

REVIEW

Reducing residual thrombotic risk in patients with peripheral artery disease: impact of the COMPASS trial

José Luis Hernández MD, PhD¹, Francisco S Lozano MD, PhD², Vincent Rimbau MD, PhD³, Manuel Almendro-Delia MD, PhD⁴, Juan Cosín-Sales MD, PhD⁵, Sergi Bellmunt-Montoya MD, PhD⁶, Javier Garcia-Alegria MD, PhD⁷, Xavier Garcia-Moll MD, FESC, FACC⁸, Juan José Gomez-Doblas MD, PhD⁹, José R Gonzalez-Juanatey MD, PhD¹⁰, Carmen Suarez Fernández MD¹¹

¹Internal Medicine Department, Hospital Marqués de Valdecilla-IDIVAL, Universidad de Cantabria, Santander, Spain; ²Department of Vascular Surgery, Hospital Clínico de Salamanca, Salamanca, Spain; ³Vascular Surgery Division, Cardiovascular Institute Hospital Clinic University of Barcelona, Barcelona, Spain; ⁴Intensive Cardiovascular Care Unit, Cardiovascular Clinical Trials & Translational Research Unit, Cardiology and Cardiovascular Surgery Division, Virgen Macarena University Hospital, Seville, Spain; ⁵Cardiology Department, Hospital Arnau de Vilanova. Facultad de Medicina, Universidad CEU-Cardenal Herrena, Valencia, Spain; ⁶Vascular Surgery Department, Universitari Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain; ⁷Department of Medicine, Hospital Costa del Sol, Marbella, Spain; ⁸Cardiology Department, Hospital Sant Pau, Barcelona, Spain; ⁹Cardiology Department, Hospital Universitario Virgen de la Victoria, CIBERCV, Malaga, Spain; ¹⁰Cardiology and Intensive Cardiac Care Department, University Hospital Santiago de Compostela, CIBERCV, Santiago de Compostela, Spain; ¹¹Internal Medicine Department, Hospital Universitario de la Princesa, Universidad Autónoma de Madrid, Madrid, Spain

Abstract

Patients with peripheral artery disease (PAD) are at a high risk not only for the classical cardiovascular (CV) outcomes (major adverse cardiovascular events; MACE) but also for vascular limb events (major adverse limb events; MALE). Therefore, a comprehensive approach for these patients should include both goals. However, the traditional antithrombotic approach with only antiplatelet agents (single or dual antiplatelet therapy) does not sufficiently reduce the risk of recurrent thrombotic events. Importantly, the underlying cause of atherosclerosis in patients with PAD implies both platelet activation and the initiation and promotion of coagulation cascade, in which Factor Xa plays a key role. Therefore, to reduce residual vascular risk, it is necessary to address both targets. In the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial that included patients with stable atherosclerotic vascular disease, the rivaroxaban plus aspirin strategy (*versus* aspirin) markedly reduced the risk of both CV

and limb outcomes, and related complications, with a good safety profile. In fact, the net clinical benefit outcome composed of MACE; MALE, including major amputation, and fatal or critical organ bleeding was significantly reduced by 28% with the COMPASS strategy, (hazard ratio: 0.72; 95% confidence interval: 0.59–0.87). Therefore, the rivaroxaban plus aspirin approach provides comprehensive protection and should be considered for most patients with PAD at high risk of such events.

Keywords: COMPASS, peripheral artery disease, residual risk, rivaroxaban.

Citation

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Introduction

Peripheral artery disease (PAD) is very common in clinical practice, although underdiagnosed.^{1,2} It has been estimated that more than 200 million people worldwide are affected by lower extremity PAD.³ The prevalence of PAD markedly increases with age, from approximately 5% in patients aged 45–49 years to around 10% in patients aged 65–74 years and nearly 20% by the age of 80 years.^{3,4} In Spain, in a

cross-sectional analysis of 1568 subjects, aged 45–74 years, the prevalence of PAD was 3.8%.⁵ In the MERITO study, the prevalence of PAD evaluated by the ankle–brachial index in patients with metabolic syndrome was 28% and in patients with a previous coronary event, cerebrovascular disease, or both, it was 34, 32, and 54%, respectively.^{6,7}

In addition, it is expected that these numbers will increase in the following years due to the aging of the population and

the increased rates of diabetes, hypertension, and smoking.³ Importantly, the majority of patients with PAD do not refer specific symptoms. Thus, according to different studies, up to one-third of patients with an ankle–brachial index <0.90 have typical intermittent claudication.^{4,8,9}

Atherosclerotic disease is the underlying cause of PAD.^{1,2} As atherosclerosis is often generalized, patients with PAD have usually more vascular beds affected. Thus, in the Reduction of Atherothrombosis for Continued Health (REACH) registry, 61.5% of patients with PAD had concomitant disease in other vascular beds (*versus* 24.7% of patients with coronary artery disease [CAD]).¹⁰ Patients with polyvascular disease have an increased risk of morbidity and mortality, being greater as a higher number of vascular beds are affected.^{11–14}

