Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation

CRD summary
This well-conducted review concluded that ezetimibe alone or in combination with a statin was effective in reducing low density lipoprotein cholesterol in short-term studies. When used alone, ezetimibe is less effective than statins. The authors' conclusions reflect the evidence and their recommendations for research appear appropriate given the lack of long-term data in the included studies.

Authors' objectives
To review the clinical and cost-effectiveness of ezetimibe for treatment of primary hypercholesterolaemia.

Searching
Twelve electronic databases were searched from inception to June 2006. Search terms were detailed in the report. Publications lists and current research registers of seven health services research-related organisations were consulted alongside keyword searching using Google search engine. Submissions of evidence to NICE (National Institute for Health and Clinical Excellence) by sponsors and references of retrieved papers were handsearched. There were no language restrictions.

Study selection
Eligible studies needed to be of adults (over 18 years) with primary (heterozygous familial or non-familial) hypercholesterolaemia. Adults with homozygous familial hypercholesterolaemia or homozygous sitosterolaemia were excluded. For patients whose condition was not adequately controlled by a statin alone, ezetimibe could be administered with a statin or a fixed-dose combination tablet that contained ezetimibe and simvastatin. The comparator for such patients was optimal statin monotherapy or treatment with a statin in combination with other lipid-regulating drugs. For patients who could not tolerate a statin or for whom it was considered inappropriate, ezetimibe could be given as monotherapy. The appropriate comparator was an alternative lipid-regulating agent or no treatment. Relevant outcomes were survival, fatal and non-fatal cardiovascular events, adverse effects of treatment and health-related quality of life (HRQoL). In the absence of clinical end points, surrogate end-point data (low density lipoprotein cholesterol (LDL-C), total cholesterol and high density lipoprotein cholesterol (HDL-C) were used. Studies needed to be randomised controlled trials (RCTs) of at least 12 weeks' duration, except for adverse events when non-randomised studies were permitted. Included studies needed to be in English and have sufficient methodological details to allow critical appraisal.

Sample sizes ranged from 246 to 1,528 patients. RCTs were of 12 to 48 weeks' duration. Mean age across the trials was 58. Between 19% and 36% of the trial population were aged 65 years and over. Mean baseline low density lipoprotein cholesterol (LDL-C) levels ranged from 3.36 to 6.50mmol/L. Patients with both primary and secondary cardiovascular disease were included in all trials. Both combination therapy (for those inadequately controlled with a statin alone) and monotherapy (for whom a statin was inappropriate or not tolerated) were evaluated. Most studies required washout or discontinuation of all ongoing lipid-altering treatments before randomisation and no information was available on pre-trial treatment history and previous treatment success. Therefore, it was unclear whether the study population was inadequately controlled with or intolerant of statins.

Two reviewers were involved in the selection of studies for the review. Disagreements were resolved by discussion.

Assessment of study quality
Study quality was assessed against criteria proposed by the Centre for Reviews and Dissemination (CRD). Quality data were assessed by one reviewer and checked by a second. Any disagreements were resolved by consensus.

Data extraction
Data were extracted by one reviewer into a standardised form and independently checked by a second reviewer. Any discrepancies were resolved by consensus.

**Methods of synthesis**
A narrative review was conducted. Meta-analyses were performed, where appropriate, using analyses based on intention-to-treat (ITT) or modified ITT. Fixed-effect and random-effects models were used. Heterogeneity was explored through consideration of study populations, methods and intervention by visualisation of the results and statistically through use of the $X^2$ test and $I^2$ measure.

**Results of the review**
No published clinical outcome trials that examined the cardiovascular benefit of ezetimibe were identified. Thirteen multicentre RCTs with surrogate end-point data were included in the review. None of the trials reported allocation concealment. Five trials did not clarify whether outcome assessors were blinded. All patients were blinded, although none of the trials assessed the success of blinding. All trials except one used ITT or modified ITT analysis. Most trials reported a power calculation. Overall trials were considered by the authors to be relatively well designed and conducted and included relatively balanced populations.

