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Rivaroxaban for high-risk patients with stable coronary artery disease: NICE recommendation

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Take Home Messages

- Patients with stable coronary artery disease remain a challenge to treat as they remain at increased risk of further cardiovascular events.
- NICE have recently recommended the combined use of low dose Rivaroxaban and Aspirin to prevent atherothrombotic events in patients with stable coronary artery disease or in patients with symptomatic peripheral artery disease at high risk of ischemic events.
- Clinicians may take time to apply the new recommendation, particularly in primary care.

Introduction

Rivaroxaban is a direct oral anticoagulant (DOAC) that works as a direct factor Xa inhibitor. Traditionally, Rivaroxaban has been used to reduce the risk of stroke and systemic embolization in patients with nonvalvular atrial fibrillation (AF) and in the treatment of deep vein thrombosis and pulmonary embolism.

In a large recent randomised controlled trial (RCT) widely known as the COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies), Eikelboom et al (2017) evaluated whether Rivaroxaban alone or in combination with Aspirin was more effective than Aspirin alone for secondary cardiovascular prevention in patients with stable atherosclerotic vascular disease.[1] Based on the COMPASS trial, the National Institute for Health and Care Excellence (NICE) recently published a new Technology Appraisal Guidance recommending the use of Rivaroxaban as an additional treatment option to Aspirin alone for high-risk patients with stable cardiovascular disease (CVD) to prevent recurrent thrombotic events.[2]

Secondary prevention in established cardiovascular disease

Cardiovascular diseases continue to cause a major health concern worldwide. An estimated 17.9 million deaths from CVDs occurred in 2016, representing 31% of deaths globally that year.[3] Data from the United Kingdom in 2017 showed that 168,421 people died of CVD, accounting for 27.7% of all deaths that year.[4] The REACH (Reduction of Atherothrombosis for Continued Health) registry showed that 5-10% of patients with established CVD continued to have new atherothrombotic events each year despite optimal medical therapy.[5] These results suggest that Aspirin alone is not sufficient for secondary cardiovascular prevention.[1]

About the author

Dr Montasir Ali graduated from medical school with first-class honours and three academic prizes. He is currently a Core Medical Trainee working in Yorkshire and the Humber Deanery and plans to pursue a career in Cardiology.

Coronary artery disease is an area in medicine that witnessed significant advancement in both diagnosis and management during the past few decades.[6] However, the progress in preventing the thrombotic events is relatively slow despite the extensive numbers of patients researched in this field.[7] Since 1950, several trials have studied the use of combined oral anticoagulants and antiplatelets (such as thienopyridines and glycoprotein IIb/IIIa inhibitors) with or without Aspirin in the context of cardiovascular prevention.[8] Evidence from RCTs has shown that the combination of warfarin and aspirin is more effective than aspirin alone in preventing cardiovascular events but at the expense of increased risk of serious bleeding complications including intracranial haemorrhage (ICH).[9] **Table 1** provides a summary of the prominent trials over the last 25 years which looked at secondary prevention of cardiovascular events.

A previous trial known as ATLAS ACS 2-TIMI 51 (Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction-51) compared the combination of Rivaroxaban and dual antiplatelet therapy (DAPT) versus placebo in the context of acute coronary syndrome (ACS). Results from this study showed

Table 1. Outlines from prominent trials looking at the prevention of secondary cardiovascular events

Year published	Abbreviated Name	Type	Conclusion
1988	ISIS-2[11]	Meta-analysis	Proved the value of Aspirin in treating acute MI
1996	CAPRIE[12]	RCT	Clopidogrel is more effective than Aspirin in reducing CV death, stroke and MI with equal safety
2001	CURE[13]	RCT	Clopidogrel adds a beneficial effect to Aspirin in patients with acute coronary syndrome than aspirin alone but with higher bleeding risk
2006	CHARISMA[14]	RCT	Clopidogrel plus Aspirin combination is not significantly more effective than Aspirin alone
2012	ATLAS ACS 2–TIMI 51[10]	RCT	Rivaroxaban reduced risk of CV death, MI and stroke but increased risk of bleeding (but not fatal bleed)
2012	TRA2P TIMI 50[15]	RCT	Vorapaxar reduced risk of CV death and ischaemic events but increased risk of severe bleeding including intracranial haemorrhage
2015	PEGASUS-TIMI 54[16]	RCT	Prolonged Ticagrelor therapy in addition to Aspirin reduced risk of CV death, MI and stroke but increased risk of bleeding

