Anticoagulation in Patients with Ischaemic Heart Disease and Peripheral Arterial Disease: Clinical Implications of COMPASS Study

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Abstract

Patients with established cardiovascular disease may suffer further cardiovascular 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) study showed an important reduction in cardiovascular events without increasing the risk of fatal and intracranial bleeding when using rivaroxaban, a novel oral anticoagulant, combined with aspirin. This article reviews the available evidence regarding the use of anticoagulant therapies for prevention of cardiovascular events, the results of the COMPASS study and how these results may affect patient management in everyday clinical practice.

Keywords

Cardiovascular disease, cardiovascular events, clinical practice, COMPASS, novel oral anticoagulants, rivaroxaban, secondary prevention, thrombosis

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Atherosclerotic cardiovascular disease (CVD) comprises a large number of related pathologies, including ischaemic heart disease and peripheral arterial disease (PAD).¹ This group of illnesses is the main cause of global morbidity and mortality and its prevalence increases remorselessly.²

Despite implementation of guideline-based therapy and optimal medical treatment, patients with established CVD may suffer further cardiovascular events (CVE). This is known as residual risk and research into therapeutic strategies to reduce this has intensified in recent years.³

Along with control of classic cardiovascular (CV) risk factors, platelet inhibition plays a central role in the prevention of new events.^{4,5} However, this inhibition only achieves a partial risk reduction, even when two antiplatelet drugs are combined.^{6–8} Antithrombotic therapies that affect the synthesis or action of fibrin – typically heparin and warfarin – have been in widespread use as anticoagulants for many decades but their prolonged use to reduce events in atheromatous disease has, until recently, been largely overlooked.

Initial studies evaluating the use of warfarin in secondary prevention of MI showed a significant benefit, although this came at the cost of a substantial risk of bleeding.^{9–11} However, the emergence of the novel oral anticoagulant (NOAC) drugs, with a better safety profile, has resulted in the re-emergence of interest into the role of anticoagulation in the prevention of CVE.^{12–15}

The recent Rivaroxaban for the Prevention of Major Cardiovascular Events in Coronary or Peripheral Artery Disease (COMPASS) study evaluated the use of rivaroxaban, an oral anticoagulant that is a selective inhibitor of factor Xa.¹⁶ Patients with established CVD in sinus rhythm were randomised to low-dose rivaroxaban plus aspirin, versus aspirin alone. There was an important reduction in CVE without increasing the risk of fatal and intracranial bleeding. However, the impact of the COMPASS study results for standard clinical practice remains to be defined.

Atherosclerotic Cardiovascular Disease

The atherosclerotic process of coronary artery disease (CAD) starts with the formation of lipid streaks in the wall of blood vessels, between the endothelium and the internal elastic lamina. These lipid streaks contain atherogenic lipoproteins and macrophage foam cells. Over time, a necrotic centre of lipids and an extracellular matrix are wrapped in a fibrous covering of smooth muscle cells, establishing the atheromatous plaque.¹⁷ The instability and rupture of the plaque has an essential role in the development of acute coronary syndrome (ACS). Rupture of the plaque exposes the highly thrombogenic core, producing platelet adhesion and aggregation.^{17,18} Furthermore, with the rupture of the plaque, cholesterol crystals are released as well as multiple proteins that activate the coagulation cascade, leading to the formation of an occlusive thrombus.¹⁸

Patients with CAD may present either with stable chronic angina, as an atheromatous plaque gradually develops with a low lipid content and thick fibrous covering, or with ACS, when a fissure appears in a plaque

with a high lipid content (vulnerable or unstable) with the consequent thrombus formation on its surface.^{18,19} Risk stratification will identify those who may benefit from revascularisation. Lifestyle modification and control of CV risk factors should be promoted for all.²⁰

Clinical practice guidelines recommend aspirin as the standard antiplatelet treatment,^{21–23} clopidogrel as an alternative in cases of intolerance or contraindication to aspirin, and a combination of antiplatelet agents in selected patients with high risk of ischaemic events.^{24,25} Dual antiplatelet therapy (DAPT) is usually prescribed for 3–12 months.^{21,24,25} In the context of ACS, there is only one study showing long-term benefit up to three years following the index ACS event. The recent Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial showed that DAPT up to 36 months with ticagrelor and aspirin decreased the primary endpoint (cerebrovascular accident and MI) with a modest increase in bleeding risk.

