Lipid modification after myocardial infarction: effect of ezetimibe on risk of death

A UK observational study suggests that, compared with simvastatin monotherapy, use of statins at higher lipid-lowering equivalent doses may be associated with a reduced risk of death after acute myocardial infarction. This is consistent with clinical trial data and the NICE clinical guideline on lipid modification. However, despite a greater reduction in cholesterol, use of ezetimibe plus a statin did not statistically significantly reduce the risk of death compared with simvastatin monotherapy. The observational nature of the study and in particular the small size of the ezetimibe group limit the conclusions that can be drawn. Nevertheless, there remains no published evidence that ezetimibe, alone or added to a statin, reduces the risk of cardiovascular disease or mortality compared with an active comparator. Healthcare professionals should continue to follow the NICE technology appraisal on ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia.

Overview and current advice

The NICE clinical guideline on lipid modification (published July 2014) recommends that when a decision is made to prescribe a statin, a statin of high intensity and low acquisition cost should be used. The only statin specifically named in the lipid modification guideline recommendations is atorvastatin. Other possible high-intensity statins are rosuvastatin 10–40 mg daily and simvastatin 80 mg daily. The MHRA has advised that there is an increased risk of myopathy associated with simvastatin 80 mg daily, and that this dose should be considered only in patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh the potential risk. The NICE full guideline on lipid modification states that, given the considerably higher cost of using rosuvastatin than using atorvastatin and in the absence of trial evidence of greater effectiveness, the guideline development group were unable to recommend the use of rosuvastatin.

The guideline recommends that people with primary hypercholesterolaemia should be considered for ezetimibe treatment in line with the relevant NICE technology appraisal: ezetimibe for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia (published November 2007). This states that ezetimibe is an option for people with primary (heterozygous-familial or non-familial) 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 lipid modification guideline recommends measuring total cholesterol, HDL cholesterol and non-HDL cholesterol in all people who have been started on 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, the guideline 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. In people with chronic kidney disease, any increase in dose should take account of the person’s renal function.

Clinicians may also wish to consider that a single cholesterol level reading may well under- or over-estimate a person’s true average cholesterol level by up to 14%.

In line with NICE guidance, adding ezetimibe to atorvastatin is an option if a greater than 40% reduction in non-HDL cholesterol is not achieved with atorvastatin after the measures recommended in the guideline have been tried and changing to a different statin is being considered. The guideline advises that, if a person is not able to tolerate a high-intensity statin, the aim should be to treat with the maximum tolerated dose. NICE recommends telling the person that any statin at any dose reduces cardiovascular disease risk. If someone reports adverse effects when taking high-intensity statins, the following strategies should be discussed with them:

- stopping the statin and trying again when the symptoms have resolved to check if the symptoms are related to the statin
- reducing the dose within the same intensity group
- changing the statin to a lower intensity group.

The NICE Pathway: lipid modification brings together all related NICE guidance and associated products on the condition in a set of interactive topic-based diagrams.

New evidence

A British observational study has used the GPRD database (now Clinical Practice Research Datalink) to compare mortality among survivors of a first myocardial infarction (MI) according to their lipid-lowering therapy. The GPRD database includes anonymised longitudinal patient data extracted from contributing GP practice databases.

The cohort of patients in this study was all those on the database diagnosed with a first acute MI (index event) between 31 December 2003 and 31 December 2008, with data of sufficient quality. Patients were excluded if they were receiving statin or ezetimibe therapy before their index event and if they had less than 1 year of data prior to their MI. All patients were started on a statin within 30 days of the index event. Three groups were defined according to therapy during the follow-up period:

- simvastatin monotherapy group – patients who continued on simvastatin alone after their MI (mean daily dose 35±10 mg), n=6990
• high potency statin group – patients who switched from simvastatin to a more potent statin during follow-up (either to atorvastatin, mean daily dose 30±22 mg, or to rosuvastatin, mean daily dose 12±8 mg), n=1883

• ezetimibe in combination with a statin – patients who had a co-prescription of ezetimibe 10 mg daily and any statin (simvastatin, mean daily dose 36±13 mg; atorvastatin, mean daily dose 35±23 mg; or rosuvastatin, mean daily dose 13±7 mg), n=724.

Patients were entered into the study from the date of the index event. Over a mean follow-up of 3.2 years, there was a decrease in total cholesterol and LDL-cholesterol from baseline in all 3 groups, with statistically significantly greater percentage decreases in these measures in the high-potency statin group and the combination therapy group compared with the simvastatin monotherapy group (mean LDL-cholesterol lowering 17.42%, 18.99% and 12.85%, respectively). However, although the risk of death was statistically significantly lower in the high-potency statin group than in the simvastatin group (adjusted hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.59 to 0.88, p<0.001), it was not statistically significantly lower in the group taking ezetimibe in combination with a statin (adjusted HR compared with the simvastatin monotherapy group 0.96, 95% CI 0.64 to 1.43, p=0.85).

Commentary

Commentary provided by the NICE Medicines and Prescribing Centre

Observational studies such as this one can show only association, not causation. Unlike in the setting of an RCT, in ‘real life’, treatment plans are chosen, changed, or actively not chosen in the light of individual patients’ risk factors, preferences and tolerability or response to other drugs. Thus observed differences in outcomes may be due to differences among the patients, not only the different treatments. The authors attempted to adjust for such confounding factors, but could not include the patients’ blood pressure, and residual confounding factors may remain. Nevertheless, the finding of a benefit from statins at greater lipid-lowering equivalent doses compared with simvastatin is broadly in line with clinical trials.

However, the small number of people in the group taking ezetimibe in combination with a statin – only 7.5% of the total cohort – severely limits the conclusions that can be drawn from the study. The very wide confidence interval around the adjusted HR for death for this group compared with the simvastatin group emphasises the imprecision of the results, indicating anything from a 36% relative reduction in risk of death to a 43% relative increase in risk.

The NICE clinical guideline on lipid modification states that health professionals should be aware that when deciding on lipid modification therapy for the prevention of cardiovascular disease, drugs are preferred for which there is evidence in clinical trials of a beneficial effect on cardiovascular disease morbidity and mortality. There remains no published evidence that ezetimibe, alone or added to a statin, reduces the risk of cardiovascular disease or mortality compared with an active comparator. The SHARP study compared simvastatin 20 mg plus ezetimibe with placebo in people with chronic kidney disease. Although this found that the combination reduced the risk of cardiovascular disease events compared with placebo, it provides no information as to how simvastatin 20 mg plus ezetimibe would compare with monotherapy with any statin at any dose on the risk of cardiovascular disease. The IMPROVE-IT study is a double blind randomised controlled trial of ezetimibe plus simvastatin compared with simvastatin monotherapy in people with stabilised high-risk acute coronary syndrome. It is scheduled to complete in September 2014 (although the schedule for publication is unknown) and should, at last, resolve this clinical question.

Study sponsorship

Funding for the study was not stated. Access to the GPRD database was funded through the Medical Research Council and no competing interests were declared.
References


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