ATLAS ACS 2–TIMI 51 Anti-Xa Therapy to Lower cardiovascular events in Addition to Standard therapy in subjects with Acute Coronary Syndrome–Thrombolysis In Myocardial Infarction 51, CAPRIE Trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events, CV cardiovascular, CHARISMA Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance, CURE Clopidogrel in Unstable Angina to Prevent Recurrent Events, ISIS2 Second International Study of Infarct Survival, MI myocardial Infarction, PEGASUS-TIMI 54 Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis In Myocardial Infarction 54, RCT randomised control trial, TIMI thrombolysis in myocardial infarction, TRA2P TIMI 50 Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis in Myocardial Infarction 50

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that combining a low dose Rivaroxaban (2.5mg twice daily (bd)) to DAPT significantly reduced the risk of CV death, MI and stroke in patients with a recent ACS compared to DAPT alone but increased rates of major bleeding without a significant increase in fatal bleeding or ICH.[10]

COMPASS Trial

As a follow on from the ATLAS trial, the investigators designed a large, double-blind, placebo-controlled RCT known as COMPASS to investigate the use of Rivaroxaban with or without Aspirin in stable atherosclerotic vascular disease. [1] It was conducted in 33 countries at over 600 centres, with a total number of 27, 395 participants.

The participants were randomly assigned to three groups; the first group received Rivaroxaban 2.5mg bd + Aspirin 100mg once daily (od); the second group received Rivaroxaban 5mg bd + Aspirin 100mg od, and the third group (controls) received Aspirin 100mg od + placebo.[1]

The primary efficacy outcome of COMPASS was the composite of cardiovascular (CV) death, stroke, or myocardial infarction (MI). The primary safety outcome was major bleeding defined as per the International Society of Thrombosis and Haemostasis (ISTH) criteria. However, unlike ISTH, the study considered any bleeding resulting in a hospital admission as major bleeding regardless of the need for overnight stay.[1] The net clinical benefit was the composite of efficacy and safety outcomes.[1]

The study results showed that the primary outcome occurred 24% less in the Rivaroxaban 2.5 mg bd + Aspirin group compared to the Aspirin alone group with a hazard ratio (HR) 0.76, 95% confidence interval (CI) 0.66-0.86; p<0.001. The rate of major bleeding was 70% higher in those receiving Rivaroxaban 2.5 mg bd + Aspirin compared with Aspirin alone, HR 1.70, 95% CI 1.40-2.05; p <0.0001. There was no significant difference with regards to fatal bleeding or ICH between the two groups.

The net clinical benefit was in favour of the Rivaroxaban 2.5 mg bd + Aspirin group HR 0.80, 95% CI 0.70-0.91; p=0.0005. The Rivaroxaban alone arm did not show a reduction in cardiovascular events and resulted in more major bleeding, including ICH compared to Aspirin only group.[1] The study was terminated prematurely after a mean of 23 months by the Independent Data and Safety Monitoring Board in their first interim analysis as per the pre-defined termination criteria for the superiority of Rivaroxaban 2.5 mg bd + Aspirin group.[1]

Critique

While randomisation in COMPASS was done particularly well, females were under-represented (22%). This raises the question of extrapolating the COMPASS results to female patients.[17] Although primary endpoint results were statistically significant for Rivaroxaban-Aspirin arm, the absolute risk reduction and relative risk reduction were modest at 1.3% and 24% respectively translating to a number needed to treat of 76.[1,18] The early termination of COMPASS automatically raises concerns regarding the overestimation of efficacy and underestimation of safety endpoints.[19,20]