However, the thrombotic process involves fibrin as well as platelets and for decades cardiologists have considered trying to modulate the coagulation cascade as well as platelet action. NOACs have only recently arrived to make such combination therapy a real possibility.

Rivaroxaban

Rivaroxaban, an oral anticoagulant with no vitamin K antagonist (VKA) activity, is a drug capable of directly and selectively inhibiting free factor Xa, as well as factor Xa linked to prothrombinase or associated with thrombi. It has an oral bioavailability close to 100 %, is not affected by food intake and its anticoagulant action has proven to be predictable – having a dose-dependent potency so it can be used in fixed doses – without the need for routine anticoagulation controls.

Rivaroxaban's use is currently approved in the prevention of venous thromboembolism in adult patients who are going to undergo a knee or hip prosthesis implantation and in the prevention of embolic events in patients with non-valvular AF. Further studies have also recently shown the potential usefulness of rivaroxaban in the prevention of atherothrombotic CVE; it is not only capable of inhibiting the thrombin formation but it can also interfere with platelet activation.²⁶

Following these observations, different mechanisms have been proposed to explain the vascular protection associated with this drug. Firstly, it significantly reduces the formation, progression and destabilisation of cholesterol plaques through an anti-inflammatory mechanism, blocking macrophage activation and it inhibits thrombotic formation over unstable plaques.²⁷ Secondly, it promotes viability, growth and migration of endothelial cells, protects them from the proinflammatory effects of factor Xa, improving endothelial function²⁸ and it facilitates vascular neoformation.²⁹ In addition, rivaroxaban's use is associated with an enhancement of bone formation and resorption parameters and an improvement of pulse wave velocities when compared with VKAs, as vitamin K is an essential cofactor in the correct functioning of phosphocalcium metabolism and its variations can precipitate the appearance of osteoporosis and, even more importantly, vascular calcification.³⁰

Anticoagulation and Cardiovascular Prevention: Pre-COMPASS Evidence

The COMPASS study provides the only available data supporting anticoagulant therapy in the prevention of events in stable CVD.¹⁶ The

use of NOACs had previously been studied in patients with unstable CVD, mainly in the context of ACS.

Initial studies carried out years ago using VKAs showed a reduction in CVE but with a substantial increase in bleeding risk. This benefit was observed with the use of moderate and high warfarin doses and an international normalised ratio (INR) greater than 2.0, but low-intensity treatment (INR less than 2.0) showed no benefit. For example, the Warfarin-Aspirin Reinfarction Study II (WARIS-II) compared the use of aspirin (160 mg daily), aspirin (75 mg) associated with warfarin (target INR 2.0–2.5) and warfarin alone (target INR 2.8–4.2). A significant reduction in CVE was observed (combined endpoint: CV death, non-fatal reinfarction, thromboembolic stroke) in the groups treated with VKA drugs as monotherapy (HR 0.81; 95 % CI [0.69–0.95], $p=0.03$) or combined with aspirin (HR 0.71; 95 % CI [0.60–0.83], $p=0.001$) compared with aspirin alone.³¹ In both groups treated with warfarin, an increase in the annual rate of non-fatal major bleeding was observed in comparison with aspirin monotherapy (0.67 % versus 0.17 %, $p<0.001$). Similar data on comparable characteristics were obtained in studies such as Combination Hemotherapy And Mortality Prevention (CHAMP),³² Antithrombotics in the Secondary Prevention of Events in Coronary Thrombosis-2 (ASPECT-2)³³ and Organization to Assess Strategies for Ischemic Syndromes (OASIS),³⁴ among others.

