

Low-dose rivaroxaban: can cardiovascular events be reduced?

Leonardo De Luca ^{1,2*}

¹Department of Cardio-Thoracic and Vascular Medicine and Surgery, Division of Cardiology, A.O. San Camillo-Forlanini, Circonvallazione Gianicolense, 87, 0052 Rome, Italy; and ²UniCamillus-Saint Camillus International University of Health Sciences, Via di Sant'Alessandro, 8, 00131 Rome, Italy

KEYWORDS

Rivaroxaban;
Peripheral artery disease;
Coronary artery disease;
COMPASS trial

Despite available effective guideline-based preventive therapies, patients with vascular diseases remain at high-risk of recurrent ischaemic events. Novel therapeutic strategies are therefore needed in order to further reduce the residual risk that is present in these high-risk patients. The Cardiovascular Outcomes for People using Anticoagulation Strategies trial demonstrated that, in patients with chronic coronary artery disease (CAD) and peripheral artery disease (PAD), a combination of rivaroxaban 2.5 mg/bid (vascular dose) and acetylsalicylic acid (ASA) 100 mg once daily, the so-called dual pathway inhibition (DPI), reduced cardiovascular death, stroke, or myocardial infarction by 24% and mortality by 18%, as compared with ASA-alone. The rationale that can explain the improvement of cardiovascular outcome is that platelet aggregation and fibrin formation are involved in arterial thrombosis and rivaroxaban is able to target both ways and has a synergic effect with ASA. The aim of this review is to discuss the potential mechanisms and added benefits of DPI, in patients with PAD and CAD.

Vascular diseases, including cerebrovascular disease, coronary artery disease (CAD) and peripheral artery disease (PAD), are a global medical problem and a leading cause of morbidity and mortality.¹ Despite available effective guideline-based preventive therapies, patients with vascular diseases are at high-risk of recurrent ischaemic events.¹ The REduction of Atherothrombosis for Continued Health (REACH) registry assessed major cardiovascular (CV) outcomes in 64 977 patients with vascular diseases or three or more CV atherosclerosis risk factors. In the secondary prevention subgroup ($n = 53\,390$), despite recommended medical therapy, the observed annual rate of CV death, myocardial infarction (MI) or stroke was 4.6%.² This rate further increased to 14.4% when considering the composite of CV death, MI, stroke, or hospitalization for unstable angina, transient ischaemic attack or worsening PAD.² These findings demonstrate that adverse vascular events are frequent complications in the natural history of apparently stable atherothrombosis, even if appropriate treatment is used.

The aim of this review is to discuss the potential mechanisms and added benefits of a new therapeutic option, derived from low-dose rivaroxaban on top of acetylsalicylic acid (ASA), the so-called dual pathway inhibition (DPI), in patients with sinus rhythm and vascular diseases.

Low-dose rivaroxaban: the central role in reducing thrombosis

Recent studies tested the effects of oral anticoagulants, specifically factor Xa inhibitors, added to ASA, in patients with vascular diseases. Notably, the coagulation system supports platelet activation and function in several ways. Thrombin, fibrinogen, and von Willebrand factor are coagulation proteins with a significant role in platelet activation or aggregation. Thrombin is also the most potent endogenous platelet activator which exerts this effect by binding to protease-activated receptors (PARs) on the platelet surface.¹ Anticoagulant drugs that reduce thrombin generation or inhibit thrombin can therefore be expected to reduce platelet activity (*Figure 1*).

The ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in

*Corresponding author. Tel: +39 06 58704419, Fax: +39 06 5870 4361, Emails: leo.deluca@libero.it; ldeluca@scamilloforlanini.rm.it