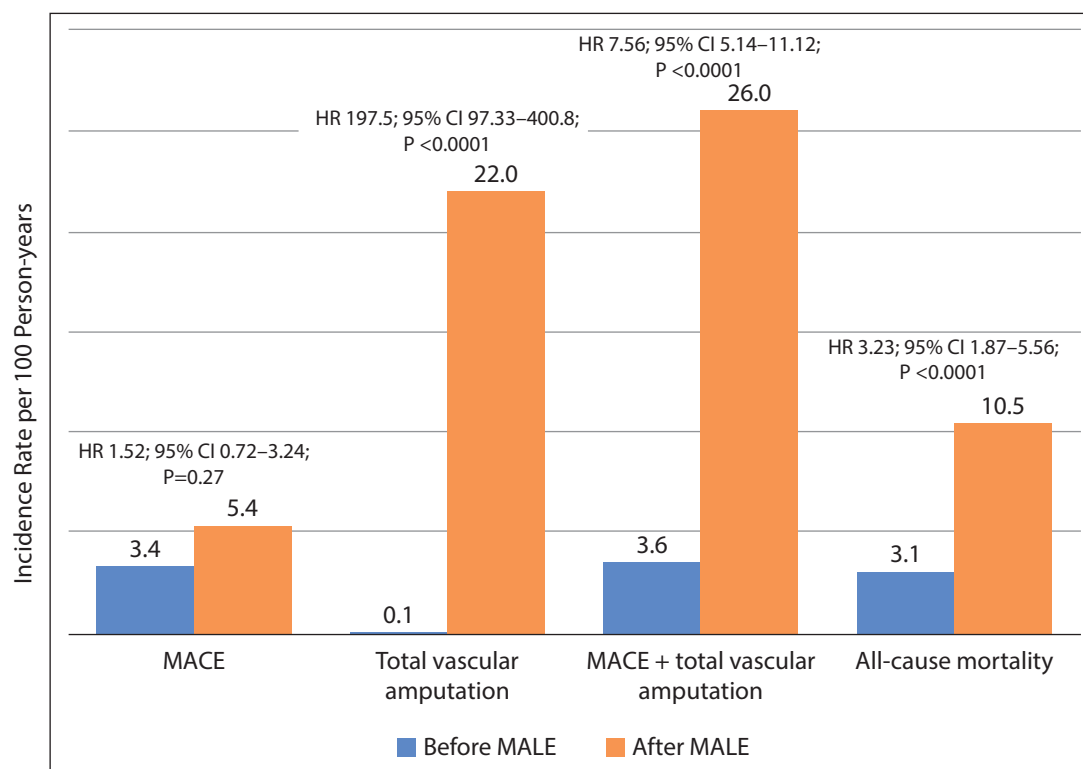
Patients with symptomatic or asymptomatic PAD have an increased risk of cardiovascular (CV) death, myocardial infarction, and stroke (major adverse cardiovascular events; MACE).¹⁵ Compared with patients without PAD, the risk of CV death is increased among patients with asymptomatic and symptomatic PAD, by 5 and 11%, respectively.¹⁶ In addition, approximately one-fifth of patients with symptomatic PAD have myocardial infarction, and around 10–15% die after a 5-year period of follow-up.¹⁷ Of the one hand, the risk of CV death, myocardial infarction, or stroke is even higher in patients

with PAD than in patients with CAD.¹² On the other hand, in patients with asymptomatic carotid stenosis, approximately two-thirds of late deaths are related to cardiac events, with an annual mortality rate of 2.9%.¹⁸

Patients with PAD are not only at high risk of MACE, but also of major adverse limb events (MALE), including severe limb ischemia and amputation.¹⁹ Thus, it has been calculated that the annual incidence of major amputation ranges between 120 and 500 per million, and in Western Europe, the PAD-related mortality reached 3.5 per 100,000 individuals (excluding stroke and myocardial infarction) in 2010, and the years of life lost due to PAD were estimated at 31.7 years per 100,000 inhabitants.^{1,20,21} Therefore, in patients with PAD, it is not only mandatory to reduce MACE, but also MALE.

In a specific substudy of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial, which analyzed the impact of MALE on the prognosis of patients with lower extremity PAD, showed that after MALE, the 1-year cumulative risk of subsequent hospitalization, vascular amputations, death, and MACE were 61.5; 20.5; 8.3; and 3.7%, respectively. Importantly, experiencing MALE dramatically increased the risk of subsequent amputations (hazard ratio [HR]: 197.5; $p < 0.0001$), and death (HR: 3.23; $p < 0.001$) (Figure 1).²²

Figure 1. Outcomes in patients before and after MALE in the COMPASS study.²²



MACE: cardiovascular death, myocardial infarction, stroke.

As a result, PAD is a very common condition in routine practice, with very high rates of MACE and MALE. Reducing both and the related complications with the appropriate prophylaxis is mandatory. In this narrative review, data about how to reduce residual risk through the best antithrombotic approach among patients with PAD, with a particular focus on the COMPASS trial, are updated in order to provide some practical recommendations about its use in this population. For this purpose, a search was performed (up to March 2020) on PubMed (MEDLINE), using the MeSH terms [peripheral artery disease] + [COMPASS] + [rivaroxaban] + [treatment]. Original data from clinical trials, prospective and retrospective studies, and more useful reviews were selected.

Antithrombotic treatment in patients with PAD

Progressive atherosclerosis is the underlying cause of PAD and results in a spectrum of symptoms that, in the case of lower extremity PAD, ranges from asymptomatic to intermittent claudication, ischemic rest pain, and major and minor trophic changes. On the other hand, acute limb ischemia (ALI) is caused by native atherosclerotic plaque disruption and thrombus formation, and in the case of patients previously revascularized, thrombosis of the stent or graft.^{1,2,20,23} After atherosclerotic plaque disruption, the thrombogenic subendothelial matrix is exposed to circulating blood, leading to activation of circulating platelets and the coagulation cascade and lastly to thrombus formation.^{24–28} As a result, to reduce CV outcomes and the risk of PAD-related complications, it is necessary not only to control CV risk factors, but also follow a comprehensive antithrombotic approach that includes not only acting on platelets but also on coagulation inhibition.²⁹

With regard to antithrombotic therapy, in patients with lower extremity PAD, the European guidelines recommend the use of long-term single antiplatelet therapy in symptomatic patients (recommendation I A) and in all patients who have undergone revascularization (recommendation I C). Furthermore, clopidogrel may be preferred over aspirin (recommendation IIb B). In addition, dual antiplatelet therapy with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation (recommendation IIa C) and may be considered in below-the-knee bypass with a prosthetic graft (recommendation IIb B). Importantly, antiplatelet therapy is not routinely indicated in patients with asymptomatic PAD (recommendation III A).¹ On the other hand, long-term single antiplatelet therapy is also recommended in patients with symptomatic carotid stenosis (recommendation I A), and dual antiplatelet therapy with aspirin and clopidogrel for at least 1 month after carotid artery stenting (recommendation I B).¹

Despite these indications, patients with PAD treated with current evidence-based recommended care have an unacceptably high residual CV risk.^{29,30} This is not surprising as the current only antiplatelet-based antithrombotic approach is

insufficient to effectively reduce not only MACE but also MALE in PAD patients.^{31,32} In addition, the 2017 European guidelines recognize that the results of the COMPASS trial were not included at the time of publication but should be updated after a critical analysis.¹

