EDITORIAL

Discontinuing rivaroxaban affects outcomes in atherosclerotic disease

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THE COMBINATION OF RIVAROXABAN AND ASPIRIN COMPARED WITH ASPIRIN ALONE significantly reduced cardiovascular outcomes in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD), a large study has shown.[1] However, when rivaroxaban therapy was discontinued at the end of the trial the benefits were lost and a higher stroke rate was seen in those originally randomised to combination therapy.[2]

The COMPASS trial (Cardiovascular Outcomes for People Using Anticoagulation Strategies) involved 27,395 patients with CAD or PAD. Initial findings, published in the *NEJM*, showed that the combination of low-dose rivaroxaban 2.5 mg twice a day and aspirin 100 mg once daily reduced the risk of the composite outcome of myocardial infarction (MI), stroke or cardiovascular death by 24% compared with aspirin alone.

Even allowing for an increase in bleeding the net benefit was still statistically significant. There was also a 47% reduction in the risk of major adverse limb events (e.g. acute limb ischaemia and amputation) and an 18% reduction in mortality.[1]

'Switching from rivaroxaban and aspirin to aspirin alone was associated with a loss of the benefits of the combination and an excess of stroke'

The trial had been planned to last 3-4 years but was halted early after a median follow-up of 23 months showed clear evidence that the combination of low-dose rivaroxaban and aspirin was beneficial.

At the end of the trial, all participants were told to stop taking the trial medications and switch to non-study low-dose aspirin (75-100 mg) once daily while awaiting regulatory approval for the trial treatment regimen.

The authors of this recent study, published in *Heart*, compared the rates of MI, stroke or cardiovascular death per 100 person-years during randomised treatment (n = 18,278) and after switching to non-study aspirin at trial cessation (n = 14,068).[2]

During randomised treatment, the combination of rivaroxaban and aspirin compared with aspirin alone significantly reduced the following outcomes:

- Composite outcome (MI, stroke or cardiovascular death) 2.2 vs 2.9/100 person-years, hazard ratio (HR) 0.76 (95% CI: 0.66-0.86)
- Stroke 0.5 vs 0.8/100 person-years, HR 0.58 (95% CI: 0.44-0.76)
- Cardiovascular death 0.9 vs 1.2/100 person-years, HR 0.78 (95% CI: 0.64-0.96)

During the first 12 months after early cessation, participants originally randomised to the combination compared with those randomised to aspirin had similar rates for the following:

- Composite outcome 2.1 vs 2.0/100 person-years, HR 1.08 (95% CI: 0.84-1.39)
- Cardiovascular death 1.0 vs 0.8/100 person-years, HR 1.26 (95% CI: 0.85-1.86)

However, a higher stroke rate 0.7 vs 0.4/100 person-years, HR 1.74 (95% CI: 1.05-2.87) was seen in those originally randomised to combination therapy. This included a significant increase in ischaemic stroke during the first six months after switching to non-study aspirin; (25 vs 7 events, 0.9 vs 0.2/100 person-years, HR 3.55 (95% CI: 1.54-8.21)

The authors conclude that in people with chronic CAD or PAD discontinuing rivaroxaban and aspirin and switching to aspirin alone was associated with a loss of the cardiovascular benefits of the combination and an excess of stroke.

This raises the wider issue of access to trial therapies post-trial particularly when these therapies have been shown to be effective during the trial.

The investigators state: 'Our study suggests that in people with chronic CAD or PAD, discontinuation of rivaroxaban 2.5 mg two times per day and aspirin 100 mg once daily and switching to non-study aspirin was associated with a loss of benefits of the combination and an excess of stroke.

'Our results highlight that extended interruption or discontinuation of low-dose rivaroxaban in people with chronic CAD or PAD should be avoided, even if low-dose aspirin is maintained, unless there is [a] major medical reason,' they add.

REFERENCES
1 Eikelboom JW, Connolly SJ, Bosch J et al. Rivaroxaban with or without aspirin in stable cardiovascular disease. *N Engl J Med* 2017;377:1319-30
2 Dagenais GR, Dyal L, Bosch JJ et al. Cardiovascular consequences of discontinuing low-dose rivaroxaban in people with chronic coronary or peripheral artery disease. *Heart* 2021;107:1130-37

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