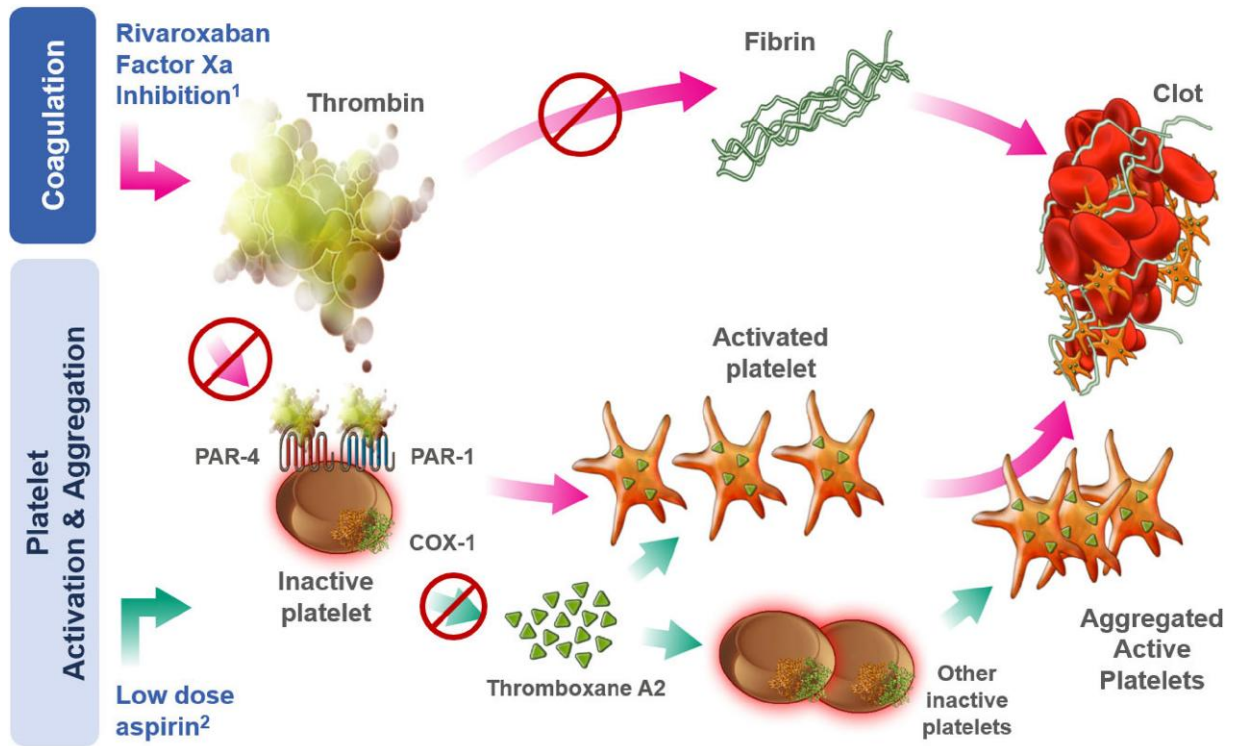


Figure 1 Components of atherothrombosis and mechanism of action of dual pathway inhibition (DPI).

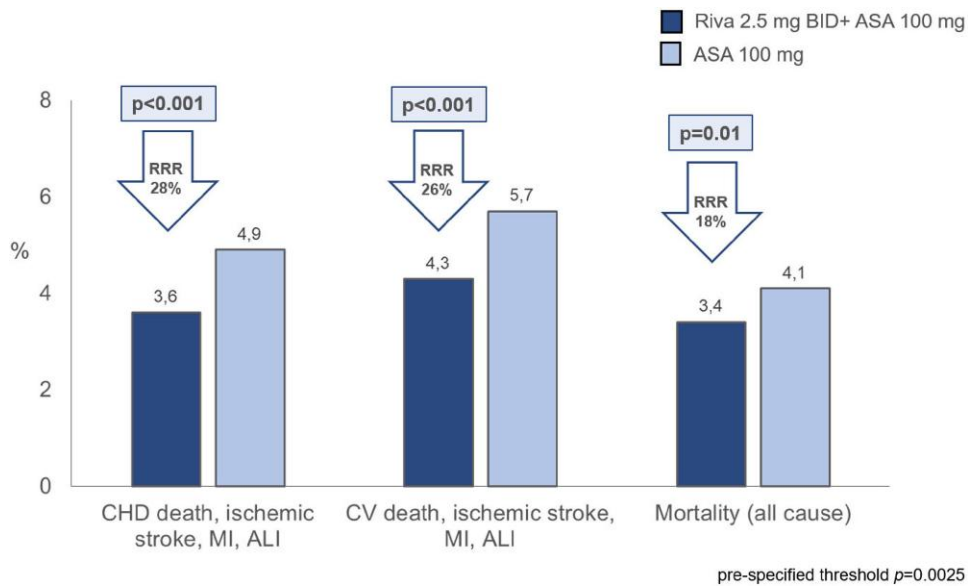


Figure 2 Pre-specified secondary endpoints in the two groups of the COMPASS trial.

Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction 51) trial was a double-blind multicentre study enrolling 15 526 stable patients after an acute coronary syndrome.³ Patients were randomized to twice-daily 2.5 or 5 mg rivaroxaban on top of ASA (+/- P2Y12 receptor inhibitor) or placebo plus ASA +/- P2Y12 receptor inhibitor. The primary efficacy endpoint was a composite of CV death, MI or stroke. The primary safety endpoint was TIMI major bleeding not

related to coronary artery bypass grafting. At a mean follow-up of 13 months, the addition of rivaroxaban 2.5 mg bid (the so-called vascular dose) twice-daily to standard therapy compared with placebo significantly reduced the primary efficacy endpoint [relative risk reduction (RRR): 16%; P=0.02]. These results were primarily driven by a reduction of CV death (RRR: 34%; P=0.002). Moreover, this strategy also reduced all-cause death (RRR: 32%; P=0.004), and the benefits were sustained



Figure 3 Major bleeding events in the two groups of the COMPASS trial.

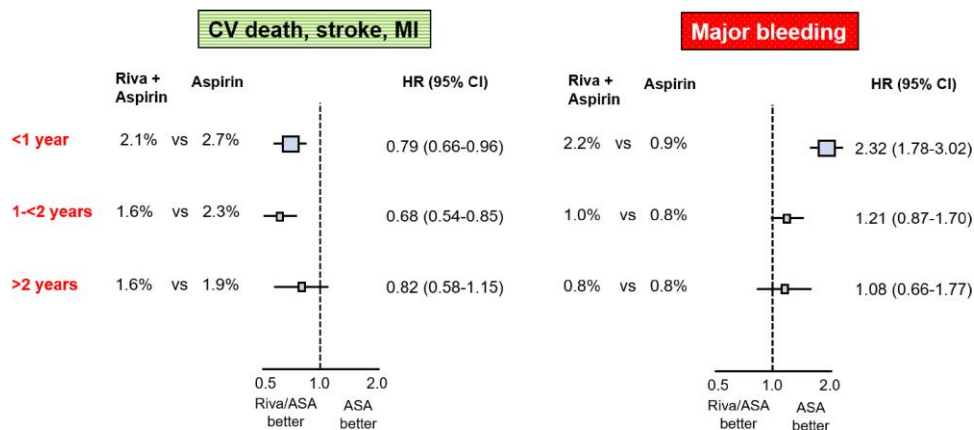


Figure 4 Landmark analysis of the COMPASS trial of primary efficacy and safety endpoints.

after stopping thienopyridines (at maximum follow-up of 31 months). Interestingly, rivaroxaban at vascular dose reduced stent thrombosis events (probable or definite, as per Academic Research Consortium definition) compared with placebo (2.9% vs. 4.5%; RRR: 39%; $P=0.002$). As for safety outcomes, even though rivaroxaban at vascular dose significantly increased the risk of major bleeding, roughly tripling the risk of TIMI major bleeding and doubling intracranial haemorrhage.³ The rationale that can explain the improvement of CV outcome is a right dose with a specific target approaching thrombotic process.

The COMPASS (Cardiovascular Outcomes for People using Anticoagulation Strategies) was a double-blind trial that randomized 27 395 subjects with stable atherosclerotic vascular disease to receive the DPI with rivaroxaban at vascular dose (2.5 mg bid) plus ASA (100 mg once daily), rivaroxaban (5 mg twice-daily), or ASA (100 mg once daily).⁴ The primary outcome was a composite of CV death, stroke, or MI. The main safety outcome was a modification of the International Society on Thrombosis and Haemostasis (ISTH) criteria for major bleeding and included fatal bleeding, symptomatic bleeding into a critical organ, bleeding into a surgical site requiring reoperation, and bleeding that led to hospitalization

(including presentation to an acute care facility without an overnight stay). Unlike the ISTH criteria, all bleeding that led to presentation to an acute care facility or hospitalization as major were considered. The study was stopped for superiority of the DPI group over ASA-alone at the first formal interim analysis for efficacy (50% of planned events), after a mean follow-up of 23 months. Patients were eligible if they met the criteria for CAD, PAD, or both.⁴ Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional risk factors [current smoking, diabetes mellitus, an estimated glomerular filtration rate (GFR) < 60 mL per minute, heart failure, or non-lacunar ischaemic stroke ≥ 1 month earlier]. Exclusion criteria were a high bleeding risk; a recent stroke or previous haemorrhagic or lacunar stroke; severe heart failure; advanced stable kidney disease (estimated GFR < 15 mL per minute); the use of dual antiplatelet therapy, anticoagulation, or other antithrombotic therapy; and non-CV conditions deemed by the investigator to be associated with a poor prognosis.

