

EDITORIAL

Which PAD patients will probably benefit more from a COMPASS strategy?

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Peripheral arterial disease (PAD) affects more than 100 million people worldwide, while 65% of these patients remain asymptomatic.¹ It is estimated that probably just 5% of patients suffering from PAD, have the typical clinical symptoms of intermittent claudication.¹ The REACH registry (including 8322 patients with PAD) has demonstrated that 3 out of 5 patients with PAD have also concomitant coronary artery disease (CAD) and/or other cardiovascular disease.² Almost 40% of the REACH population had concomitant PAD and CAD, while 13% of them suffered from poly-vascular disease affecting more than 2 vascular beds.² Symptomatic PAD patients are in higher risk not only for major cardiovascular events (myocardial infarction and stroke, 20%) but also, for PAD progression and limb amputation (4-27%/year).³ In this group of patients, all-cause mortality and cardiovascular mortality is estimated between 10-37% and 9-25%, respectively.³

The European Society of Vascular Surgery (ESVS) Guidelines published in 2017 in collaboration with the European Society of Cardiology (ESC) for the management of PAD recommended that symptomatic PAD patients should be under treatment with single antiplatelet therapy with clopidogrel or aspirin (Class I A), showing a slight preference to clopidogrel.⁴ However, at the time being, more than 20 years after the publication of CAPRIE trial⁵, aspirin is the antiplatelet drug mostly used for these patients.⁶ These guidelines also recommend no antiplatelet therapy for the asymptomatic PAD patients (Class III A).⁴ For asymptomatic patients, antiplatelet therapy with aspirin seems to offer no clear benefit in diabetic and/or non-diabetic populations.^{7,8} Double antiplatelet therapy (DAPT) may offer a slight benefit in very high risk patients in the prevention of cardiovascular events, significantly increasing at the same time the risk of major bleeding.⁹ Thus, the indications of DAPT are doubtful and restricted only to patients at very high risk for cardiovascular events and limb loss, if they are at low risk for bleeding.¹⁰ Oral anticoagulation with vita-

min K antagonists has been proved inadequate for PAD patients, offering no benefit, while leading in excessive bleeding and should not be used.⁴

In late 2017, the COMPASS trial evaluated the role of low dose rivaroxaban (2.5mg x 2) in combination with aspirin (100mg x 1), in comparison to aspirin alone, in the prevention of secondary cardiovascular events in almost 27000 stable atherosclerotic cardiovascular patients.¹¹ The rationale was that this dual inhibition pathway stopping platelets activation and aggregation through aspirin and at the same time reducing thrombin generation through low-dose rivaroxaban, would probably have more favorable results in reducing secondary cardiovascular end-points.¹¹ The primary outcome was a composite of cardiovascular death, stroke or MI. The study was stopped due to low dose rivaroxaban-plus aspirin superiority after a mean follow-up of 23 months.¹¹ Dual inhibition pathway (low-dose rivaroxaban plus aspirin) had significantly better cardiovascular outcomes, reducing major adverse cardiovascular events (MACE) among patients with stable atherosclerosis, being also the first study documenting a significantly 22% reduction in cardiovascular mortality in such patients.¹¹ Although intracranial and fatal bleeding were not significantly increased,¹¹ more major bleeding events occurred in the dual inhibition pathway group than in the aspirin alone group.¹¹ However, a significant net clinical benefit was reported for patients receiving this novel dual antithrombotic therapy. A pre-defined analysis of PAD sub-population in COMPASS trial, including 7470 patients, has further confirmed the benefit on MACE and mortality prevention.¹² Furthermore, a substantial reduction in major adverse limb events (MALE) and an incredible 70% decline in major amputations, was recorded in the group treated with low-dose rivaroxaban plus aspirin compared to aspirin alone.¹² However, although fatal or critical organ bleeding was not increased, major bleeding was also significantly higher in the dual path group.¹² Keeping in mind that bleeding risk in PAD patients is rationally increased, the higher bleeding rate in this group of patients is usually expected.

