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Rivaroxaban in patients with ischaemic chronic cardiomyopathy and obstructive peripheral arterial disease: rationale for treatment and results

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Patients with overt clinical atherosclerosis (ATS) or with previous peripheral vascular events have a high risk of ischaemic complications. A careful control of cardiovascular (CV) risk factors has been shown to improve prognosis, likely driven by a decrease progression of ATS. Prevention of occlusive complications is, on the other hand, based on antithrombotic therapy. So far, this therapeutic goal has been pursued through antiplatelet therapy with aspirin and P2Y12 receptor inhibitors. Anticoagulant therapy with full-dose vitamin K inhibitors, although effective in some arterial conditions, is burdened by high bleeding risk, and by low long-term compliance. In the COMPASS study, the association of aspirin with the factor Xa inhibitor, rivaroxaban, in a dose of one-fourth of the dose used in atrial fibrillation, decreased by more than 20% the incidence of CV events in patients with multi-district ATS. The positive effect was also observed as far as major peripheral complications, the like of critical limb ischaemia or limb amputations. This positive preventive effect was in addition to the effect of other preventive measures, such as the use of statins, ACE inhibitors, and aspirin itself. As compared to the aspirin-only treatment, the association with low-dose rivaroxaban had a significantly higher bleeding risk, which should be carefully considered when evaluating the individual risk/benefit ratio of the combined treatment.

Introduction

Atherosclerosis (ATS) is a chronic degenerative pathology of the arteries that recognizes traditional risk factors ('Framingham'), such as advanced age, high blood pressure, smoking, diabetes, and dyslipidaemia, in addition to male sex and poor physical activity. These risk factors and an individual or family predisposition contribute in the vast majority of cases to the development of the pathology in its more or less extensive, often multi-district, locations. The most recent ESC (European Society of Cardiology) guidelines on the diagnosis and treatment of peripheral arterial disease,[1] declare first of all that the finding of a manifestation of ATS in a vascular territory implies an increase in the global cardiovascular (CV) risk, so 'every vascular area affected by ATS must be considered a CV risk marker'.

The prevention of major CV (MACE) and peripheral (MALE) events is to be pursued in the long term through the aggressive treatment of major CV risk factors and, with particular regard to peripheral arterial disease, total abstention from smoking and dietary and lifestyle modifications.[2] Statins[3] and PCSK9 evolocumab[4] inhibitor have been shown to reduce MACE and MALE in the long term. Treatment of arterial hypertension, particularly with ACE inhibitors and sartanes[5] has been shown to reduce CV events in patients with multi-district arterial disease. Diabetes mellitus is clearly a risk factor for peripheral as well as coronary arterial disease, but data on the effectiveness of hypoglycaemic therapies in reducing the risk of MACE and MACE are not conclusive, and the 2017 PAD (Peripheral Arterial Disease) guidelines do not even mention the treatment of diabetes among preventive measures.[1]

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On the other hand, occlusive complications, with consequent acute or chronic organ damage, are of a thrombotic nature and, as such, a potential therapeutic target for antithrombotic drugs. In general, the evidence on the efficacy of antithrombotic therapies in peripheral arterial disease is modest. The therapeutic indications in revascularized patients are mostly extrapolated from those on coronary angioplasty.[6] The indications relating to asymptomatic patients who are at increased risk of MACE[7] are even less clear and unanimous.

Preventive efficacy of antiplatelet drugs in patients with peripheral arterial disease

The current ESC guidelines on peripheral arterial disease (which include patients with lower limb disease and those with carotid disease) recommend the use of antithrombotic therapies in the secondary prevention of CV events, in the presence of symptoms and after revascularization procedures.[1] The key messages are as follows:

