Chronic ischaemic heart disease and rivaroxaban: which patients derive the greatest benefit?

Leonardo Bolognese* and Massimo Felici

Dipartimento Cardio-neuro-vascolare, Azienda Sudest Toscana, Italy

Patients with established cardiovascular (CV) disease may suffer further CV events, despite receiving optimal medical treatment. Although platelet inhibition plays a central role in the prevention of new events, the use of anticoagulant therapies to reduce events in atheromatous disease has, until recently, been overlooked. The recent Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) trial showed that rivaroxaban 2.5 mg twice daily given with low-dose aspirin reduces the incidence of the composite endpoint of stroke, heart attack, and death in patients with stable coronary artery disease. Although there are some limitations to the study, COMPASS offers promising conclusions and may change secondary prevention in patients with stable CV disease. This article reviews the results of the COMPASS study and how these results may affect patient management in everyday clinical practice.
randomized clinical trial of a non-vitamin K antagonist direct oral anticoagulant in patients with chronic CAD, peripheral artery disease (PAD), or chronic CAD plus PAD (n = 27 395). It was planned as an event-driven trial designed to continue until at least 2200 patients experienced a primary endpoint. Approximately 18% of the population had poly-vascular disease (CAD+PAD); 73% had CAD alone, and 9% had PAD alone. Patients were randomized to three arms: rivaroxaban 2.5 mg twice daily plus aspirin 100 mg, rivaroxaban 5 mg twice daily monotherapy, and aspirin 100 mg monotherapy. Patients with recent surgical coronary revascularization were also included. The primary outcome was the composite of CV death, AMI, and stroke. The main safety outcome was major bleeding according to the modified International Society on Thrombosis and Haemostasis criteria, including fatal bleeding, symptomatic haemorrhage in critical organs (including intracranial bleeding), haemorrhage at a surgical site that required reoperation, or any haemorrhage requiring hospitalization. The secondary efficacy outcomes were the composite of major thrombotic events (death caused by ischaemic stroke, AMI, acute ischaemia of the limbs, and death caused by CAD), the composite of ischaemic stroke, MI, acute ischaemia of the limbs, and CV death, and death from any cause. Because of efficacy observed in the very-low-dose rivaroxaban plus ASA arm at the first interim analysis, the Data Safety Committee recommended stopping the trial early with a mean follow-up of 23 months after 1323 primary outcome events among 27 395 patients. After a mean follow-up of 23 months, it was shown that rivaroxaban plus aspirin, compared with aspirin alone, significantly improved the composite of CV death, AMI, and stroke in patients with stable CVD. Specifically, it was found that the primary outcome occurred in 4.1% of the rivaroxaban plus aspirin group vs. 4.9% in the rivaroxaban monotherapy group and in 5.4% of patients who only received aspirin (P < 0.001 for rivaroxaban plus aspirin vs. aspirin monotherapy; there were no significant differences for rivaroxaban alone vs. aspirin). With regard to secondary outcomes, a benefit of rivaroxaban plus aspirin vs. aspirin was also observed. This difference in favour of the rivaroxaban plus aspirin group was seen in total mortality (3.4% vs. 4.1% in aspirin, P = 0.01) and stroke (0.9% rivaroxaban plus aspirin vs. 1.6% in aspirin-treated patients, P < 0.001). However, no significant differences in the incidence of AMI or heart failure were observed between the groups. Concerning the primary outcome of safety, there were more haemorrhagic events in the rivaroxaban plus aspirin group than in the control arm of aspirin (3.1% vs. 1.9%, P < 0.001), primarily bleeding that required medical assistance or hospitalization, mostly gastrointestinal bleeding. Encouragingly, there was no difference in fatal, intracranial, or symptomatic bleeding in a critical organ. When comparing rivaroxaban alone with aspirin, a significantly higher number of bleeding events were observed in the rivaroxaban group (2.8% vs. 1.9%, P < 0.001), including symptomatic bleeding in a critical organ. Analysis of net benefit that included death, infarction, stroke, fatal bleeding, or bleeding in a critical organ, showed a benefit for rivaroxaban plus aspirin (4.7% vs. 5.9% in aspirin, P < 0.001). There was no significant difference between rivaroxaban monotherapy and aspirin monotherapy.

