High-risk patients benefit from lowering of LDL-cholesterol

Susan Mayor PhD

A recent study shows that further reducing LDL-cholesterol achieves a greater reduction in cardiovascular events and that treatment with a non-statin drug can reduce events better in terms of lowering cholesterol to reduce cardiovascular events. The findings support those GPs who follow a more intensive LDL-cholesterol management strategy in high-risk patients. It also provides clear evidence of the clinical benefit of lowering LDL-cholesterol that has previously been lacking.

Study design and key results

The international IMPROVE-IT study randomised 18,144 high-risk patients who had suffered an ACS, including unstable angina, non-ST segment elevation myocardial infarction (NSTEMI) and ST segment elevation myocardial infarction (STEMI), in the previous 10 days to lipid-lowering therapy with either ezetimibe 10mg plus simvastatin 40mg (Inegy) or simvastatin 40mg alone. All patients were considered at high risk for further events, with at least one high-risk feature including new ST changes, diabetes or prior myocardial infarction (MI). They had an initial LDL-cholesterol of 3.2mmol/L or lower if not previously treated with lipid-lowering therapy on prescription or <2.6mmol/L if they had been on prescribed lipid-lowering treatment.

Results showed that patients treated with ezetimibe plus simvastatin combination therapy had a 6.4 per cent lower risk of major cardiovascular events at seven years compared to those treated with simvastatin alone,' said Mark Signy, consultant cardiologist at Western Sussex NHS Trust and an investigator on the IMPROVE-IT study. A total of 32.7 per cent of these high-risk patients taking ezetimibe and simvastatin suffered a major cardiovascular event compared to 34.7 per cent of patients taking simvastatin alone (hazard ratio 0.936, p=0.016).

Further results showed a significant reduction in individual cardiovascular end-points, including a 16 per cent

Lowering LDL-cholesterol to below 1.8mmol/L significantly reduces major cardiovascular events in high-risk patients who have suffered an acute coronary syndrome (ACS). The IMPROVE-IT study, reported at the American Heart Association 2014 Scientific Sessions, showed that adding the cholesterol absorption inhibitor ezetimibe (Ezetrol) to simvastatin could lower LDL-cholesterol compared to simvastatin alone.

‘The results provide a real step forward in our understanding of the role of LDL-cholesterol reduction in preventing cardiovascular disease,’ said Terry McCormack, a GP and cardiology GPSI, in Whitby, North Yorkshire. ‘This is the first trial showing clinical benefit when adding a non-statin agent (ezetimibe) to a statin. And results show that lower is
reduction in MI with ezetimibe plus simvastatin compared to simvastatin monotherapy and a 20 per cent reduction in ischaemic stroke. ‘The reduction in stroke was very important to see, particularly as this is the event that patients tend to fear most,’ he said.

Dr Signy noted that the lower LDL-cholesterol in patients treated with ezetimibe and simvastatin (mean level of 1.37mmol/L at one year) compared to those on simvastatin alone (mean of 1.8mmol/L) reaffirmed the LDL hypothesis that lowering LDL-cholesterol reduces cardiovascular events. ‘We have previously not had the evidence that going this low further reduces cardiovascular events,’ he said.

There were no significant differences between the two treatment groups in adverse events of particular interest, including myopathy and rhabdomyolysis, gallbladder adverse events, liver enzyme elevations more than three times the upper limit of normal and cancer. Myopathy was reported in 0.2 per cent of patients treated with ezetimibe and simvastatin and in 0.1 per cent of those randomised to simvastatin alone.

‘We now have outcome data to show that LDL-cholesterol reduction with a combination of ezetimibe plus simvastatin, in comparison with a statin alone, has a significant and well-tolerated further cardiovascular benefit in high-risk patients, even those with relatively low baseline cholesterol levels,’ Dr Signy suggested. He predicted that the findings are likely to change clinical practice so that most ACS patients will be given lipid-lowering therapy with ezetimibe 20mg plus atorvastatin 40mg as initial treatment, with the aim of reducing LDL-cholesterol to 1.4–1.5mg/L.

**Implications for primary care**

Dr McCormack considers that the findings strengthen the evidence base for GPs in working to optimise LDL reduction in secondary prevention of CVD in high-risk patients. The results support setting the LDL target even lower for high-risk patients to achieve maximum benefit to prevent recurrent heart disease and stroke, he suggested. This is in line with the recent Joint British Societies recommendations for the prevention of CVD (JBS3), which recommended a target for non-HDL cholesterol of <2.5mmol/L, which equates to <1.8mmol/L for LDL-cholesterol.

He suggests that the evidence from the IMPROVE-IT trial provides support for use of ezetimibe in secondary prevention of CVD. ‘We have been treating patients with a combination of a statin plus ezetimibe for some time. So it’s encouraging to have the evidence from a large clinical trial that this combination reduces major cardiovascular events.’ He noted that the number needed to treat (NNT) is only 50 to achieve the reduction in risk of cardiovascular events seen in the IMPROVE-IT trial.

In routine patient care, Dr McCormack’s practice currently treats high-risk patients with a high-intensity statin, such as 40mg or 80mg atorvastatin. ‘We add ezetimibe in patients not achieving the LDL-cholesterol target,’ he reported. Ezetimibe is also prescribed in combination with a high-dose statin for patients with familial hypercholesterolaemia (FH).

Patients being managed for secondary prevention of CVD who are intolerant to high-dose statin are treated with ezetimibe plus a low intensity statin, with a combination of 10mg ezetimibe plus 10mg atorvastatin achieving similar LDL-cholesterol reduction to 80mg atorvastatin. ‘But GPs in some areas of the country have been encouraged not to use ezetimibe because of the previous lack of outcome evidence,’ he noted. ‘The results of this trial now give us that evidence.’

In view of ongoing debate about potential side-effects with statins, he found the safety data with combination ezetimibe/statin therapy reassuring. ‘This is in line with what we have seen in clinical practice. We have been adding ezetimibe to statins for some time and have not seen a problem with side-effects,’ he reported.

Summing up the new findings, Dr McCormack concluded, ‘This trial answered two important questions: could reducing LDL-cholesterol even further achieve greater reduction in cardiovascular events and could treatment with a non-statin drug reduce events? And the answer was ‘yes’ to both of these questions.’

**References**


**Declaration of interests**

None to declare.

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