- In patients with carotid stenosis >50%, even in the absence of specific data, a single antiplatelet therapy (APT) with aspirin 75 mg (clopidogrel in case of intolerance) is indicated which becomes dual antiplatelet therapy (DAPT) for at least 1 month after carotid stenting. Dual antiplatelet therapy with aspirin and clopidogrel can also be considered for the first month after transient ischaemic attach for a single small study.[8]
- In patients with lower limb disease, APT is not recommended in asymptomatic cases but in symptomatic cases or after revascularization.[9] In symptomatic patients, clopidogrel is the drug of first choice, compared to aspirin, based on a post-hoc analysis of the CAPRIE[10] study, with a 24% reduction in CV mortality and 22% of MACE. Alternatively, ticagrelor may be used, which is not superior to clopidogrel in the EUCLID[11] study. Dual antiplatelet therapy is currently recommended only in the first month after revascularization.[1]
- Anticoagulant therapy is recommended only if there are other proven indications (atrial fibrillation, valve prosthesis, and venous thromboembolic disease) and may be associated with APT in the case of recent revascularization.

Anti-platelet therapy in patients with ischaemic heart disease and peripheral arterial disease

To correctly frame the preventive efficacy of antithrombotic drugs, with the relative increase in haemorrhagic risk, it must be considered that, among patients with ischaemic heart disease, those with multi-district arterial disease have decidedly more severe clinical features[12] and, even after correction for other prognostic determinants, they are at greater risk of primary and recurrent CV events, even fatal.[13]

The most solid indications, although evolving based on recent data, on antithrombotic therapy in ischaemic heart disease (CAD) are those relating to patients after myocardial infarction.[14] Among patients with peripheral arterial disease and previous acute coronary syndrome, prolongation of DAPT beyond the first 12 months of the index event has been shown to significantly reduce the composite risk of death, heart attack, or cerebrovascular events in the PRODIGY study [hazard ratio (HR) 0.54, 95% confidence interval (CI) 0.31–0.95].[15] In the PEGASUS study, which compared DAPT with ticagrelor (60 or 90 mg) and aspirin to aspirin alone in patients with myocardial infarction between the previous 1 and 3 years, 5% of patients had peripheral arterial disease. In these patients, DAPT with ticagrelor (combined doses) and aspirin had a particularly beneficial effect with an absolute MACE reduction of 4.1% (NNT = 25) and an increase in bleeding risk of only 0.12% (NNH = 834).[16] In addition to the prevention of ischaemic recurrences, in patients with peripheral arterial disease, the combined doses of ticagrelor significantly reduced the risk of critical limb ischaemia and peripheral revascularization (HR 0.65, 95% CI 0.44–0.95).[16]

The COMPASS study: a paradigm shift

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) study[17] tested the hypothesis, as an alternative to the sole antiplatelet hypothesis, in over 27 000 patients, that a purely anticoagulant therapy with selective factor Xa block, or a combination of aspirin and half the dose anti-Xa may be superior to APT with aspirin alone in patients with stable atherosclerotic disease. Patients should not have indication for DAPT or full anticoagulation. Rivaroxaban doses were 5 mg twice daily as mono-therapy, or 2.5 mg twice daily in combination with 100 mg aspirin. It should be remembered that these doses do not have a proven anticoagulant activity of such magnitude to guarantee adequate cardioembolic protection in patients with atrial fibrillation, in which the approved doses of rivaroxaban are 20 and 15 mg per day in relation to the glomerular filtration rate.

Enrolment criteria included high-risk characteristics in secondary prevention, i.e. history of myocardial infarction in the previous 20 years, symptomatic multivessel coronary artery disease, previous aorto-coronary bypass or previous multivessel angioplasty, and/or presence of peripheral vascular disease (previous surgical or percutaneous interventions on peripheral vessels, limb amputation due to obliterating vascular disease, and carotid disease). If patients were under the age of 65 years, in order to be enrolled they had to have atherosclerotic disease in more than one district or to have at least two high-risk factors including diabetes mellitus, at least mild renal failure, heart failure, and active cigarette smoking. previous non-cerebral ischaemic event. The study excluded patients with a high risk of bleeding, previous haemorrhagic or lacunar stroke, advanced heart failure, and severe renal failure. About 90% had coronary artery disease and 30% had peripheral arterial disease. Over 60% of patients had a history of myocardial infarction. The study was stopped early due to the evident superiority of the aspirin + rivaroxaban group in reducing the primary composite endpoint of CV mortality,

stroke, and myocardial infarction after a mean follow-up of 23 months.