The net clinical benefit was in favour of Rivaroxaban 2.5 mg bd + Aspirin, which according to the COMPASS trialists was compatible with the findings from the ATLAS ACS TIMI 51 trial.[1] However, the individual component analysis shows that the benefit of Rivaroxaban-Aspirin combination was driven by prevention of stroke (HR 0.58, 0.44-0.76; p<0.0001) rather than the prevention of MI (HR 0.86, 0.70-1.05; p=0.14). The mechanism for this is not fully understood or explained by the trial investigators. In a subsequent analysis of COMPASS outcomes by Sharma *et al* (2019) stroke prevention was attributed to the synergistic effect of Aspirin as an antiplatelet and Rivaroxaban as an anticoagulant supporting the previous assumption that anticoagulant-antiplatelet combination reduces the risk of non-cardiac embolism into the brain's circulation.[21] This is supported by the finding that Rivaroxaban 10 mg od is an insufficient dose for stroke prevention in patients with AF (who were excluded in COMPASS).[22] The mechanism of stroke in AF is attributed to embolism from a thrombus within the left atrial appendage and can be prevented with Rivaroxaban 20 mg once daily.[23] Nevertheless, the question about the mechanism of the selective beneficial effect of these agents in brain circulation compared to coronary arteries as evident by COMPASS results is yet to be answered. According to others, a differential effect of these agents on different vascular beds in response to vascular inflammation cannot be excluded.[24]

NICE recommendation

NICE recommended the combination of Aspirin and Rivaroxaban for the prevention of atherothrombotic events in patients over the age of 65 years with symptomatic PAD or stable CAD as an option for preventing atherothrombotic events. In the under 65 years age group to qualify for this regime, they must have either:

1. proven atherosclerosis in at least two vascular beds; or
2. at least two other risk factors such as smoking, diabetes mellitus, heart failure, chronic kidney disease (excluding patients with estimated glomerular filtration rate of 15ml/min or below) or previous non-lacunar ischaemic stroke.

NICE recommends a thorough assessment of patients' bleeding risks along with an informed discussion to carefully weigh up the benefit of preventing ischaemic events, such as myocardial infarction and stroke, against the risk of bleeding as a result of this drug combination.[2] The treatment doses approved by NICE are 2.5mg bd for Rivaroxaban and Aspirin in the range between 75-100mg od.

Despite different inclusion criteria, Bayer used the Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin (PEGASUS) trial's combination of Aspirin 100mg od + Ticagrelor 60mg bd as a comparator to Aspirin + Rivaroxaban in their submission for NICE approval.[2]

In the PEGASUS trial, participants required to have had a myocardial infarction (MI) in the last 1-3 years of inclusion, whereas a history of MI within the last 20 years was acceptable in the COMPASS.[1,14] Due to the lack of other approved comparators and the absence of head to head comparison between the COMPASS and PEGASUS trials, the company has used the Bucher approach in their submission for NICE approval as an Indirect Treatment Comparison method. This is a well-known and acceptable way of indirectly comparing the cost and clinical effectiveness of a new treatment or technology to an existing one in similar scenarios.[25] It is noteworthy that, based on the PEGASUS trial, NICE has recommended the extended use of Ticagrelor 60mg bd in combination with Aspirin for a maximum of 3 years post MI for prevention of recurrent events.[26] Similarly, one could anticipate that despite the recent NICE approval of the low dose Rivaroxaban with Aspirin in secondary prevention of CV events, the clinical uptake of this recommendation is likely to be low due to bleeding risk concerns.

Conclusion

The evidence is still growing to support the combination of antiplatelets with anticoagulants in preventing the ischaemic events such as stroke and myocardial infarction. Further evidence is needed regarding the optimum combination of drugs. Careful patient selection and risk stratification need to be undertaken to prevent the risk of serious bleeding complications. Besides selecting the best drug combination for their individual patients, clinicians should not forget to adopt a holistic multi-strategic approach that includes important non-pharmacological measures such as weight reduction, dietary modifications, regular exercise and smoking cessation.

Disclosures

None.

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