Thus, the evidence supporting the use of aspirin or clopidogrel to prevent MACE in PAD patients remains insufficient. In a meta-analysis of 18 clinical trials involving 5269 individuals with PAD, treatment with aspirin alone resulted in a statistically nonsignificant reduction in MACE, and only a significant decrease in nonfatal stroke (Table 1).³³ In another meta-analysis of 287 studies, aspirin reduced the risk of MACE among patients with atherosclerotic vascular disease, including those with PAD.³⁴ In patients with symptomatic PAD and no history of stroke/transient ischemic attack included in the REACH registry, despite 61% of patients treated with aspirin and 83% with at least one antiplatelet agent, MACE rates reached 4.7% during the first year and increased continuously by 4–5% per year; the limb ischemic event rate was 5.7% at 2 years.³⁵ In the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial, among 19,185 patients with atherosclerotic vascular disease, including recent ischemic stroke, recent myocardial infarction, or symptomatic PAD, after a mean follow-up of 1.91 years, compared with aspirin, clopidogrel significantly reduced the risk of MACE, including the subgroup of patients with PAD (Table 1).³⁶ In the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance (CHARISMA) study, in the subgroup of patients with prior myocardial infarction, ischemic stroke, or symptomatic PAD, while the combination of clopidogrel plus aspirin (*versus* aspirin alone) significantly reduced the risk of MACE by 17%, there was a nonsignificant reduction of 13% in the PAD subpopulation. No reduction of mortality was observed. Moderate bleeding, but not severe bleeding, was more common with the combination (Table 1).³⁷

This limited efficacy of antiplatelet agents in patients with PAD has not only been limited to the traditional antiplatelet agents, such as aspirin or clopidogrel, but also with the newer ones. The Trial to Assess the Effects of Vorapaxar in Preventing Heart Attack and Stroke in Patients with Atherosclerosis–Thrombolysis in Myocardial Infarction 50 (TRA 2P–TIMI 50) study compared vorapaxar plus aspirin *versus* aspirin in patients with chronic atherosclerotic vascular disease. In the subgroup of 3787 patients with chronic symptomatic PAD, vorapaxar did not reduce the risk of MACE, but significantly reduced the rates of hospitalization for ALI and peripheral artery revascularization by 42 and 16%, respectively. Major bleeding was more common with the combination (Table 1).³⁸ Ticagrelor, 90 mg, twice daily was compared with clopidogrel, 75 mg, once daily in 13,885 patients with symptomatic PAD in the Effects of Ticagrelor and Clopidogrel in Patients with Peripheral Artery Disease (EUCLID) trial. After a median follow-up of 30 months, rates of MACE, ALI, CV death, and major bleeding were similar between both groups (Table 1).³⁹ In the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to

Table 1. Efficacy and safety of antithrombotic treatment in patients with peripheral artery disease.^{33,36–41}

Study	Treatment	Study population	Results
Berger, et al ³³	Aspirin versus control	Meta-analysis of randomized trials (5269 patients with PAD)	<ul style="list-style-type: none"> CV death: RR: 0.94; 95% CI: 0.74–1.19; <i>p</i>=0.59 Nonfatal myocardial infarction: RR: 1.04; 95% CI: 0.78–1.39; <i>p</i>=0.81 Non-fatal stroke: RR: 0.66; 95% CI: 0.47–0.94; <i>p</i>=0.02 MACE: RR: 0.88; 95% CI: 0.76–1.04; <i>p</i>=0.13
CAPRIE ³⁶	Clopidogrel versus aspirin	19,185 patients with atherosclerotic vascular disease (ischemic stroke, recent myocardial infarction, or symptomatic PAD)	<ul style="list-style-type: none"> MACE: <ul style="list-style-type: none"> Overall population: RR: 0.87%; 95% CI: 0.3–16.5%; <i>p</i>=0.043 PAD population: RR: 23.8%; 95% CI: 8.9–36.2%; <i>p</i>=0.0028
CHARISMA ³⁷	Clopidogrel + aspirin versus aspirin	9478 patients with documented prior MI, ischemic stroke, or symptomatic PAD	<ul style="list-style-type: none"> MACE: <ul style="list-style-type: none"> Overall population with CV atherosclerotic disease: HR: 0.83; 95% CI: 0.72–0.96; <i>p</i>=0.01 PAD population: HR: 0.87; 95% CI: 0.67–1.13; <i>p</i>=0.29 All-cause mortality: HR: 0.91; 95% CI: 0.77–1.09; <i>p</i>=0.32 CV mortality: HR: 0.87; 95% CI: 0.70–1.09; <i>p</i>=0.22 Severe bleeding: HR: 1.12; 95% CI: 0.81–1.53; <i>p</i>=0.51 Moderate bleeding: HR: 1.60; 95% CI: 1.16–2.20, <i>p</i>=0.004
TRA 2P–TIMI 50 ³⁸	Vorapaxar +aspirin versus aspirin	3787 patients with a history of claudication and an ankle-brachial index of <0.85 or prior revascularization for limb ischemia	<ul style="list-style-type: none"> MACE: HR: 0.94; 95% CI: 0.78–1.14; <i>p</i>=0.53 Hospitalization for ALI: HR: 0.58; 95% CI: 0.39–0.86; <i>p</i>=0.006 Hospitalization for artery revascularization: HR: 0.84; 95% CI: 0.73–0.97; <i>p</i>=0.017 Major bleeding: HR: 1.62; 95% CI: 1.21–2.18; <i>p</i>=0.001
EUCLID ³⁹	Ticagrelor (90 mg) versus clopidogrel	13,885 patients with symptomatic PAD	<ul style="list-style-type: none"> MACE: HR: 1.02; 95% CI: 0.92–1.13; <i>p</i>=0.65 ALI: HR: 1.03; 95% CI: 0.79–1.33; <i>p</i>=0.85 CV death: HR: 1.07; 95% CI: 0.92–1.23; <i>p</i>=0.40 Major bleeding: HR: 1.10; 95% CI: 0.84–1.43; <i>p</i>=0.49

(Continued)

Table 1. (Continued)