The primary outcome event occurred in 4.1% of DPI and 5.4% of ASA-alone patients (HR: 0.76; 95% CI: 0.66 to 0.86; $P < 0.001$). The secondary composite outcome of

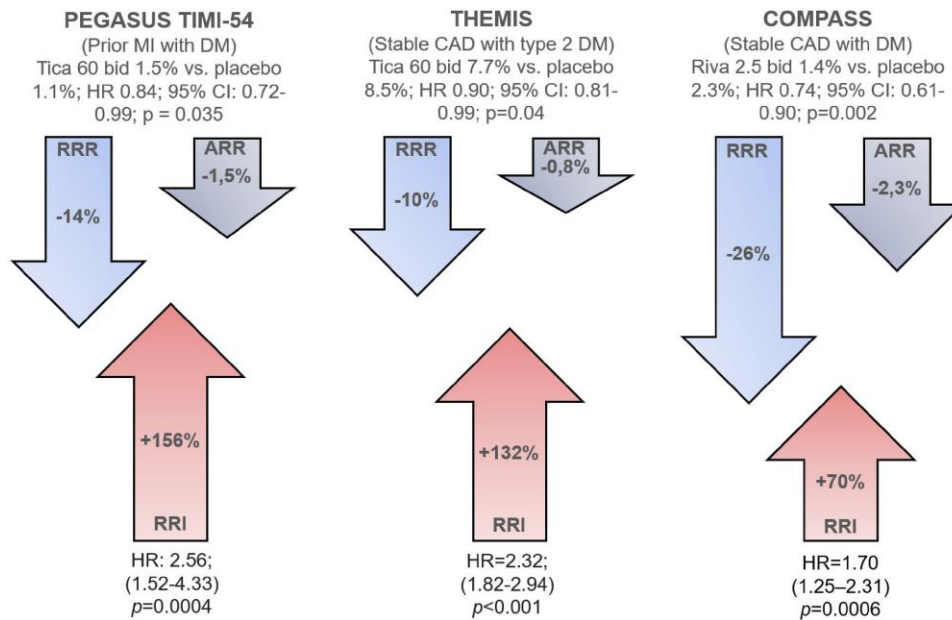


Figure 5 Relative risk reduction (RRR) and absolute risk reduction (ARR) in ischaemic outcome and relative risk increase (RRI) in bleeding events observed in pre-specified diabetic subgroups enrolled in recent trials on antithrombotic therapies.

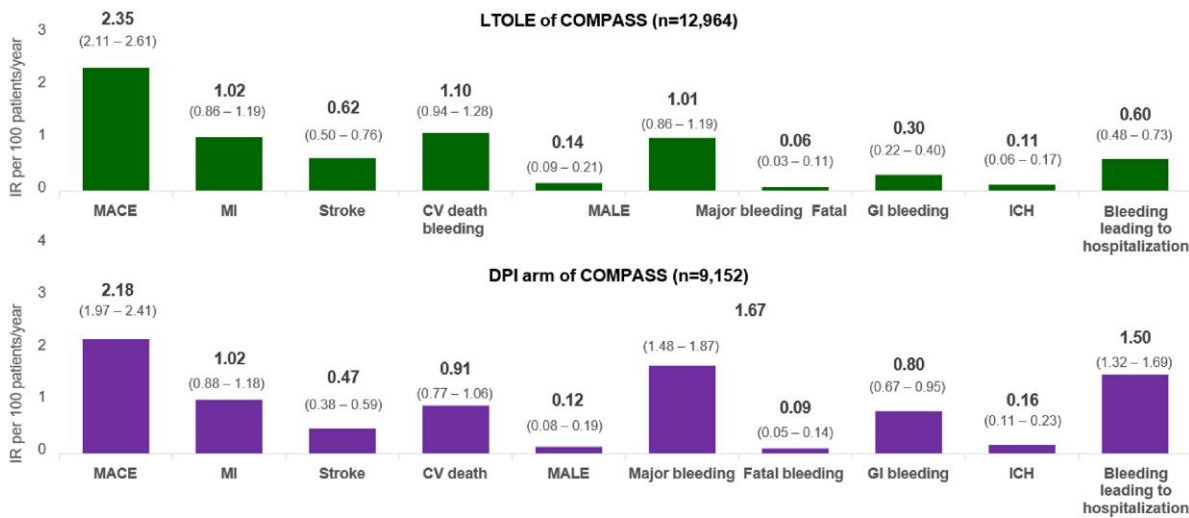


Figure 6 Efficacy and bleeding risk observed in COMPASS-LTOLE and COMPASS trial.

