Stable angina and antithrombotic drugs

Addition of rivaroxaban to aspirin: uncertain benefits, proven harms

● **In a randomised trial involving around 27 000 patients, most of whom had stable angina, with an average follow-up of 23 months, addition of *rivaroxaban* to low-dose *aspirin* led to a significant increase in serious bleeding. Efficacy of *rivaroxaban* in this situation remains uncertain due to the methodological weaknesses of this trial.**

In patients with stable angina, or following an acute coronary syndrome without coronary stenting, *aspirin* is the first-choice antithrombotic treatment. It reduces the risk of myocardial infarction in cases of stable angina and reduces mortality after myocardial infarction (1). In these situations, it has not been shown that the addition of another antiplatelet agent or an anticoagulant provides a better harm-benefit balance than *aspirin* alone (1).

A very large multi-centre randomised trial compared, in these situations, *aspirin* versus *rivaroxaban* (an oral anticoagulant which inhibits factor Xa) versus *aspirin* combined with *rivaroxaban* (2,3).

A trial with a very large number of patients. This trial included 27 395 patients with coronary artery disease, symptomatic lower limb arterial disease, or carotid artery stenosis. Coronary disease was defined by a myocardial infarction within the last 20 years, or involvement of at least two coronary arteries, with or without a history of myocardial infarction, bypass grafting or coronary angioplasty (2). Patients aged less than 65 years also had to have arterial disease in two different vascular beds, or at least two of the following risk factors: smoking (current or stopped for less than one year); diabetes; creatinine clearance less than 60 ml/min; moderate heart failure, or ischaemic stroke more than one month ago (3). The main exclusion criteria were a high risk of bleeding, a history of haemorrhagic or lacunar stroke, and a need for treatment with an anticoagulant or dual antiplatelet therapy (2).

After randomisation the patients were divided into three groups: *aspirin* 100 mg per day, versus *rivaroxaban* 5 mg twice per day, versus *aspirin* 100 mg per day combined with *rivaroxaban* 2.5 mg twice per day (2). The primary outcome measure was a composite of ischaemic or haemorrhagic stroke, myocardial infarction or cardiovascular death (2).

Around 91% of patients included had coronary artery disease (2). A secondary analysis carried out on this sub-group of patients was published separately (3).

The trial was stopped prematurely when one of the two interim analyses planned in the protocol showed a statistically significant difference in efficacy based on the primary outcome measure. The average duration of follow-up was at that time 23 months (2). The level of evidence for these results is weakened by the fact that the basis for the decision to interrupt or continue the trial was disproportionately biased towards cardiovascular efficacy endpoints rather than adverse effects.

No advantage from rivaroxaban alone versus aspirin alone. At the time of stopping the trial, there was no statistically significant difference between the *rivaroxaban* alone group and the *aspirin* alone group as regards the primary outcome measure. Serious bleeding occurred in 2.8% of patients in the *rivaroxaban* group versus 1.9% of patients in the *aspirin* group ($p < 0.001$) (2).

Addition of rivaroxaban to aspirin: no clear advantage. When the trial was stopped, mortality was 3.4% in the *rivaroxaban* plus *aspirin* group versus 4.1% in the *aspirin* alone group (no statistically significant difference) (2). The combination of *rivaroxaban* plus *aspirin* reduced the frequency of the primary outcome measure in comparison to *aspirin* alone: 4.1% versus 5.4% ($p<0.001$). There was no effect on the risk of myocardial infarction and there was, above all, a reduction in the risk of stroke: 0.9% versus 1.6% ($p < 0.001$) i.e. one stroke avoided for every 140 or so patients treated for 23 months (2). The results in terms of stroke with persistent disability were not reported.

Serious bleeding, mainly gastrointestinal, was more frequent in the *rivaroxaban* plus *aspirin* group: 3.1% versus 1.9% with *aspirin* alone ($p < 0.001$) i.e. approximately one additional serious haemorrhage for every 80 patients treated for 23 months. There were 15 fatal bleeds in the *rivaroxaban* plus *aspirin* group versus 10 in the *aspirin* alone group (2).

The analyses carried out on the sub-group of patients with coronary artery disease supported these results (3).

In practice Addition of *rivaroxaban* to *aspirin* increases the risk of serious bleeding. Given the conditions under which this trial was prematurely terminated, which was largely for efficacy reasons, plus the weak statistical significance, it has not been shown that the harm-benefit balance of this addition is favourable. *Aspirin* alone remains the first-choice antithrombotic drug in the majority of patients with coronary disease.

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Selected references from Prescrire's literature search

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3- Connoly SJ et al. "Rivaroxaban with or without aspirin in patients with stable coronary artery disease : an international, randomised, double-blind, placebo-controlled trial" *Lancet* 2018; **391**: 205-218.