Study	Treatment	Study population	Results
PEGASUS-TIMI 54 ⁴⁰	Ticagrelor, 60/90 mg, + aspirin versus aspirin	1143 patients with PAD and prior myocardial infarction (1–3 years)	<p>Ticagrelor 90 mg:</p> <ul style="list-style-type: none"> MACE: <ul style="list-style-type: none"> Ticagrelor, 90 mg: HR: 0.81; 95% CI: 0.57–1.15; $p=0.24$ Ticagrelor, 60 mg: HR: 0.69; 95% CI: 0.47–0.99; $p=0.045$ MALE: <ul style="list-style-type: none"> Ticagrelor, 90 mg: HR: 0.49; 95% CI: 0.30–0.81; $p=0.005$ Ticagrelor, 60 mg: HR: 0.81; 95% CI: 0.53–1.24; $p=0.33$ Ischemic stroke: <ul style="list-style-type: none"> Ticagrelor, 90 mg: HR: 0.47; 95% CI: 0.19–1.14; $p=0.095$ Ticagrelor, 60 mg: HR: 0.52; 95% CI: 0.22–1.22; $p=0.13$ CV death: <ul style="list-style-type: none"> Ticagrelor, 90 mg: HR: 0.83; 95% CI: 0.50–1.38; $p=0.46$ Ticagrelor, 60 mg: HR: 0.47; 95% CI: 0.25–0.86; $p=0.014$ Major bleeding: <ul style="list-style-type: none"> Ticagrelor, 90 mg: HR: 1.46; 95% CI: 0.39–5.43; $p=0.57$ Ticagrelor, 60 mg: HR: 1.18; 95% CI: 0.29–4.70; $p=0.82$ <p>Ticagrelor 60 mg:</p> <ul style="list-style-type: none"> MACE: Yes MALE: No Ischemic stroke: No CV death: Yes
COMPASS ⁴¹	Rivaroxaban, 2.5 mg, + aspirin versus aspirin	7470 patients with chronic PAD	<ul style="list-style-type: none"> MACE: HR: 0.72; 95% CI: 0.57–0.90; $p=0.0047$ Stroke: HR: 0.54; 95% CI: 0.33–0.87 CV death: HR: 0.82; 95% CI: 0.59–1.14 MALE: HR: 0.54; 95% CI: 0.35–0.84; $p=0.0054$ All vascular amputations: HR: 0.40; 95% CI: 0.20–0.79; $p=0.0069$ Major amputation: HR: 0.30; 95% CI: 0.11–0.80; $p=0.011$ Major bleeding: HR: 1.61; 95% CI: 1.12–2.31; $p=0.0089$ Fatal bleeding or symptomatic bleeding into a critical organ: HR: 1.10; 95% CI: 0.59–2.05 Fatal or symptomatic bleeding into a critical organ or surgical site bleeding leading to re-operation: HR: 1.13; 95% CI: 0.64–2.01 Net clinical benefit: HR: 0.72; 95% CI: 0.59–0.87; $p=0.0008$ <p>MACE: Yes</p> <p>Stroke: Yes</p> <p>CV death: No</p> <p>MALE: Yes</p> <p>All vascular amputations: Yes</p> <p>Major amputation: Yes</p>

ALI, acute limb ischemia; CV, cardiovascular; PAD, peripheral artery disease; MACE: CV death, myocardial infarction, or stroke; MALE, major adverse limb event.

Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS–TIMI 54) trial, 21,162 patients with prior myocardial infarction (1–3 years) were randomized to receive ticagrelor, 90 mg, twice daily plus aspirin and ticagrelor, 60 mg, twice daily plus aspirin or placebo plus aspirin. Compared with aspirin in monotherapy, the combination of ticagrelor, 90 mg, and aspirin did not significantly reduce the risk of MACE, ischemic stroke, or CV death, but significantly reduced the risk of MALE by 51%. By contrast, ticagrelor, 60 mg, plus aspirin significantly reduced the risk of MACE and CV deaths by 31 and 53%, respectively, but not the risk of MALE or ischemic stroke (Table 1).⁴⁰ All these data clearly indicate that treating PAD patients with antiplatelets (single or dual antiplatelet therapy) does not provide a comprehensive approach with the double target of reducing MACE and MALE.⁴¹

On the other hand, full anticoagulation with vitamin K antagonists has not been shown to provide further protection compared with single antiplatelet therapy in patients with PAD.^{42,43}

Finding an antithrombotic regimen that targets both platelet and anticoagulation cascade activation may be more effective in preventing MACE and MALE in patients with PAD.^{25,26,44–47} In addition, experimental data have shown that the inhibition of Factor Xa decreases inflammation and platelet-dependent thrombin generation; attenuates neointima formation after vascular injury; has protective, repairing, and fibrinolytic effects on vascular endothelium; and stabilizes atherosclerotic plaque and reduces its progression. Of note, most of these positive data on experimental models have been obtained specifically with rivaroxaban.^{48–52} All these data strongly suggest that an inhibition of Factor Xa, as rivaroxaban, could exert a positive impact on patients with PAD. This hypothesis has been tested in the COMPASS study.

The COMPASS study was a double-blind superiority trial that included a total of 27,395 subjects with chronic atherosclerotic vascular disease (CAD or PAD). Patients were randomly allocated to receive rivaroxaban, 2.5 mg, twice daily combined with aspirin, 100 mg, once daily, rivaroxaban, 5 mg, twice daily or aspirin, 100 mg, once daily. At baseline, mean age was 68 years, 91% of patients had CAD (62% previous myocardial infarction; 73% only CAD; 18% CAD and PAD), and 27% had PAD (9% only PAD). The study was prematurely stopped due to the beneficial effects found with rivaroxaban, 2.5 mg, twice daily (vascular dose of rivaroxaban) plus aspirin over aspirin after a mean follow-up of only 23 months.^{53,54} This is very relevant as the Kaplan–Meier survival curves between rivaroxaban plus aspirin and aspirin alone separated over time, mainly after the first year of treatment, but the excess of bleeding risk dramatically fell after 1 year of therapy.^{53,54} As a result, compared with the traditional approach of aspirin alone in patients with chronic atherosclerotic vascular disease, the net clinical benefit of the rivaroxaban plus aspirin approach increases over time.