ischaemic stroke, MI, acute limb ischaemia, or death 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 ischaemic stroke, MI, acute limb ischaemia, or cardiovascular death also occurred in fewer patients in the DPI group than in the ASA-alone group (4.3% vs. 5.7%; HR: 0.74; 95% CI: 0.65-0.85; $P < 0.001$) (Figure 2). At the end of follow-up, 313 patients (3.4%) allocated to the DPI and 378 patients (4.1%) allocated to ASA-alone died (HR: 0.82; 95% CI: 0.71-0.96; $P = 0.01$).⁴ Compared with ASA, the combination reduced CV death (1.7% vs. 2.2%; HR: 0.78; 95% CI: 0.64-0.96; $P = 0.02$).⁵ There were fewer deaths following MI, stroke, and CV procedures, as

well as fewer sudden cardiac, other, and unknown causes of CV deaths and coronary heart disease deaths.

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: 1.70; 95% CI: 1.40-2.05; $P < 0.001$), mainly owing to a difference in bleeding that led to presentation to an acute care facility or hospitalization (Figure 3). Most of the excess major bleeding was into the gastrointestinal tract, with no significant between-group difference in the rate of fatal bleeding, intracranial bleeding, or symptomatic bleeding into a critical organ.⁶ At the landmark analysis, the majority of bleeding events occurred in the first year of treatment with DPI, while the ischaemic benefits were

consistent over the overall duration of the trial (Figure 4).

The risk of the composite net clinical benefit outcome of cardiovascular death, 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: 0.80; 95% CI: 0.70-0.91; $P < 0.001$).^{4,7}

Effects of low-dose rivaroxaban in different populations of the COMPASS trial

The effects of rivaroxaban at vascular dose plus ASA as compared with ASA-alone on the primary outcome and on major bleeding were consistent among subgroups that were defined according to age, sex, geographic region,

race or ethnic group, body weight, renal function, and history of CV risk factors (tobacco use, hypertension, diabetes, or dyslipidemia).⁴ Results in participants who met the eligibility criteria for CAD (90.5% of the overall trial population)⁸ and PAD⁹ were also consistent. Indeed, in patients with PAD the DPI compared with ASA-alone reduced the composite primary endpoint by 38% (5% vs. 7%; HR: 0.72, 95% CI: 0.57-0.90, $P = 0.0047$), 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 increasing of major bleeding, as attempt the net clinical benefit was favourable to the use of low-dose rivaroxaban add to ASA.⁹ The benefits of treatment of DPI were consistent across all subgroups of PAD patients.⁹

In patients enrolled in COMPASS and receiving a percutaneous coronary intervention (PCI), the DPI was associated with reductions in the primary composite outcome compared to ASA 100 mg alone. This benefit was consistent irrespective of the extension of CAD (single or multivessel CAD), the time from PCI occurrence (as early as 1 year and as far as 10 years previous) and the presence of a previous MI. In patients with previous PCI number needed to treat (NNT) to prevent the occurrence of one primary endpoint with DPI in comparison with ASA-alone was 50, while in those without a previous PCI the NNT was 43.¹⁰

In addition, the use of DPI in the COMPASS trial achieved the primary efficacy outcome, with a consistent hazard ratio (HR) in those with GFR 60 mL/min [GFR 60 mL/min, 3.5% rivaroxaban plus aspirin, 4.5% aspirin alone; HR: 0.76; 95% confidence interval (CI): 0.64-0.90; and those with GFR <60 mL/min (6.4% rivaroxaban plus aspirin, 8.4% aspirin alone, HR: 0.75; 95% CI: 0.60-0.94).¹¹ There was no significant interaction by the categories of renal

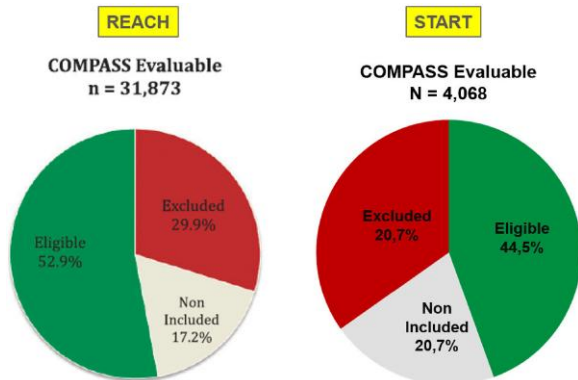


Figure 7 Proportion of COMPASS-eligible patients in REACH and START registry.

