**Medicines Evidence Commentary**

commentary on important new evidence from Medicines Awareness Weekly

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**Acute coronary syndrome: ezetimibe added to simvastatin (IMPROVE-IT study)**

The large, multicentre randomised controlled trial IMPROVE-IT found that adding ezetimibe to simvastatin 40 mg after acute coronary syndrome produced a greater reduction in risk of cardiovascular events than simvastatin 40–80 mg alone. However, the effect of the combination on this risk is that which would be predicted from the degree of LDL cholesterol-lowering seen with a high-intensity statin such as atorvastatin 20–80 mg daily. The study provides no reason to depart from recommendations in the NICE lipid modification guideline.

**Overview and current advice**

The NICE guideline on lipid modification recommends that people with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the technology appraisal for that drug in this indication: **Ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia** (which is being updated; publication expected February 2016). This states that ezetimibe is an option for people with primary hypercholesterolaemia in 2 broad situations:

- As an alternative to a statin in adults in whom statins are contraindicated or not tolerated.
- In addition to a statin in adults who have started statin treatment but whose serum total or LDL cholesterol concentration is not appropriately controlled (either after appropriate dose titration or because dose titration is limited by intolerance to the initial statin therapy) and consideration is being given to changing from initial statin therapy to an alternative statin.

The NICE guideline on lipid modification advises that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. ‘High intensity’ refers to a combination of drug and dose that is expected to achieve a reduction in LDL cholesterol more than 40% (see guideline **Appendix A**); atorvastatin is the only statin specifically named in the guideline. The recommended starting dose for primary prevention is 20 mg daily and the recommended starting dose for secondary prevention (including acute coronary syndrome [ACS]) is 80 mg daily in most people (20 mg daily in people with chronic kidney disease). NICE recommends measuring total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on high-intensity statin...
treatment after 3 months of treatment, aiming for a greater than 40% reduction in non-HDL cholesterol. If this reduction in non-HDL cholesterol is not achieved, NICE recommends:

- discussing adherence and the timing of the dose
- optimising adherence to diet and lifestyle measures
- considering increasing the dose if the person started on less than atorvastatin 80 mg daily and they are judged to be at higher risk because of comorbidities, risk score or using clinical judgement.

Adding ezetimibe to atorvastatin is therefore an option recommended in NICE guidance for people with primary hypercholesterolaemia if a greater than 40% reduction in non-HDL cholesterol is not achieved with atorvastatin after the measures recommended in the NICE lipid modification guideline have been tried and changing to a different statin is being considered. Ezetimibe also has a role in the care of people with familial hypercholesterolaemia, as described in the relevant NICE guideline, who were outside the scope of the lipid modification guideline.

NICE guidance on drug therapy for lipid modification is summarised in the NICE Key Therapeutic Topic. The NICE Pathway: cardiovascular disease prevention brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A large randomised controlled trial (RCT) conducted in 1147 centres (the IMPROVE-IT study) compared the effects of ezetimibe plus simvastatin and simvastatin alone in people with ACS. Men and women 50 years of age and older (mean age 64 years, n=18,144) were eligible for inclusion if they had been admitted to hospital within the preceding 10 days for ACS. Exclusion criteria included use of statin therapy that had LDL cholesterol-lowering potency greater than 40 mg of simvastatin. Most (76%) participants were male, 27% had diabetes mellitus, 88% had undergone coronary angiography and 70% had undergone percutaneous coronary intervention during the index hospitalization, 34% were taking statin drugs at the time of the index event, and 77% received statin therapy during their hospital stay.

Participants received standard medical and interventional treatment for ACS and were randomised to simvastatin 40 mg plus either ezetimibe 10 mg or placebo (all once daily). Randomisation was done centrally and stratified according to prior use of lipid-lowering therapy, type of ACS, and status with respect to enrolment in the concurrent EARLY ACS trial. The simvastatin dose was increased to 80 mg for elevated LDL cholesterol levels in 27% of the patients in the simvastatin monotherapy group and in 6% of the patients in the simvastatin–ezetimibe group: it is not clear whether or how adjustment was made for this in the analysis. The study continued until each patient had been followed for a minimum of 2.5 years and until the target number of events (5250) was reached. Follow-up was for a median of 6 years.