Overall, compared with aspirin, the rivaroxaban plus aspirin combination reduced the risk of MACE by 24% (HR: 0.76; 95%

CI: 0.66–0.86; $p < 0.001$). This beneficial effect was independent of the presence of PAD (p for interaction was 0.61). The risk of ischemic stroke, myocardial infarction, ALI, or death from CAD was also reduced by 28% with the combination (HR: 0.72; 95% CI: 0.63–0.83; $p < 0.001$), and also the risk of MACE or ALI by 26% (HR: 0.74; 95% CI: 0.65–0.85; $p < 0.001$). The risk of stroke and hospitalization for CV causes was also significantly reduced by the rivaroxaban plus aspirin approach. But more importantly, there was a trend toward a lower risk of both CV death and death from any cause with the combination of rivaroxaban plus aspirin compared with aspirin. Although the risk of major bleeding was increased with the combination (HR: 1.70; 95% CI: 1.40–2.05; $p < 0.001$), the risk of fatal bleeding or intracranial bleeding did not significantly differ between the groups.⁵⁴

Importantly, while there was an absolute risk reduction of 0.5% in CV death between aspirin alone and the rivaroxaban plus aspirin approach (from 2.2 to 1.7%; $p = 0.02$) and an absolute risk reduction of 0.7% in death from any cause (from 4.1 to 3.4%; $p = 0.01$), there was a nonsignificant absolute increase of 0.1% in fatal bleeding (from 0.1 to 0.2%; $p = 0.32$), without any difference in the risk of nonfatal symptomatic intracranial hemorrhage (0.2% in both groups; $p = 0.77$).⁵⁴ In summary, in patients with chronic atherosclerotic vascular disease, the beneficial effect of the combination of rivaroxaban plus aspirin on MACE is much higher than the possible increase in bleeding risk.

Efficacy and safety of the vascular dose of rivaroxaban in patients with established PAD

The COMPASS substudy included a total of 7470 patients with PAD. The definitions of PAD, according to the COMPASS criteria, are summarized in Table 2. Briefly, to be included, patients should have a history of PAD of the lower extremities (previous revascularization, amputation, or intermittent claudication), of the carotid arteries (previous revascularization or asymptomatic $\geq 50\%$ carotid artery stenosis), or patients with ischemic heart disease and an ankle–brachial index < 0.90 . Although all these patients were included according to PAD criteria, there were relevant differences in the clinical profile of these subgroups of patients. With regard to the exclusion criteria, patients who required dual antiplatelet therapy for any clinical condition or with a high risk of bleeding were excluded from the study (Table 2).^{41,53}

Mean age of patients with PAD was 68 years, 81% had symptomatic PAD, 55% symptomatic PAD of lower extremities, 26% previous carotid revascularization or $\geq 50\%$ carotid stenosis, 20% CAD and an ankle–brachial index < 0.90 , and 4.5% prior limb or foot amputation. In addition, 66% of patients with PAD had concomitant CAD and 28% renal insufficiency (Table 3).⁴¹

Among PAD patients, compared with aspirin, the rivaroxaban plus aspirin approach significantly reduced the risk of MACE by 28%; the risk of ischemic heart disease death, myocardial

Table 2. Definition of peripheral artery disease and main exclusion criteria in the COMPASS trial.^{41,53}

<ul style="list-style-type: none"> • Definition of PAD (any of the following): <ul style="list-style-type: none"> ○ Previous aortofemoral or limb bypass surgery, or percutaneous transluminal angioplasty revascularization of the iliac/infringuinal arteries, or ○ Previous limb/foot amputation due to arterial vascular disease, or ○ History of intermittent claudication and ≥1 of the following: <ul style="list-style-type: none"> • an ankle/arm blood pressure ratio <0.90 • significant peripheral artery stenosis (≥50%) (detected by angiography or duplex ultrasound) • previous carotid revascularization or asymptomatic carotid artery stenosis ≥50% (detected by duplex ultrasound or angiography). 	<ul style="list-style-type: none"> • Main exclusion criteria: <ul style="list-style-type: none"> ○ high risk of bleeding ○ stroke ≤30 days or any history of hemorrhagic or lacunar stroke ○ severe heart failure (LVEF < 30% or NYHA class III or IV) ○ eGFR < 15 mL/min ○ need for dual antiplatelet therapy, or anticoagulation.
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eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease.

Table 3. Baseline clinical characteristics of patients with peripheral artery disease (lower extremities or carotid) included in the COMPASS trial.⁴¹

Total population	
Patients with PAD (n)	7470
Symptomatic PAD of the lower extremities (n)	4129
Previous carotid revascularization or carotid stenosis ≥50% (n)	1919
CAD who had an ABI <0.90 (n)	1422
Biodemographic data	
Mean age, years	68
Men (%)	71
Cardiovascular risk factors	
Hypertension (%)	80
Diabetes (%)	44
Smoking status (%)	
Current	27
Former	46
Never	27
Vascular disease	
CAD (%)	66
Renal insufficiency (%)	28
Previous stroke (%)	7
Concomitant medications	
Antiplatelets (%)	87
Lipid-lowering drugs (%)	83
Renin–angiotensin system inhibitors (%)	70

ABI, ankle–brachial index; CAD, coronary artery disease; PAD, peripheral artery disease.

