in FIGURE 1. The effects of rivaroxaban at the vascular dose plus ASA vs ASA alone on the primary outcome and on major bleeding were consistent across the subgroups defined by age, sex, geographic region, race or ethnicity, body weight, renal function, and history of cardiovascular risk factors (smoking, hypertension, diabetes, or dyslipidemia).[12] Consistent results were also observed among participants meeting the criteria for CAD (90.5% of the total population)[17] and PAD.[18] Indeed, in the patients with PAD, the DPI, in comparison with ASA alone, reduced the composite primary end point by 38% (5% vs 7%; HR, 0.72; 95% CI, 0.57–0.9; $P = 0.0047$), and major adverse limb events including major amputation by 46% (1% vs 2%; HR, 0.54; 95% CI, 0.35–0.82; $P = 0.0037$), even if there was an increase in major bleeding.[18] The benefits of DPI treatment were shared by all subgroups of the high-risk patients enrolled in the COMPASS trial.[18-23]

The VOYAGER PAD trial Recently, the results of the VOYAGER PAD (Vascular Outcomes Study of ASA Along with Rivaroxaban in Endovascular or Surgical Limb Revascularization for PAD) trial have been published.[24] This was a double-blind, multicenter study in which 6564 patients aged 50 years or older, with moderate to severe symptomatic PAD and successful peripheral revascularization (65% with endovascular procedures and 35% with surgery), were enrolled. The patients were randomized to receive rivaroxaban 2.5 mg twice daily together with ASA or ASA alone. The primary efficacy outcome was a composite of acute limb ischemic events, major amputation for vascular causes, MI, ischemic stroke, and cardiovascular mortality.

At a median follow-up of 28 months, the addition of a vascular dose of rivaroxaban significantly decreased the primary efficacy end point (RRR, 15%; $P = 0.009$). The results were predominantly driven by a 33% relative decrease in acute limb ischemic events ($P = 0.03$), with early separation of the Kaplan–Meier curves and consistent outcomes across the subgroups.[25-27] Despite this, there was no significant reduction in all-cause mortality ($P = 0.34$). Although no significant differences in hemorrhagic events between the 2 groups were described according to the TIMI classification, DPI was associated with increased ISTH-defined significant bleeding as compared with ASA monotherapy; however, there were no differences in intracranial hemorrhage or fatal bleeding.[24]

Practical considerations based on the subgroup analyses of recent trials on dual pathway inhibition One of the most awaited analyses of the COMPASS trial, for its practical implications, was the one on the use of proton pump inhibitor therapy for the reduction of the upper gastrointestinal tract events associated with DPI. Indeed, the COMPASS participants were randomly assigned to groups receiving pantoprazole (40 mg daily) or placebo with a 3 × 2 partial factorial design. The primary outcome, a composite of overt bleeding, upper gastrointestinal bleeding from a gastroduodenal lesion or of unknown origin, occult bleeding, symptomatic gastroduodenal ulcer or at least 5 erosions, upper gastrointestinal obstruction, or perforation, did not differ at 3 years between the 2 groups (HR, 0.88; 95% CI,

0.67–1.15; $P = 0.35$).[28] Pantoprazole only reduced bleeding from the gastroduodenal lesions (HR, 0.52; 95% CI, 0.28–0.94; $P = 0.03$),[28] and entailed an increased risk of enteric infections.[29] Therefore, the routine use of proton pump inhibitors in the patients receiving DPI is not generically recommended for reducing gastrointestinal events, with the exception of those with known gastroduodenal lesions.

Other important pieces of evidence from the COMPASS trial suggest that DPI is even more effective in the patients at a high or very high thrombotic risk and/or in more fragile individuals. Indeed, the relative net clinical benefits of DPI were consistent in all patients, regardless of the number of concomitant medical conditions, with the greatest absolute benefit in the patients taking at least 4 concomitant cardiovascular medications.[30] Other analyses suggested a consistent reduction in the primary outcome of DPI, as compared with ASA, among more fragile patients, such as those who underwent coronary artery bypass grafting 4 to 14 days before the randomization ($P = 0.34$)[31] or those with a history of stroke ($P = 0.4$).[32]