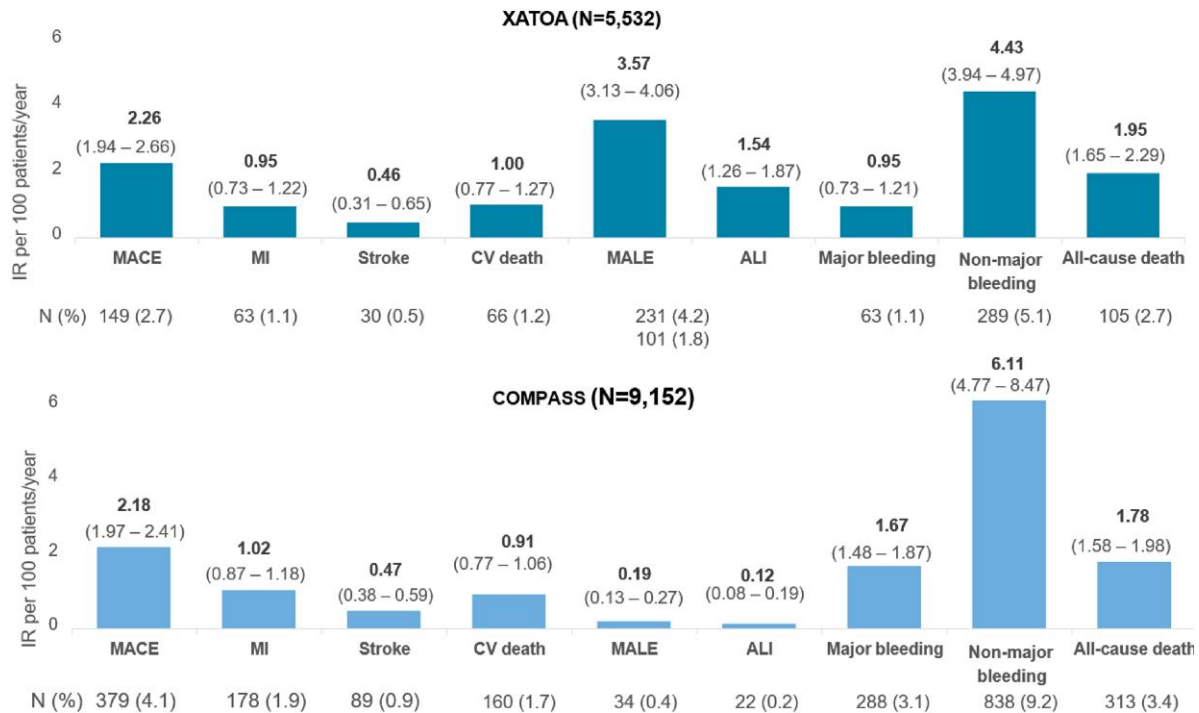


Figure 8 Comparison of ischaemic and bleeding events occurring in XATO registry and COMPASS trial.

function as for the primary efficacy and safety outcomes analysis.¹¹

Patients with diabetes mellitus and established CAD or PAD are at high-risk of future vascular events. A consistent and similar RRR was seen for benefit of DPI ($n=9152$) vs. placebo plus ASA ($n=9126$) in patients both with ($n=6922$) and without ($n=11\,356$) diabetes mellitus for the primary efficacy end point (HR: 0.74, $P=0.002$; and HR: 0.77, $P=0.005$, respectively, P interaction = 0.77) and all-cause mortality (HR: 0.81, $P=0.05$; and HR: 0.84, $P=0.09$, respectively; P interaction = 0.82).¹² However, although the absolute risk reductions appeared numerically larger in patients with vs. without diabetes mellitus, both subgroups derived similar benefit (2.3% vs. 1.4% for the primary efficacy end point at 3 years, P interaction < 0.0001; 1.9% vs. 0.6% for all-cause mortality, P interaction = 0.02; 2.7% vs. 1.7% for major vascular events, P interaction < 0.0001). Because the bleeding hazards were similar among patients with and without diabetes mellitus, the pre-specified net benefit for rivaroxaban appeared particularly favourable in the patients with diabetes mellitus (2.7% vs. 1.0%; P interaction = 0.001).¹² The benefit/risk ratio observed with the DPI strategy was more favourable compared with other antithrombotic therapies tested in the past (Figure 5). Accordingly, among the 5902 subjects with a history of heart failure and CAD or PAD, the DPI reduced the incidence of major adverse CV events compared with ASA-alone (5.5% vs. 7.9% HR: 0.68, 95% CI: 0.53-0.86), and the rate of re-hospitalization for heart failure and all-cause mortality (both P for interaction = 0.05) in patients with heart failure compared with those without.¹³