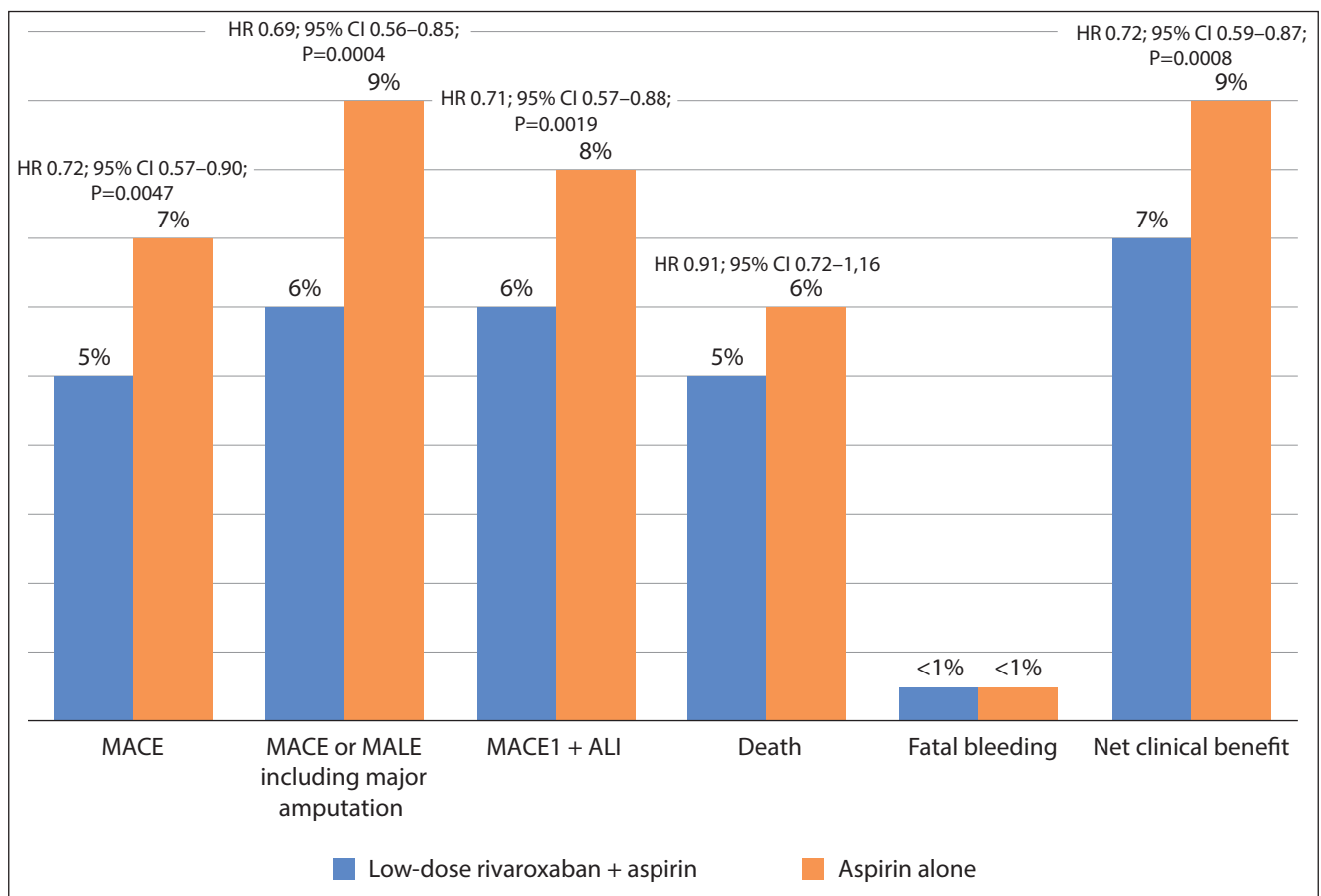
infarction, ischemic stroke, and ALI by 32%; the risk of CV death, myocardial infarction, ischemic stroke, and ALI by 29%; and the risk of MACE plus MALE by 31% (HR: 0.69; 95% CI: 0.56–0.85; $p=0.0004$). In addition, the risk of stroke was significantly reduced by the combination of rivaroxaban plus aspirin (HR: 0.54; 95% CI: 0.33–0.87), and there was a trend toward a lower risk of CV death (HR: 0.82; 95% CI: 0.59–1.14) and death for any cause (HR: 0.91; 95% CI: 0.72–1.16) (Figure 2).⁴¹ Of note, the effects of low-dose rivaroxaban plus aspirin *versus* aspirin alone on the combined outcome of MACE and MALE including major amputation were consistent regardless the presence of CAD (p for interaction was 0.33).⁴¹

Compared with the traditional approach of aspirin alone, the combination of rivaroxaban plus aspirin markedly reduced the prespecified limb outcomes. Thus, the rivaroxaban plus aspirin approach significantly reduced the risk of ALI by 44%, the risk of MALE by 46%, the risk of all vascular amputations by 60%, and the risk of major amputations by 70% (Figure 3).⁴¹

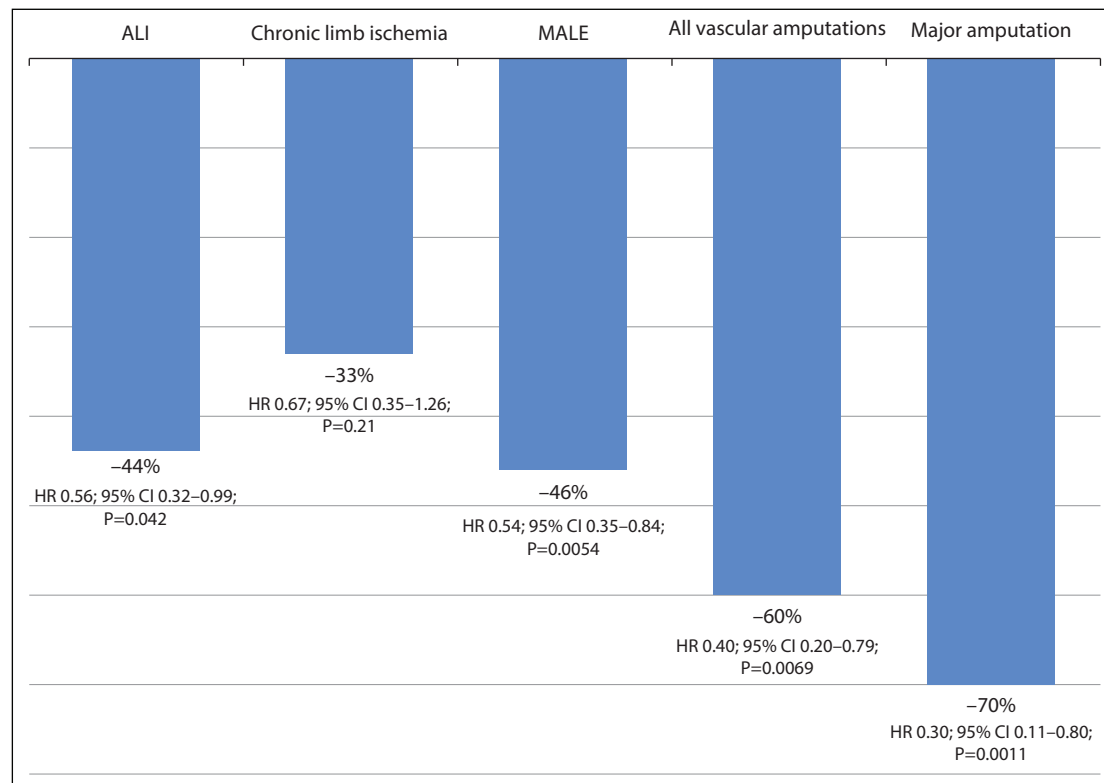
Major bleeding occurred more frequently with the combined therapy than with aspirin alone (3 *versus* 2%; HR: 1.61; 95% CI: 1.12–2.31; $p=0.0089$), mainly gastrointestinal. Importantly, fatal bleeding and non-fatal symptomatic intracranial hemorrhage occurred in less than 1% of patients, regardless of the assigned group (Figure 2).⁴¹