Globally, the best risk/benefit ratio was demonstrated by the combination of rivaroxaban 2.5 mg × 2 and aspirin 100 mg: as shown in *Figure 1*, this therapy significantly reduced the risk of the composite ischaemic endpoint (−24%), CV mortality (−22%), and stroke (−42%): the latter effect was achieved by a 49% reduction in ischaemic stroke ($P < 0.001$), while the haemorrhagic one (much more rare) increased by 49% (ns). On the other hand, rivaroxaban 5 mg × 2 mono-therapy did not show the same protective effect against ischaemic events. However, both rivaroxaban-based strategies increased the risk of major bleeding by more than 50% compared to aspirin mono-therapy.

Two prospective sub-analyses were conducted on patients in whom the main enrolment criterion was coronary artery disease (91% of the total population),[18] and in those mainly included for peripheral arterial disease (27% of the population).[19] It is evident by subtraction that 18% of the population had both coronary artery disease and peripheral arterial disease, but this additional subgroup was not analysed separately. As shown in *Figure 1*, the results of these sub-analyses are almost the same as the main one, with greater amplitude of the confidence limits due to the lower number.

Results with rivaroxaban compared to aspirin in patients with peripheral arterial disease

The subgroup of patients with peripheral arterial disease was truly remarkable for complexity and constituted itself a large trial with 7470 patients in the three groups. In total, 44% of patients were diabetic, 80% had symptomatic arterial disease, 27% had already undergone vascular interventions, and over 4% amputations. As shown in *Figure 1*, the risk of the primary endpoint was reduced by the combined therapy by 28% ($P = 0.0047$), CV mortality by 18% (NS), myocardial infarct by 24% (NS), and stroke by 48% ($P < 0.05$), compared with a 61% increase in bleeding risk ($P = 0.0089$).

Of great interest was the evaluation of MALE which included acute ischaemic events affecting the limbs and peripheral amputations.[19] Despite the very high-risk characteristics of the population, and despite the fact that around 25% of patients persisted in the smoking habit, the total risk of MALE, which included acute and chronic ischaemia and amputations, was 2.2% with aspirin at 23 months average follow-up (1% per year). This risk was almost halved with rivaroxaban, especially with 2.5 mg associated with aspirin. Significant reductions were obtained with rivaroxaban 2.5 × 2 and aspirin in the risk of MALE and total or major amputations (*Figure 2*). These data refer to the risk of the first event after randomization. The risk of subsequent complications in the 128 patients who experienced MALE during the study was dramatically worse: in the year following the event, 61.5% was subject to further hospitalization, 20.5% to vascular amputation, the 8.3% to death. Globally, the risk of these additional vascular events was reduced by 24% ($P = 0.02$) with rivaroxaban 2.5 × 2 plus ASA against ASA[20] alone.

The role of rivaroxaban in the secondary prevention of atherosclerotic disease

The role of the dual low-dose therapy of rivaroxaban and aspirin in the secondary prevention of CV events in patients