In 2018, a sub-analysis of the COMPASS PAD population for MALE confirmed the role of dual-path inhibition in reducing amputations and re-interventions.¹³ In this sub-analysis, patients that had undergone revascularization (with bypass and/or angioplasty), amputation or had severe progressive limb ischemia (Fontaine Class 3 or 4) were at higher risk for event recurrence with a total vascular amputation rate at 23%.¹³ Low-dose rivaroxaban plus aspirin treatment was associated with a reduction in MALE incidence at 43% and a decrease in total

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vascular amputations at 58%.¹³ A more recent risk stratification analysis, confirmed the initial COMPASS PAD study findings. Using the REACH registry risk score and the Classification and Regression Trees survival analysis, Anand *et al.* stratified PAD COMPASS trial population in higher and lower risk for vascular event recurrence.¹⁴ In the higher risk group, dual COMPASS therapy had favorable outcomes with a reduction of 30 events per 1000 patients in 30 months of follow-up.¹⁴ Additionally, over time, dual inhibition pathway treatment was associated with a considerable reduction in event recurrence.¹⁴ In terms of major bleeding, an absolute overall risk was estimated at less than 1% in 30 months.¹⁴ It seems that in those higher risk group, the absolute risk of severe bleeding is low and the net clinical benefit even more favorable for patients treated with low-dose rivaroxaban plus aspirin compared with aspirin alone. This analysis showed also that patients with poly-vascular disease and especially those suffering from PAD and CAD are at highest risk for cardiovascular events and are these who benefit more from a COMPASS strategy, with only a small increase in bleeding risk.¹⁴ Furthermore the authors confirmed that PAD patients suffering also from heart failure (HF), renal impairment with moderate affected eGFR (30-50 ml/min) and diabetes mellitus (DM) were also in higher cardiovascular risk and had a substantial reduction of cardiovascular and limb events if they received the dual pathway inhibition therapy.¹⁴ These findings were even more strengthened with the simultaneous publication of the COMPASS-eligible PAD population included in the REACH registry analysis, which confirmed that PAD patients with concomitant CAD disease and those with co-morbidities such as HF, renal impairment and DM are at higher risk for cardiovascular events and also showed that adding more co-morbidities in a single patient the cardiovascular risk is exacerbating, while the bleeding risk is slightly increasing.¹⁵ On the other hand in the COMPASS PAD analysis 22% of PAD patients were asymptomatic and these presented just 0.5% of major adverse cardiovascular and limb events during the follow-up period (in fact only 5 events in absolute numbers).¹⁶ Therefore it is quite obvious that these asymptomatic PAD patients do not have something to earn from a dual inhibition strategy, while they will be at increased risk for bleeding.

Taking into consideration the above mentioned findings, it is important in clinical practice to identify the specific group of PAD patients that are at higher risk for MACE or MALE and will benefit the most from a dual-inhibition pathway treatment. It seems that asymptomatic patients with PAD and patients that are at high bleeding risk will not benefit by dual antithrombotic therapy. On the other hand, PAD patients with poly-vascular disease (≥ 2 vascular beds and especially these having concomitant CAD), as well as PAD patients with certain co-morbidities as heart failure, renal insufficiency and diabetes mellitus are very likely to benefit more from this novel combination anti-thrombotic treatment. Last but not least, PAD patients with prior revascularization or amputation, as well as symptomatic PAD patients (especially these presenting with severe disease deterioration), seems to also benefit from dual inhibition therapy.^{14,17} It has to be mentioned that for the time

being this novel strategy has not been included in any PAD guidelines as the publication of COMPASS studies came out after the most recent guidelines had been published. However in the very recent ESC guidelines regarding cardiovascular patients with diabetes, the dual pathway inhibition strategy is suggested for the first time for PAD patients with DM with a class IIa recommendation.¹⁸

In conclusion, the “ideal” PAD patient that should receive dual-path inhibition treatment is that having the highest risk for cardiovascular and limb events and an acceptable bleeding risk; such a patient would probably have the greatest absolute benefit. The clinician has in any case to estimate individually for each patient the benefit and the risks of this novel dual antithrombotic therapy and personalize the optimal medical treatment. For sure this novel strategy opens new horizons in cardiovascular medicine and PAD in particular, for the secondary prevention of cardiovascular and limb events, while it would be of great interest to see in the future direct comparisons of this approach with clopidogrel alone or with clopidogrel plus aspirin.

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