As a result, while the proportion of patients with MACE plus MALE decreased from 9 to 6% and the risk of death from 6 to 5% with the combined therapy, the risk of fatal bleeding was <1% in both groups (Figure 2). In addition, the net clinical benefit outcome composed of MACE, MALE, including major amputation, and fatal or critical organ bleeding was reduced by 28% with the rivaroxaban plus aspirin strategy compared to aspirin alone (HR: 0.72; 95% CI: 0.59–0.87; $p=0.0008$). As a result, during a 21-month period, for every 1000 patients treated with the COMPASS strategy, 27 events of MACE or MALE, including major amputation, would be prevented, but 1 fatal and 1 critical organ hemorrhage would occur.⁴¹

Figure 2. Effects of treatment on MACE, MACE or MALE including major amputation, MACE plus acute limb ischemia, death and fatal bleeding in patients with chronic peripheral artery disease from the COMPASS study.⁴¹



MACE: Cardiovascular death, myocardial infarction, MACE1: Cardiovascular death, myocardial infarction, ischemic stroke; MALE: major adverse limb event; ALI: acute limb ischemia.

Figure 3. Effects of treatment on prespecified limb outcomes in patients with chronic peripheral artery disease from the COMPASS study.⁴¹

ALI: acute limb ischemia; MALE: Major adverse limb event

Beneficial effects of the vascular dose of rivaroxaban in patients with established PAD and other clinical conditions

Many patients with PAD have other vascular beds affected, thus increasing the risk of CV morbidity and mortality.^{10–14} In the COMPASS trial, two-thirds of patients with PAD had concomitant CAD,⁴¹ and among patients with CAD, 20% of patients had also PAD, defined according to COMPASS inclusion criteria.⁵⁵ In those patients with ischemic heart disease, the presence of PAD did not modify the effects of the rivaroxaban plus aspirin approach on the primary outcome (p for interaction was 0.37), major bleeding (p for interaction was 0.46), and net clinical benefit (p for interaction 0.24).⁵⁵

Chronic kidney disease increases both the risk of bleeding and MACE.^{56,57} In the COMPASS study, rates of MACE and major bleeding were more common in those patients with renal insufficiency than in those individuals with normal function. Importantly, while the beneficial effect of the rivaroxaban plus aspirin approach over aspirin on MACE was independent of renal function, there was no excess hazard of major bleeding.⁵⁸

Approximately one-third of patients with symptomatic PAD have heart failure (HF).⁵⁹ In fact, the risk of HF is doubled in patients with PAD⁶⁰ or even more in elderly patients.⁶¹ In the COMPASS trial, although patients with severe HF were excluded from the study, 22% of patients had a history of mild-to-moderate HF. In the COMPASS trial, in patients with chronic ischemic heart disease or PAD and a history of mild or moderate HF, the rivaroxaban plus aspirin approach (*versus* aspirin) resulted in a similar relative but higher absolute risk reduction in MACE and mortality compared to those patients without HF, with a similar excess hazard for major bleeding, independently of the presence of HF.⁶²

Discussion

Patients with PAD are at a very high risk of both MACE and MALE, and treatment should be necessarily focused on both targets.^{19,63,64} Thus, although CV death is the main cause of mortality in this population,^{15–17} it should not be forgotten that in patients with PAD who experience MALE, the risk of death increases by 3 and the risk of subsequent vascular amputation by 200.²² The traditional approach with antiplatelet treatment with a single or dual antiplatelet therapy has failed in providing complete protection of patients with PAD. For example, in the

PEGASUS–TIMI 54 study, while ticagrelor, 60 mg, reduced the risk of MACE, no beneficial effect was obtained on limb outcomes.⁴⁰ In the CHARISMA trial, the combination of clopidogrel plus aspirin did not reduce the risk of MACE compared with aspirin in monotherapy.³⁶ Full anticoagulation with vitamin K antagonists has not been shown to provide further protection over antiplatelet therapy in PAD patients.^{42,43} By contrast, the COMPASS trial demonstrated in the PAD population that compared with aspirin, 100 mg, once daily in monotherapy, the rivaroxaban, 2.5 mg, twice daily plus aspirin, 100 mg, once daily approach significantly reduced the risk of MACE by 28% and the risk of MALE by 46%. Even more, the combination of vascular doses of rivaroxaban (2.5 mg twice daily) plus aspirin reduced by 60% the risk of all vascular amputations and by 70% the risk of major amputations (Table 1).⁴¹ The development of atherosclerosis in patients with PAD includes both platelet and coagulation cascade activation, with Factor Xa playing a key role. The good results of the COMPASS trial are in line with the underlying cause of atherosclerosis.^{24–28,48–52} Importantly, a great proportion of patients with PAD in clinical practice meet the inclusion criteria of the COMPASS trial, indicating that the results of this study can be extended to this population.^{65–67} As a result, all these data strongly suggest that the rivaroxaban plus aspirin approach should be considered as the first choice for the treatment of patients with PAD to achieve the double target of MACE and MALE. In fact, current guidelines recommend the use of the combination of aspirin plus rivaroxaban, 2.5 mg, twice daily in different clinical settings. Thus, the 2019 ESC Guidelines of chronic coronary syndromes recommend the use of the rivaroxaban plus aspirin approach in those patients at high or moderate risk of ischemic events, but without a high bleeding risk (recommendation IIb).⁶⁸ However, despite the COMPASS trial showing a trend toward a reduction of mortality rates in this population, but not other antithrombotic approaches (i.e. clopidogrel, ticagrelor, or prasugrel), these guidelines performed the same recommendation for all these drugs. Nonetheless, in the light of the results of clinical trials, net clinical benefit clearly favors rivaroxaban over other antithrombotic strategies, and the recommendations of use should not have been the same. On the other hand, the 2019 ESC Guidelines on diabetes, prediabetes, and CV diseases indicate that the low-dose rivaroxaban, 2.5 mg, twice daily plus aspirin, 100 mg, daily may be considered in patients with diabetes and symptomatic lower extremity artery disease (recommendation IIa).⁶⁹ The global vascular guidelines on the management of chronic limb-threatening ischemia state that low-dose aspirin and rivaroxaban, 2.5 mg, twice daily should be considered to reduce adverse CV events and lower extremity ischemic events in patients with chronic limb-threatening ischemia (grade 2; level of evidence B).⁷⁰