The substantial advantages of NOACs compared with well-managed warfarin have been demonstrated in large randomised clinical trials – Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation –Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) with edoxaban, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial with apixaban, Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET-AF) with rivaroxaban and Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) with dabigatran.^{35–38}

Following these trials, several studies have been carried out recently to evaluate the potential role of this pharmacological group in secondary prevention of atherothrombotic CVE.

In the RandomizEd Dabigatran Etxilate Dose Finding (RE-DEEM) study, patients who had suffered an ACS (ST-elevation MI or non-ST-elevation MI) were randomly assigned to receive dabigatran (50, 75, 110 or 150 mg) plus conventional therapy consisting of a thienopyridine (e.g., clopidogrel) and aspirin, or placebo plus conventional therapy.³⁹ The use of dabigatran was associated with up to a fourfold increase in risk of clinically relevant minor bleeding and major bleeding, and showed a dose-dependent relationship. CVE were less common in patients treated with higher doses of dabigatran (110 and 150 mg). The Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) study that tested the use of apixaban in a similar clinical trial had to be stopped early because of a considerable increase in the risk of bleeding in patients receiving this new anticoagulant.⁴⁰

Rivaroxaban is the best studied of the NOACs; as well as the COMPASS study other trials have evaluated its efficacy and safety in the prevention of CVE.

In patients with ACS, the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2 - TIMI 51) study showed a significant reduction in the risk of CV death,

acute MI (AMI) and stroke (HR 0.84; 95 % CI [0.74–0.96], $p=0.008$) with both tested dosages of rivaroxaban (2.5 mg or 5.0 mg twice daily), compared with placebo.⁴¹ Only the 2.5 mg dose reduced all-cause mortality (2.9 % versus 4.5 %, $p=0.002$). Compared with placebo, rivaroxaban led to an increase in the rates of major and intracranial bleeding and a non-significant increase in fatal bleeding. On the other hand, the Study to Compare the Safety of Rivaroxaban Versus Acetylsalicylic Acid in Addition to Either Clopidogrel or Ticagrelor Therapy in Participants With Acute Coronary Syndrome (GEMINI-ACS-1) compared the use of aspirin 100.0 mg and rivaroxaban 2.5 mg twice daily added to clopidogrel or ticagrelor after ACS.⁴² The bleeding rate at the end of follow-up was similar in both groups (HR 1.09; 95 % CI [0.80–1.50], $p=0.584$), as well as CV morbimortality (HR 1.06; 95 % CI [0.77–1.46], $p=0.731$) and all-cause mortality.

The Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention (PIONEER AF-PCI) of patients with non-valvular AF who underwent percutaneous coronary intervention, compared the use of low dosages of rivaroxaban (15.0 mg daily or 10.0 mg daily in a single dose) with very low dosages of rivaroxaban (2.5 mg twice daily) together with DAPT versus triple standard therapy of aspirin/clopidogrel/warfarin, for one, six or 12 months. At 12 months the rate of significant bleeding was lower in the two groups receiving rivaroxaban, with similar rates of CV death, AMI or stroke. In addition, treatment with rivaroxaban was associated with a significant reduction in the risk of hospitalisation compared with conventional triple therapy.

The COMPASS Study

Study Design and Results

The COMPASS clinical trial was based on the existing evidence that anticoagulation with VKA drugs with or without aspirin is superior to aspirin monotherapy in secondary prevention of AMI, although with an increased risk of bleeding, including intracranial haemorrhage.

The authors of the COMPASS study hypothesised that there is benefit in administering rivaroxaban in patients with coronary or vascular events, at doses lower than those used in the anticoagulation of non-valvular AF.

The study took 27,395 patients with stable CVD (CAD, PAD or both) and randomised them 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 revascularisation 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 hospitalisation. 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 CHD), the composite of ischaemic stroke, MI, acute ischaemia of the limbs and CV death, and death from any cause.