Regarding the VOAYAGER PAD trial, there are 2 subgroup analyses that need to be discussed. The first subgroup analysis demonstrated that regardless of the revascularization strategy (surgical vs endovascular approach), the effects on efficacy or safety end points in the DPI group were consistent ($P = 0.17$ and $P = 0.73$, respectively).[33] Another subgroup analysis of the VOYAGER PAD trial demonstrated consistent efficacy and safety outcomes in the patients treated with a background combination of clopidogrel and ASA or ASA alone ($P = 0.92$ and $P = 0.71$, respectively). Nevertheless, DPI use was associated with more major bleeding events at 1 year in the patients receiving clopidogrel for over 30 days, as compared with those treated for shorter periods ($P = 0.07$).[34] Therefore, these analyses suggest that the DPI produces clinical benefits regardless of the revascularization strategy in the patients with PAD, and that although it is possible to introduce DPI in the patients already receiving DAPT with clopidogrel, caution must be exercised especially in the individuals at a greater risk of hemorrhagic events.

Effects of a vascular dose of rivaroxaban in real-world cohorts The patients enrolled in the COMPASS trial who completed the follow-up until the end of the antithrombotic randomization (regardless of the randomized treatment allocation or whether they continued the randomized treatment until the final visit) were eligible to participate in the long-term open-label extension (LTOLE).[35] In the LTOLE study, all participants received DPI regardless of their initial treatment assignment in the COMPASS trial, with a mean follow-up of 15.7 months, and a maximum of 3 years. The combination of rivaroxaban at 2.5 mg twice daily and ASA at 100 mg was associated with incidence rates of adverse cardiovascular outcomes (cardiovascular mortality, stroke, or MI) similar to those observed during the randomized phase.[35] Notably, similar and frequently lower incidence rates for hemorrhage, including gastrointestinal and intracranial bleeding, were observed in the LTOLE with DPI vs the COMPASS trial.

In the real-world context, the proportion of COMPASS-eligible patients in the REACH[36] and Italian START (Stable Coronary Artery Diseases Registry)[37] registries is well represented; in fact, they account for approximately half of the investigated populations (52.9% in REACH and 44.5% in START). Specifically, in both registries, ischemic outcome increased proportionally to the number of enrichment criteria without a significant change in the safety profile (increase in ischemic risk relative to hemorrhage risk in the patients with multiple enrichment criteria). Multiple enrichment criteria at inclusion (diabetes mellitus, age >65 years, asymptomatic carotid disease, PAD, history of heart failure, renal impairment, current smoking, and history of ischemic stroke) were associated with a significant increase in the risk of major adverse events and a modest absolute increase in the rate of major bleedings in the COMPASS-like population.[36,37] In a post hoc analysis of the COMPASS trial, the participants were classified as high-risk based on their REACH or Cardiac Arrest Risk Triage scores (2 or more vascular beds affected, history of heart failure, or renal insufficiency).[38] Those with high-risk characteristics had a lower incidence of major adverse cardiovascular events, acute limb ischemia, and total vascular amputation when treated with DPI in comparison with ASA alone, while the incidence of major hemorrhage events was comparable. Notably, eligible individuals with an increasing number of risk factors presented a raising benefit from DPI, represented by a reduced number needed-to-treat[38] (FIGURE 2). Therefore, the patients with multiple comorbidities represent a high-risk subgroup that may derive the greatest benefit-to-risk ratio from DPI.

The XATOA (Xarelto in Combination with Acetylsalicylic Acid) international registry is the largest evidence for the efficacy and safety of DPI in a real-world setting.[39] In XATOA, DPI was prescribed to 70.7% of the patients due to a high cardiovascular risk (including at least 1 of the following: history of hypertension, diabetes, hyperlipidemia, chronic renal dysfunction, smoking, family history of vascular disease, age >65 years, or high body mass index). After DAPT, 794 patients (14.4%) initiated DPI treatment. Prior to enrollment, a substantial proportion of the patients were only taking ASA. In accordance with the COMPASS approach, the majority of patients (88.2%) did not receive an additional antiplatelet agent during the course of the study, and only 9.3% received DAPT in addition to low-dose rivaroxaban.[39]