The COMPASS trial showed that the rivaroxaban plus aspirin approach had a higher risk of major bleeding than aspirin alone. However, there was no excess in fatal or intracranial bleeds. Of note, as the risk of MACE or MALE (7 and 2%, in the aspirin group, respectively) was much higher than the risk of fatal or

intracranial bleeding (<1%), the reduction in the risk of these outcomes by the combination of rivaroxaban plus aspirin was greater than the possible risk of fatal or intracranial bleeding. In addition, most of the major bleedings had a gastrointestinal origin and rarely are fatal or leave permanent sequelae.⁴¹ In addition, compared with aspirin alone, the risk of major bleeding was increased with the rivaroxaban plus aspirin approach only during the first year of treatment, but not during the following years.⁵⁵ Therefore, the concern about the risk of bleeding should not be to avoid the use of the combination of the vascular dose of rivaroxaban plus aspirin in patients with PAD at high risk of MACE or MALE. However, it should be emphasized that as these data are provided from post-hoc subgroup analysis, the generalization of the results may be limited.

Rivaroxaban, 2.5 mg, twice daily, coadministered with 75–100 mg aspirin, once daily is currently indicated for the prevention of atherothrombotic events in adult patients with CAD or symptomatic PAD at high risk of ischemic events.⁷¹ However, it is important to ascertain which patients with chronic atherosclerotic vascular may benefit more from the COMPASS strategy.^{24,31,44,64,72,73} In patients with PAD, not only those patients at high risk of MACE but also at high risk of MALE should be taken into account.^{22,74–76} A recent analysis of the COMPASS trial showed that patients with ≥ 2 vascular beds affected, HF, renal insufficiency, diabetes, or having a high REACH score had the highest risk of recurrent vascular events.⁷⁴ Other recent analysis of the COMPASS trial showed that those patients with PAD and Fontaine classification III or IV ischemia, history of peripheral revascularization, prior amputation, or patients with MALE, treated with aspirin alone as antithrombotic therapy, had the highest risk of recurrent limb events.²² Considering these studies and other recommendations, excepting for those patients with any of the main exclusion criteria of the COMPASS trial (high risk of bleeding, recent stroke, severe HF or renal insufficiency, and need for dual antiplatelet therapy or anticoagulation), those patients with PAD who meet any of the criteria for high risk of MACE or MALE may be considered for the treatment with the rivaroxaban plus aspirin approach (Table 4). On the other hand, the Vascular Outcomes study of ASA along with rivaroxaban in Endovascular or surgical limb Revascularization for PAD (VOYAGER PAD) study has shown in patients with PAD who have undergone lower-extremity revascularization that rivaroxaban, 2.5 mg, twice daily plus aspirin was associated with a significantly lower incidence of the composite outcome of ALI, major amputation for vascular causes, or MACE compared with aspirin alone. In addition, the incidence of TIMI major bleeding was similar between both groups, but the incidence of International Society on Thrombosis and Haemostasis (ISTH) major bleeding was significantly higher with the combination.⁷⁷

A number of studies have analyzed whether the combination of the vascular dose of rivaroxaban plus aspirin is a cost-effective approach according to different National Healthcare Systems. All of them have shown that in those patients with

Table 4. Patients with peripheral artery disease who may benefit more from a COMPASS strategy.^{22,31,74–76}

To reduce MACE	To reduce MALE
<ul style="list-style-type: none"> • ≥2 vascular beds • Previous stroke/transient ischemic attack • Coronary artery disease • Heart failure • Renal insufficiency • Diabetes • High REACH score 	<ul style="list-style-type: none"> • Fontaine classification III or IV ischemia • History of peripheral revascularization (surgery or angioplasty) • Previous ischemic limb events • Previous amputation or high risk of amputation • Patients with MALE, treated with aspirin alone as antithrombotic therapy

MACE, major adverse cardiovascular events (cardiovascular death, stroke, myocardial infarction); MALE, major adverse limb events: acute or chronic limb ischemia, including all major vascular amputations.

lower extremity PAD or carotid artery disease, rivaroxaban plus aspirin therapy is effective and cost effective in the prevention of recurrent CV disease compared to the traditional approach of aspirin therapy alone.^{78–80} These data emphasize its use in clinical practice for the majority of patients with PAD at high risk of vascular or limb events.

In light of all these data, more efforts are required to implement the COMPASS strategy in patients with PAD in routine practice. Thus, guidelines should be updated including the information of the COMPASS trial and its substudies, indicating those patients who may benefit more from this approach. In addition, specific educational activities for general practitioners, vascular specialists, cardiologists, and internists would be very helpful to better understand the benefits and risks of the rivaroxaban plus aspirin approach for PAD patients. Importantly, screening of PAD should be emphasized not only by general practitioners but also by other specialists who manage patients with vascular disease, regardless of the vascular bed affected. Moreover,

more cost-effective studies are mandatory in order to facilitate a potential reimbursement by the authorities.

Conclusions

Patients with PAD have a high risk of both adverse vascular and limb outcomes. The underlying cause of atherosclerosis in PAD patients implies not only platelet activation but also the initiation and promotion of coagulation cascade, in which Factor Xa plays a key role. The traditional antithrombotic approach with only antiplatelet agents (single or dual antiplatelet therapy) has failed to provide complete protection in PAD patients. By contrast, the rivaroxaban plus aspirin strategy markedly reduces the risk of both MACE and MALE, and related complications, with a low risk of bleeding. Therefore, the rivaroxaban plus aspirin approach provides a comprehensive protection and should be considered for many patients with PAD at high risk of such events.

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Correspondence: José Luis Hernández, Hospital Universitario de Marqués de Valdecillas, Av. Valdecilla, 25, 39008 Santander, Cantabria, Spain. hernandezjluis@gmail.com

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