Chronic stable coronary artery disease cohort

Of the 24 824 patients with CAD, 62% had multi-vessel CAD and 69% had a history of prior MI. Of the 17 028 patients with prior MI, 7% were enrolled within 1 year of the event, 14% within 1 to 2 years, 29% within 2 to 5 years, and 50% >5 years after MI, with a mean of 7.1 years. Very-low-dose rivaroxaban plus ASA reduced MACE by 26% [4.0% vs. 6.0%; hazard ratio (HR) 0.74; P < 0.0001], an effect that was driven by significant reductions in stroke and death without influence on MI. Low-dose rivaroxaban alone vs. ASA alone was associated with a non-significant reduction in MACE (5.0% vs. 6.0%; HR 0.89; P = 0.094). Similar to the overall trial population, the 66% increase in the major bleeding associated with very-low-dose rivaroxaban plus ASA vs. ASA alone (3.0% vs. 2.0%; HR 1.66; P < 0.0001) was mainly driven by gastrointestinal bleeding (2.0% vs. 1.0%; HR 2.13; P < 0.0001). The net clinical outcome (defined as CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ) occurred in 5% of patients receiving very-low-dose rivaroxaban plus ASA vs. 6.0% with ASA alone (HR 0.78; 95% CI 0.78–0.003). In an exploratory analysis, the reduction in MACE with very-low-dose rivaroxaban plus ASA vs. ASA alone was consistent in patients with and without prior MI [HR 0.74; 95% confidence interval (CI) 0.63–0.88; and HR 0.76, 95% CI 0.58–0.98; P for interaction = 0.91] and patients with a prior MI <2 years (HR 0.70, 95% CI 0.48–1.01), 2 to 5 years (HR 0.81, 95% CI 0.59–1.10), and >5 years (HR 0.72, 95% CI 0.57–0.91) before enrolment. Results were also independent of history of PCI, although in the subgroup of patients with a history of CABG, combination therapy was not beneficial (HR 0.99, 95% CI 0.77–1.28; vs. HR 0.66, 95% CI 0.56–0.78 in the subgroup without prior CABG; P for interaction = 0.01). Patients with stable clinical symptoms, i.e., in the absence of MI events, PCI, or CABG ≥2 years before enrolment, had a benefit with low-dose rivaroxaban plus ASA similar to those who had MI, PCI, or CABG <2 years before enrolment.

Critical appraisal of the COMPASS trial

There are some characteristics of the study which are of particular relevance for the implications of the tested therapy in clinical practice.

Because of efficacy observed in the very-low-dose rivaroxaban plus ASA arm at the first interim analysis, the Data Safety Committee recommended stopping the trial early with a mean follow-up of 23 months after 1323 primary outcome events among 27 395 patients. Whenever a trial is stopped early for overwhelming efficacy, it is questioned whether the observed effect might be more exaggerated than if the trial had continued through to completion.

The survival graph indicates another issue: until 1.5 years of follow-up, the curves are indistinguishable. After 1.5 years, however, there seems to be an increasing difference between the rivaroxaban and aspirin arms; in
fact, the rivaroxaban arm gets closer to combination therapy. So, what would happen if we followed the subjects for another year? At the very least it seems ambiguous to decide whether rivaroxaban or combination therapy is better in the longer run. More generally, the study highlights a general issue that occurs in many clinical trials: an extended follow-up period would often be desirable, in particular to study whether treatment effects vary over time.

The combination of aspirin with rivaroxaban 2.5 mg b.i.d. reduced the primary efficacy endpoint of MACE by 1.3% and increased the primary safety endpoint of major bleeding by 1.2% during a mean follow-up of 23 months. While the benefit measured by the primary efficacy is almost balanced by the primary safety endpoint, the authors report a significant reduction of a net benefit with a relative risk reduction by 20%. However, this net benefit does not include the primary safety endpoint of major bleeding defined by modified criteria of ISTH major bleeding but only fatal or critical organ bleeding. Had the net-clinical-benefit outcome been defined as CV death, stroke, MI, or major bleeding, no advantage of the combination of rivaroxaban plus aspirin would have been found (7.2% vs. 7.3%).