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 versus 4.9 % in the rivaroxaban monotherapy group and in 5.4 % of patients who only received aspirin ($p<0.001$ for rivaroxaban plus aspirin versus aspirin monotherapy; there were no significant differences for rivaroxaban alone versus aspirin).

With regard to secondary outcomes, a benefit of rivaroxaban plus aspirin versus aspirin was also observed. This difference in favour of the rivaroxaban plus aspirin group was seen in total mortality (3.4 % versus 4.1 % in aspirin, $p=0.01$) and stroke (0.9 % rivaroxaban plus aspirin versus 1.6 % in aspirin treated patients, $p<0.001$). However, no significant differences in 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 % versus 1.9 %, $p<0.001$), primarily bleeding that required medical assistance or hospitalisation, 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 % versus 1.9 %, $p<0.001$), including symptomatic bleeding in a critical organ. There were no differences in the rate of other adverse events reported in any of the three trial arms.

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 % versus 5.9 % in aspirin, $p<0.001$). There was no significant difference between rivaroxaban monotherapy and aspirin monotherapy. These differences persisted in the subgroup analysis.

Because of the major mortality benefit, COMPASS was stopped early at 23 months. The authors showed that the rivaroxaban plus aspirin combination is beneficial for secondary prevention of CVE, with a small risk of major bleeding, predominantly non-fatal bleeding. It is noteworthy that isolated rivaroxaban did not show superiority to aspirin.

COMPASS Results in Absolute Terms

The primary event rate of the COMPASS study was reduced by 24 % in the group that received rivaroxaban plus aspirin (4.1 % versus 5.4 %). This means that 154 patients would be needed to treat to prevent one major CVE.

The rate of major bleeding with aspirin was 1.9 %, while the rate of major bleeding with 2.5 mg of rivaroxaban plus aspirin was 3.1 %, an absolute annualised difference of 0.6 %. These results indicate that the number needed to harm would be 166; nine additional haemorrhagic events would occur for every 10 CVE prevented.

Clinical Implications of the COMPASS Study

There is general agreement on prescribing DAPT in the context of ACS, as well as single antiplatelet therapy in patients with stable CAD.^{21–24} In the last decade, the use of anticoagulation in both scenarios has begun to play an important part and many studies testing combinations of antithrombotic drugs have been conducted.

NOACs are established as the anticoagulants of choice for patients with AF or venous thromboembolism and the role of NOACs in patients with CVD and sinus rhythm is now much clearer. Several trials

have been published with NOACs in patients post-ACS (ATLAS ACS 2–TIMI 51, RE-DEEM, APPRAISE-2). The COMPASS study provides data strongly supporting anticoagulant therapy in the prevention of CVD in stable CVD. COMPASS was stopped early because of overwhelming efficacy, demonstrating the evident benefit of the combination of low-dose aspirin plus rivaroxaban 2.5 mg twice daily for the secondary prevention of CVD.

Future questions of novel combination therapies remain, for example, about the addition of a second antiplatelet drug to aspirin versus a very low dose of a factor Xa inhibitor, or a platelet P2Y inhibitor or thrombin-receptor antagonist plus low dose factor Xa inhibitor, which could possibly offer greater efficacy by reducing AMI, but with more bleeding risk.⁴⁴

It must not be forgotten that the COMPASS study included different subgroups of patients with stable CVD, such as those with a history

of ACS in the past 20 years, patients with multivessel coronary disease who underwent percutaneous coronary intervention or coronary artery bypass graft surgery, or those with PAD. These diverse subgroups may have different responses to the different therapies, so a more personalised approach might be needed. However, despite these limitations, the COMPASS trial shows encouraging results and represents a turning point in the management of patients with established CVD.

Conclusion

The 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 CAD. Although there are some limitations to the study, COMPASS offers promising conclusions and may change secondary prevention in patients with stable CVD. Of course, this is a complex field and further investigation is needed in this fascinating and fast evolving topic. ■

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