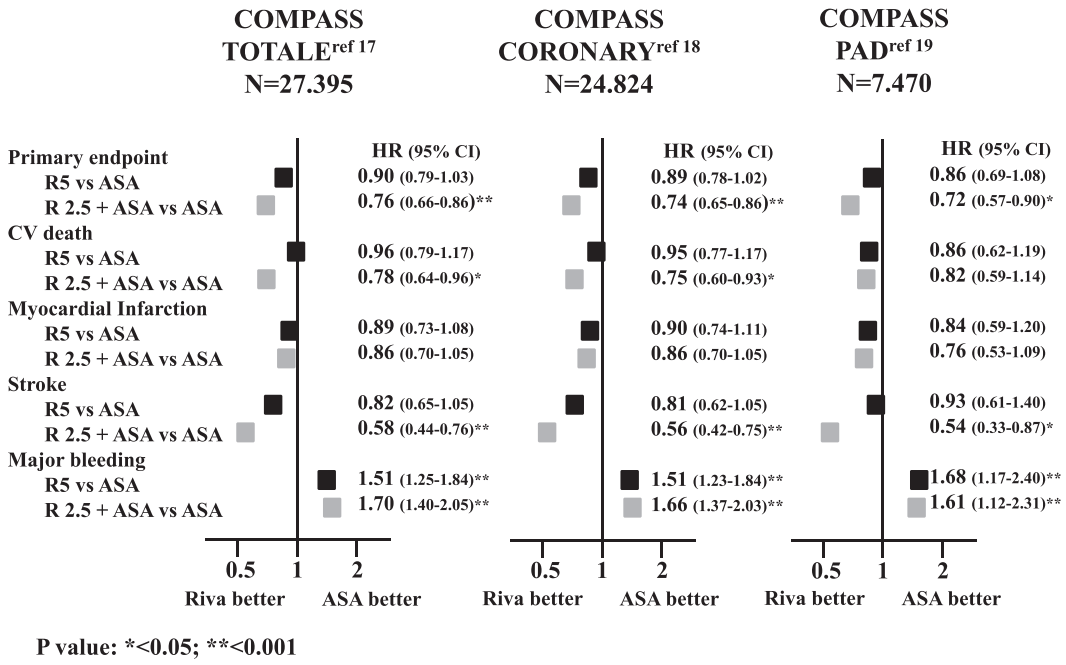

Figure 1 Effect of rivaroxaban 5 mg × 2, and rivaroxaban 2.5 mg × 2 associated with aspirin 100 mg, compared to aspirin 100 mg in study COMPASS[17] and in the two sub-analyses relating to patients with coronary artery disease[18] and those with peripheral arterial disease.[19] Data are expressed as hazard ratios and 95% confidence limits.

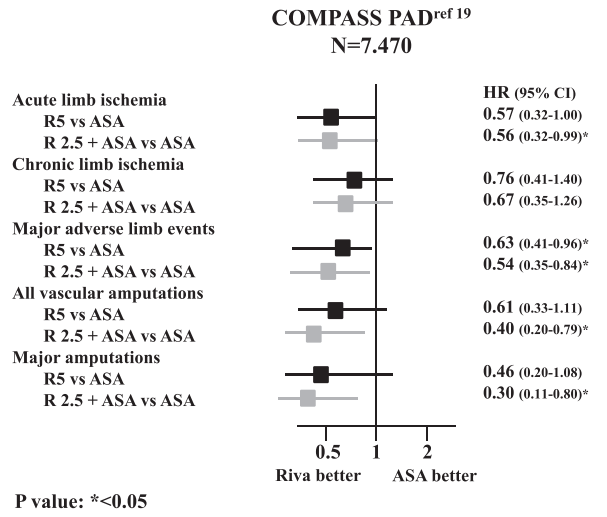

Figure 2 Effect of rivaroxaban 5 mg × 2, and rivaroxaban 2.5 mg × 2 associated with aspirin 100 mg, compared to 100 mg aspirin in the subgroup of patients with peripheral arterial disease[19] in the COMPASS study. Data are expressed as hazard ratios and 95% confidence limits.

with atheromatous disease was summarized in an authoritative editorial published in 2018 in the *European Heart Journal*.[21] Given that all antithrombotic, alone or combined therapies, increase the bleeding risk in relation to the potency of the drug, to the doses and to the number of associated drugs, and premise the primary importance of the 'Framingham' risk factor abatement, even the DAPT with clopidogrel, ticagrelor or vorapaxar had previously been shown to reduce ischaemic events compared to aspirin alone.[21] However, the extent of efficacy in reducing CV and peripheral events has been shown to be greater for the low-dose combination of rivaroxaban and aspirin than for various DAPT strategies, and, above all, this therapeutic strategy has shown a reduction in total and CV mortality not observed with DAPT strategies. The effect of reducing CV events with the low dose of rivaroxaban (−24%) was shown to be additive to that of aspirin (−19%), antihypertensive therapies (−20%), ACE inhibitors (−18%), and reduction of LDLc (−21% for mMol), as well as of revascularization in cases with higher risk. The additive effect of these therapies also appears to be shown by the decreasing CV mortality observed in the last 30 years both in the general population and in the control groups of secondary prevention trials.

Conflict of interest: none declared.

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