Risk factors for CV disease (smoking, obesity, hypercholesterolaemia, hypertension, and diabetes) expose patients to specific medical needs in terms of additional pharmacotherapy. In frail, elderly and multimorbid patients, polypharmacy is very frequent. In COMPASS trial the addition of low-dose rivaroxaban to ASA have shown a net clinical benefit regardless the number of concomitant drugs and comorbidities. According to this evidence, multiple comorbidities and polypharmacy should not dissuade the addition of rivaroxaban to ASA.¹⁴

Effects of low-dose rivaroxaban in real-world cohorts

Patients enrolled in COMPASS who completed follow-up until the end of the antithrombotic randomization (irrespective of randomized treatment allocation or whether they continued randomized treatment until the final visit) and those who continued to meet the COMPASS inclusion and exclusion criteria were eligible to participate in LTOLE (Long-Term Open Label Extension).¹⁵ All participants received DPI in LTOLE study regardless of the original treatment assignment in COMPASS with a mean follow-up of 15.7 months with up to further 3 years. The combination of rivaroxaban 2.5 mg bid and ASA 100 mg was associated with incidence rates of adverse CV outcome (CV death, stroke, or MI) consistent to those seen during the randomized phase.¹⁵ Notably, similar, and often lower incidence rates for bleeding, including gastrointestinal and intracranial bleeding have been observed in the LTOLE with DPI as compared with COMPASS trial (Figure 6).

In the real-world setting, the proportion of COMPASS-Eligible Patients in the REACH¹⁶ and Italian START (STable Coronary Artery Diseases RegisTry)¹⁷ registries are well represented, in fact they are about half (52,9% in REACH and 44,5% in START Registry) (Figure 7). In particular, in both registries, ischaemic outcome increased according to the number of enrichment criteria, without a significant change of safety profile (disproportionate increase in ischaemic vs. bleeding risk in patients with multiple enrichment criteria). In COMPASS-Like population, patients with multiple enrichment criteria at inclusion (diabetes mellitus, age >65 years, asymptomatic carotid disease, PAD, history of heart failure, renal impairment, current smoking status, and history of ischaemic stroke) presented a significant increase in the risk of major adverse events, and a modest absolute increase in the rate of major bleedings.^{16,17} Accordingly, in a post hoc analysis of the COMPASS trial subjects were classified as high-risk according to REACH scoring (two or more vascular beds affected, history of heart failure, or renal insufficiency) or CART scoring (two or more vascular beds affected, history of heart failure, or diabetes)¹⁸ Those with high-risk features presented a lower incidence of major adverse CV events, acute limb ischaemia, or total vascular amputation when treated with DPI compared with ASA, with a similar rate of major bleeding events.

The XATOA (Xarelto in Combination With Acetylsalicylic Acid) international registry could be considered the largest evidence for efficacy and safety outcome of DPI in a real-world scenario.¹⁹ In XATOA, physicians identified high cardiovascular risk as the reason for initiating DPI in 70.7% of patients (including at least one of the following: history of hypertension, diabetes, hyperlipidaemia, chronic renal dysfunction, smoking, family history of vascular disease, age >65 years, or high body mass index). There were 794 patients (14.4%) who initiated DPI after DAPT therapy. A large proportion of patients were on ASA only, before enrolment. In line with COMPASS strategy, most patients (88.2%) did not receive another antiplatelet agent during the study, and only 9.3% received DAPT on top of low-dose rivaroxaban.¹⁹ The rate of ischaemic events, identified as major CV events, was 2.26 (per 100 patient-years) and in COMPASS trial was 2.18 (per 100 patient-years). Major adverse limb events were higher in XATOA than in COMPASS observation because of deep difference in PAD population recruitment, counting 58.9% of the overall population vs. 27.3% of the trial. Incidences of major bleeding were lower in XATOA (0,95; IR per 100 patient-years) compared with COMPASS trial (1,67; IR per 100 patient-years), confirming the safety of DPI in real clinical practice (Figure 8).