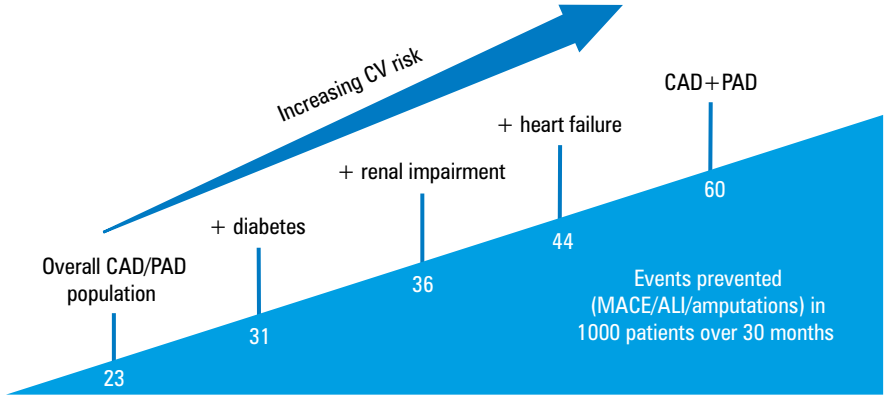

FIGURE 2 Number needed-to-treat obtained by DPI in the patients meeting the COMPASS criteria with different and cumulative risk factors

Abbreviations: ALI, acute limb ischemia; CV, cardiovascular; DPI, dual pathway inhibition; MACE, major adverse cardiovascular events; others, see **FIGURE 1**

The incidence of ischemic events identified as significant cardiovascular events was 2.26 (per 100 patient-years) vs 2.18 (per 100 patient-years) in the COMPASS trial. Major adverse limb events were more frequent in the XATOA observation than in the COMPASS observation due to a profound disparity in the recruitment of the PAD population, which comprised 58.9% of the overall population vs 27.3% in the trial. The lower incidence of severe bleeding in the XATOA (incidence rate [IR] per 100 patient-years, 0.95) than in the COMPASS trial (IR per 100 patient-years, 1.67) confirmed the safety of DPI in actual clinical practice.

The external applicability of the VOYAGER PAD results has recently been tested in some real-world cohorts.[40-43] The RECCORD (Recording Courses of Vascular Diseases) registry was an observational registry prospectively recruiting patients undergoing endovascular revascularization for symptomatic PAD in Germany.[42,43] In comparison with the VOYAGER PAD population, the rate of patients aged at least 75 years was considerably higher (37.7% vs 22.5%). In addition, the registry patients were more commonly active smokers (51.8% vs 33.6%), but less frequently suffered from diabetes mellitus (36.4% vs 44.7%). More patients in the registry had undergone previous endovascular repair (50.7% vs 38.7%) or suffered from critical limb-threatening ischemia (24.3% vs 19.5%).[42,43]

Indications for dual pathway inhibition in current clinical guidelines The current guidelines of the European Society of Cardiology (ESC)[1] on the management of chronic coronary syndromes suggest adding a second antithrombotic drug to ASA for long-term secondary prevention in patients with a high (class of recommendation [CoR], IIa; level of evidence [LoE], A) and moderate (CoR, IIb; LoE, A) risk of ischemic events and without high bleeding risk. The same level of recommendation for DPI in secondary prevention is reported in the last ESC guidelines on the management of acute coronary syndromes.[44] Among treatment options for dual antithrombotic therapy in combination with ASA, rivaroxaban 2.5 mg twice daily is recommended in the patients with multivessel CAD and / or at least 1 year after MI.[1] The ESC guidelines on diabetes, prediabetes, and cardiovascular diseases underline that in the patients with diabetes and chronic symptomatic lower extremity artery disease (LEAD) without a high bleeding risk, a combination of low-dose rivaroxaban (2.5 mg twice daily) and ASA (100 mg once daily) should be considered (CoR, IIa; LoE, B).[45]

In the case of the patients with LEAD, consensus documents[46] support the use of DPI both in the chronic symptomatic disease (long-term) and in the postrevascularization period (surgical and endovascular procedures), especially in the patients at a very high risk. Accordingly, the Canadian Cardiovascular Society guidelines for PAD[47] suggest treatment with the vascular dose of rivaroxaban in combination with ASA (80–100 mg daily) for the management of patients with symptomatic LEAD who are at a high risk for ischemic events (such as those with high-risk comorbidities, postperipheral revascularization, limb amputation, ulcers, etc.).