Also, the trend for reduction of mortality, usually a hard equivalent of a net benefit, without reaching significance according to the study protocol does not give firm support for a net benefit. In fact, multiplicity testing to control the overall type I error set a threshold for formal significance at \( P = 0.0075 \). According to this pre-specified threshold, the difference in mortality—the 3.4% with rivaroxaban plus aspirin and 4.1% with aspirin alone—did not make the cut for statistical significance (HR 0.82, 95% CI 0.71–0.96; \( P = 0.01 \)).

The pronounced effect of rivaroxaban plus ASA on ischaemic stroke (42% RRR) compared with a non-significant reduction of MI (14% RRR) sheds light on the potential mechanism leading to the reduction of the primary efficacy endpoint. COMPASS excluded patients receiving anticoagulation but not patients with AF; 8% of all strokes occurred in 392 such patients. Furthermore, many thousands of patients would be expected to have subclinical AF in this high-risk elderly group.

Risk stratification for identifying subsets of patients with the greatest net clinical benefit

The challenge for clinicians implementing novel therapies into clinical practice is having a comprehensive understanding of the benefits and risks of those therapies in a specific patient population. Understanding the balance of safety and efficacy is most critical for therapies with clear risks, such as antithrombotic drugs, where bleeding requires careful consideration of not only relative risk and benefit but also absolute differences. When trying to find a specific patient population in the COMPASS trial who may benefit from an intensified antithrombotic treatment, there is no clear evidence from subgroup analyses of the primary efficacy and safety endpoint. However, there is a visual trend both for a particularly pronounced reduction of CV events and a reduced risk of major bleeding in patients aged <65 years. According to the entry criteria, these younger patients were additionally required to have atherosclerotic changes of at least two vascular beds or at least two additional risk factors. Thus, one may speculate that young high-risk patients may particularly benefit from intensified antithrombotic treatment.

Recently, Anand et al. provide additional analyses of the response to rivaroxaban-aspirin stratified by ischaemic risk using an expanded ischaemic composite of MACE and MALE. The authors identified several key enhancers of risk, including poly-vascular disease (>2 vascular beds), heart failure, estimated glomerular filtration rate <60 mL/min, diabetes, and age >75 years. These high-risk features were predictably associated with greater risk and therefore greater absolute risk reductions with rivaroxaban. When accounting for bleeding risk, there appeared to be a broad net benefit, but with the greatest absolute benefits in the highest risk patients. The primary message is that higher-risk patients have a greater benefit and net clinical benefit from dual pathway inhibition than on aspirin alone. In a complementary paper by Darmon et al., the authors used the REduction of Atherothrombosis for Continued Health (REACH) registry of stable atherothrombotic patients to identify a COMPASS-like population. They evaluated the effect of multiple added factors on the primary ischaemic endpoint of MACE alone. Added factors included age >65 years, asymptomatic carotid disease, diabetes, heart failure, chronic kidney disease, history of ischaemic stroke, PAD, and current smoking. After multivariable analysis, each added criterion, except asymptomatic carotid artery stenosis, was associated with a higher risk of MACE with a lower increase in risk for major bleeding, suggesting that targeting the combination of rivaroxaban plus aspirin to such high-risk populations could help optimize the risk-benefit balance.

Conclusions

There is no clear therapeutic strategy for intensified antithrombotic treatment in addition to aspirin in the entire population of stable CV patients as the reduction of the primary efficacy endpoint with tested strategies is comparable with the corresponding increase in the primary safety endpoint. COMPASS trial provides us with a new direction of thrombotic risk reduction as one of the important therapeutic pathways to improve clinical outcomes in patients with chronic stable CAD. Whether the COMPASS results are sufficient to justify the extrapolation of low-dose rivaroxaban to the overall population of stable CAD patients remains unclear. Risk stratification can identify higher-risk patients (two or more vascular beds affected, heart failure, renal insufficiency, or diabetes) in whom the benefits are substantial. This approach will likely help clinicians personalize the COMPASS results, where individual high-risk patient characteristics should inform the clinical decision to add low-dose rivaroxaban to background aspirin therapy in an otherwise stable patient.

Conflict of interest: none declared.
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