The primary efficacy outcome was a composite of death from cardiovascular disease, a major coronary event (nonfatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularisation occurring at least 30 days after randomisation), or nonfatal stroke, assessed from the time of randomisation until the first occurrence of 1 of the events. Kaplan–Meier event rates for the primary end point at 7 years were 32.7% in the simvastatin–ezetimibe group and 34.7% in the simvastatin-monotherapy group (absolute risk reduction, 2.0 percentage points; hazard ratio [HR] 0.936; 95% confidence interval [CI] 0.89 to 0.99; p=0.016). This is equivalent to a number needed to treat of 50 over 7 years. Similar results were seen for the 3 secondary efficacy end points (which were similar to the primary outcome). Of the individual components of the primary outcome, only nonfatal MI showed a statistically significant reduction in risk with ezetimibe (HR 0.87, 95% CI 0.80 to 0.95, p=0.002), although the rates of nonfatal stroke were not reported. The mean LDL
cholesterol was 2.4 mmol/L in each study group at study entry. After 1 year of treatment it was 1.8 mmol/L in the simvastatin-monotherapy group (25% reduction from baseline) and 1.4 mmol/L in the simvastatin–ezetimibe group (42% reduction from baseline).

No statistically significant between-group differences were seen in the percentage of patients who had elevations in alanine aminotransferase (ALT) more than 3 times the upper limit of normal or in the rates of gallbladder-related adverse events; cholecystectomy; muscle-related adverse events; or new, relapsing, or worsening cancer. In both groups, 42% of the participants discontinued the study medication prematurely, however the percentage of potential follow-up that was achieved (number of patient-years of follow-up as a proportion of potential patient-years of follow-up) was 91% for the primary end point and 97% for all-cause mortality. The number of people who said that they decided to discontinue study medication because of an adverse event was similar in both groups: 10.1% of the patients in the simvastatin-monotherapy group and in 10.6% of those in the simvastatin–ezetimibe group.

Commentary

Commentary provided by the NICE Medicines and Prescribing Centre

Although ezetimibe was licensed in the UK more than a decade ago, IMPROVE-iT provides the first published evidence that it can reduce the risk of cardiovascular outcomes compared with an active comparator. IMPROVE-iT also helps provide reassurance regarding the tolerability of ezetimibe. An editorial published alongside IMPROVE-iT helps to put the results into perspective. The editorial authors point out that the results support the so-called ‘LDL hypothesis’; that is, that excess LDL cholesterol is a causal factor in the development of atherosclerotic vascular disease and that reducing LDL cholesterol levels, regardless of the means, should therefore produce a corresponding reduction in cardiovascular events. In fact, as the IMPROVE-iT authors themselves state, event-rate reduction seen with the addition of ezetimibe was almost exactly the same as that predicted by the cholesterol treatment trialists’ (CTT) analysis of statin trials from 2005 (an observed HR of 0.80 per millimole reduction in LDL cholesterol compared with a predicted HR of 0.78). The authors of the editorial state ‘IMPROVE-iT should not be interpreted as showing anything uniquely beneficial about the use of ezetimibe. …[rather], a patient who is currently being treated with 40 mg of simvastatin would be expected to benefit just as much from a higher-intensity statin regimen as from the addition of ezetimibe, assuming equivalent reductions in LDL cholesterol levels’. In IMPROVE-iT, the mean 25% LDL cholesterol reduction seen in the simvastatin monotherapy group was less than the 37% reduction expected according to the modelling supporting the NICE lipid guideline (see guideline Appendix A), but the 42% mean reduction seen in the simvastatin–ezetimibe group was about that expected from atorvastatin 20 mg according to that same modelling. A daily dose of 80 mg atorvastatin, as recommended by NICE for people with ACS, would be expected to produce an average reduction in LDL cholesterol of about 55%.

An update of the NICE technology appraisal of ezetimibe is scheduled for publication in February 2016. Until then, IMPROVE-iT provides no reason to depart from NICE guidance on the place of ezetimibe in therapy, as outlined in the introduction to this evidence commentary and in the NICE Key Therapeutic Topic.

If a person’s non-HDL cholesterol does not appear to have fallen by 40% or more after 3 months of treatment with atorvastatin monotherapy, it is important to think about 2 possible factors. Firstly, an analysis of data from the LIPID study found that a single cholesterol level reading may well under- or over-estimate a person's true average cholesterol level by up to 14%. Secondly, like any drug, a statin will have diminished effectiveness if it is not taken as intended. A meta-analysis of 20 studies (n=376,162) found a summary adherence rate of 57% (95% CI 51% to 64%) for statins in primary
prevention and 76% (95% CI 70% to 82%) in secondary prevention, over a median of 24 months. It is therefore essential to ascertain a person’s ideas, concerns and expectations about statin therapy, and their adherence to it. The NICE lipid modification guideline gives advice on what to do if someone experiences adverse effects of statin therapy. A previous medicines evidence commentary discussed a large observational study that suggested that many people who have discontinued statins because of an adverse event, especially muscle pain, may be able to restart the same or a different statin.

### Study sponsorship

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### References


### About this Medicines Evidence Commentary

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