In conclusion, on the basis of the available data and according with current international guidelines, low-dose rivaroxaban in combination with ASA should be considered for prevention of atherothrombotic events in each patient with CAD or symptomatic PAD at high-risk of ischaemic events and low bleeding risk.^{1,20}

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C *et al.* 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;**41**:407-477.
2. Bhatt DL, Eagle KA, Ohman EM, Hirsch AT, Goto S, Mahoney EM *et al.* Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. *JAMA* 2010;**304**:1350-1357.
3. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C *et al.* Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012;**366**:9-19.
4. Eikelboom JW, Connolly SJ, Bosch J, Dagenais GR, Hart RG, Shestakovska O *et al.* Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;**377**:1319-1330.
5. Eikelboom JW, Bhatt DL, Fox KAA, Bosch J, Connolly SJ, Anand SS *et al.* Mortality benefit of rivaroxaban plus aspirin in patients with chronic coronary or peripheral artery disease. *J Am Coll Cardiol* 2021;**78**:14-23.
6. Eikelboom JW, Bosch JJ, Connolly SJ, Shestakovska O, Dagenais GR, Hart RG *et al.* Major bleeding in patients with coronary or peripheral artery disease treated with rivaroxaban plus aspirin. *J Am Coll Cardiol* 2019;**74**:1519-1528.
7. Steffel J, Eikelboom JW, Anand SS, Shestakovska O, Yusuf S, Fox KAA. The COMPASS trial: net clinical benefit of low-dose rivaroxaban plus aspirin as compared with aspirin in patients with chronic vascular disease. *Circulation* 2020;**142**:40-48.
8. Connolly SJ, Eikelboom JW, Bosch J, Dagenais G, Dyal L, Lanan F *et al.* Rivaroxaban with or without aspirin in patients with stable coronary artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:205-218.
9. Anand SS, Bosch J, Eikelboom JW, Connolly SJ, Diaz R, Widimsky P *et al.* Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. *Lancet* 2018;**391**:219-229.
10. Bainey KR, Welsh RC, Connolly SJ, Marsden T, Bosch J, Fox KAA *et al.* Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). *Circulation* 2020;**141**:1141-1151.
11. Fox KAA, Eikelboom JW, Shestakovska O, Connolly SJ, Metsarinne KP, Yusuf S. Rivaroxaban plus aspirin in patients with vascular disease and renal dysfunction: from the COMPASS trial. *J Am Coll Cardiol* 2019;**73**:2243-2250.
12. Bhatt DL, Eikelboom JW, Connolly SJ, Steg PG, Anand SS, Verma S *et al.* Role of combination antiplatelet and anticoagulation therapy in diabetes mellitus and cardiovascular disease: insights from the COMPASS trial. *Circulation* 2020;**141**:1841-1854.
13. Branch KR, Probstfield JL, Eikelboom JW, Bosch J, Maggioni AP, Cheng RK *et al.* Rivaroxaban with or without aspirin in patients with heart failure and chronic coronary or peripheral artery disease. *Circulation* 2019;**140**:529-537.
14. Vanassche T, Verhamme P, Anand SS, Shestakovska O, Leong DP, Fox KAA *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**:462-473.
15. Eikelboom JW, Bosch J, Connolly SJ, Tyrwitt J, Fox KAA, Muehlhofer E *et al.* Long-term treatment with the combination of rivaroxaban and aspirin in patients with chronic coronary or peripheral artery disease: outcomes during the open label extension of the COMPASS trial. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:786-795.
16. Darmon A, Bhatt DL, Elbez Y, Aboyans V, Anand S, Bosch J *et al.* External applicability of the COMPASS trial: an analysis of the REduction of Atherothrombosis for Continued Health (REACH) registry. *Eur Heart J* 2018;**39**:750-757.
17. De Luca L, Formigli D, Meessen J, Uguccioni M, Cosentino N, Paolillo C *et al.* COMPASS criteria applied to a contemporary cohort of unselected patients with stable coronary artery diseases: insights from the START registry. *Eur Heart J Qual Care Clin Outcomes* 2021;**7**:513-520.
18. Darmon A, Sorbets E, Ducrocq G, Elbez Y, Abtan J, Popovic B *et al.* Association of multiple enrichment criteria with ischemic and bleeding risks among COMPASS-eligible patients. *J Am Coll Cardiol* 2019;**73**:3281-3291.
19. Fox KAA, Aboyans V, Debus ES, Zeymer U, Cowie MR, Patel M *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**:825-836.
20. Lim GB. Antithrombotic therapy: COMPASS points to low-dose rivaroxaban and aspirin for secondary prevention. *Nat Rev Cardiol* 2017;**14**:630-631.