Future directions Ongoing studies are assessing the benefits of DPI in comparison with different antiplatelet strategies in several populations, including patients with intracranial atherosclerotic disease and recent cerebrovascular accidents (NCT04142125 and NCT05047172). The APERITIF (Direct Oral Anticoagulants for Prevention of Left Ventricular Thrombus After Anterior Acute Myocardial Infarction) trial evaluates the rate of left ventricular thrombus at 1 month, as detected by the validated delayed enhancement on cardiovascular magnetic resonance imaging in patients receiving DPI or DAPT after anterior, high-risk acute MI (NCT05077683). Finally, the COMPASS CLAUDICATION trial assesses the benefits in terms of change in claudication distance from baseline to 24 hours, as measured by the 6-minute walking test and the treadmill

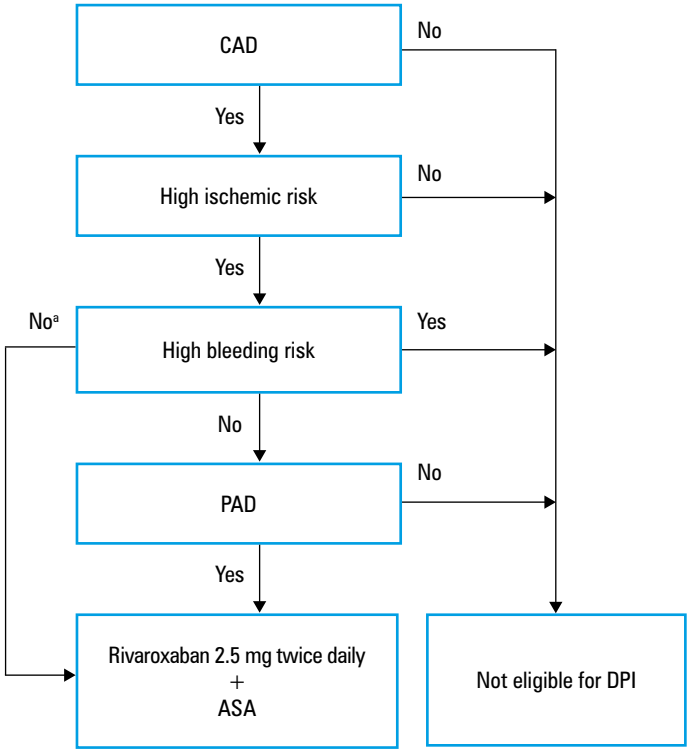

FIGURE 3 Practical indications for dual pathway inhibition in the patients with coronary artery disease

a In some countries, the presence of peripheral artery disease is needed for prescription and reimbursement.

Abbreviations: ASA, acetylsalicylic acid; others, see FIGURES 1 and 2

test, of DPI vs ASA alone in patients with PAD with limiting claudication (NCT04853719).

Conclusions In conclusion, the ATLAS ACS 2-TIMI 51,[10] COMPASS,[12] and VOYAGER PAD[23] trials demonstrated that rivaroxaban reduced the number of atherothrombotic events that were previously believed to be predominantly platelet--related.[48-51] Based on the trial results and current international guidelines, it is appropriate to consider adding the vascular dose of rivaroxaban to standard ASA in the patients with CAD (+/– PAD) (FIGURE 3) or symptomatic LEAD at a higher ischemic risk (FIGURE 4) to reduce the risk of cardiovascular mortality, MI, stroke, acute limb ischemia, and major amputation.[52] Notably, based on recently published observational studies, the DTI strategy seems safe and effective at long-term follow-up even in real-world populations, with an incremental benefit in the patients with multiple risk factors.

Given the increased risk for significant bleeding events (excluding fatal and symptomatic hemorrhage into a critical organ), this strategy should be considered on an individual basis in the patients whose thrombotic risk may be greater than the bleeding risk (FIGURE 5). Such patients should be evaluated at least annually to assess continuation of DPI based on clinical characteristics, tolerance to the therapy, and bleeding risk, which should be interpreted as a dynamic

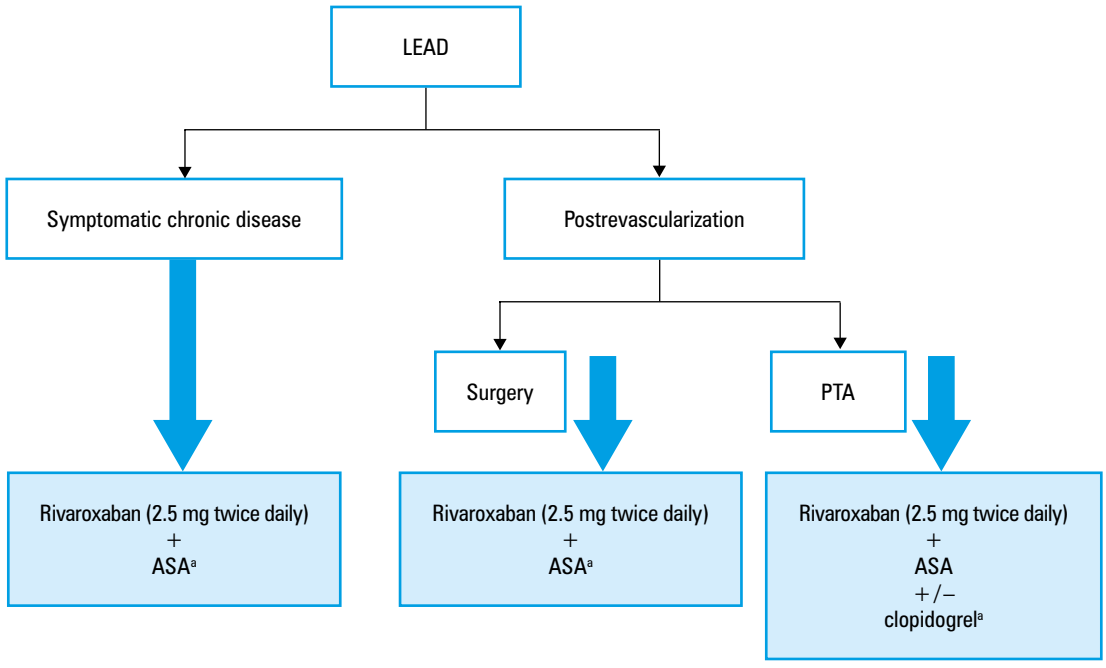

FIGURE 4 Practical indications for dual pathway inhibition in the patients with LEAD

a Acetylsalicylic acid or clopidogrel alone for high bleeding risk

Abbreviations: LEAD, lower extremity artery disease; PTA, percutaneous transluminal angioplasty; others, see FIGURE 3

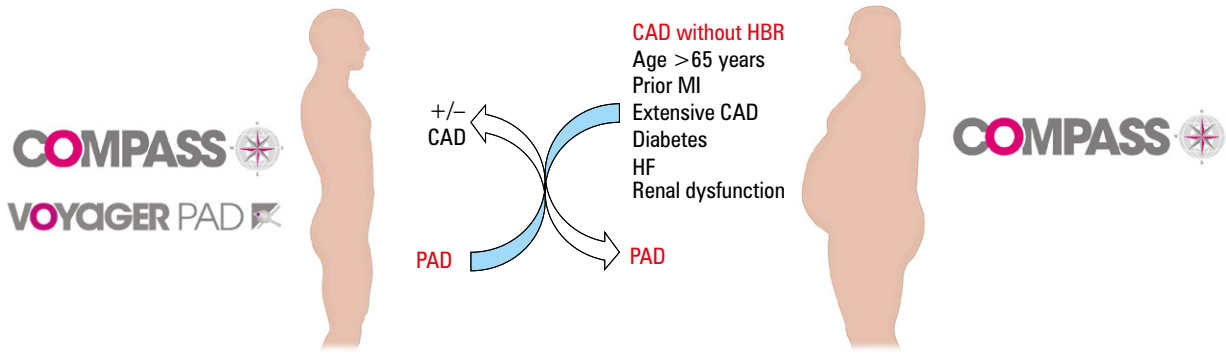

FIGURE 5 Schematic representation of current indications for low-dose rivaroxaban
Abbreviations: HBR, high bleeding risk; HF, heart failure; others, see **FIGURE 1**

and potentially evolving issue. The assessment of bleeding risk according to the Academic Research Consortium for High Bleeding Risk criteria is a valuable tool in this setting, as recommended by the current guidelines.[44]

ARTICLE INFORMATION

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