**Fixed-dose combination therapy (for those inadequately controlled by statin):** The combination of ezetimibe and statin was associated with a statistically significant reduction in LDL-C (-13.94%, 95% CI -14.90 to -12.98, p<0.00001, $I^2$=5.8%) and total cholesterol (-10.36%, 95% CI -11.09 to -9.63, p<0.00001, $I^2$=5.65%) compared with statin alone based on six trials (3,610 patients). No RCTs of ezetimibe plus statin compared to other lipid-lowering drugs were identified.

**Titrated Combination therapy (for those inadequately controlled by statin):** All four trials (1,800 patients) found that co-administration of ezetimibe and statin was significantly more effective in reducing LDL-C (p<0.05) compared with statin alone. One study compared ezetimibe plus statin versus other lipid-lowering drugs. This study found that low-moderate doses of atorvastatin/rosuvastatin plus niacin achieved similar LDL-C reductions compared with the highest doses of rosvastatin monotherapy or ezetimibe/simvastatin.

**Monotherapy (for those where a statin was inappropriate or not tolerated):** All included studies compared monotherapy with placebo. A meta-analysis of all seven trials (2,577 patients) demonstrated that ezetimibe significantly reduced LDL-C levels compared with placebo (WMD -18.56, 95% CI -19.68 to -17.44, $I^2$=55.4%).

There were no significant differences in LDL-C across subgroups based on various patient characteristics.

Ezetimibe therapy appeared to be well tolerated compared to statin monotherapy or to placebo. The low frequency of adverse events may have been related to the short follow-up time. Long-term adverse effects were unknown.

No studies of HRQoL data were located.

**Cost information**
A detailed assessment of cost-effectiveness was conducted alongside the review of clinical effectiveness. Results ranged from £21,000 to £50,000 per QALY when ezetimibe was compared with no treatment in patients with baseline LDL-C values of 3.0 to 4.0mmol/L. Results for patients with baseline LDL-C values over 5.0mmol/L were below £30,000 per QALY. Adding ezetimibe to ongoing statin treatment compared with maintaining statin treatment at the current dose resulted in values that ranged from £19,000 to £48,000 per QALY. Adding ezetimibe to ongoing statin treatment compared with changing to a more potent statin had results that ranged from £1,500 to £116,000 per QALY.

**Authors' conclusions**
Short-term RCT evidence demonstrated that ezetimibe was effective in reducing LDL-C when administered as monotherapy or in combination with a statin. When used as monotherapy, it was less effective than statins.

**CRD commentary**
This review was based on clear inclusion criteria for participants, interventions, outcomes and study designs. The search for studies was extensive and thorough and included attempts to find unpublished studies. Studies in languages other
than English were excluded, which risked language bias. Quality was assessed and its overall impact on the results was discussed. Study selection, data extraction and quality assessment were carried out by more than one reviewer, which helped to minimise bias. Meta-analysis techniques were used appropriately with consideration of heterogeneity.

This was a well-conducted review and the authors' conclusions reflect the evidence presented. Their recommendations for research appear appropriate given the lack of long-term data and clinical outcomes in the included studies.

**Implications of the review for practice and research**

**Practice:** The authors did not state any specific implications for practice.

**Research:** The authors stated a need for further research into the long-term clinical effectiveness of ezetimibe in reducing cardiovascular events. There were ongoing studies that would provide these data. The authors recommended additional research into subgroups that might be more likely to benefit from this treatment. They stated a requirement for evidence on effectiveness and safety of the co-administration of ezetimibe with other lipid-lowering drugs. They recommended investigating the evidence of effectiveness in patients who had not yet reached target levels of cholesterol lowering in addition to those with very high baseline levels of plasma cholesterol. The authors recommended assessment of long-term adverse events. Future research should investigate lifetime adherence to combination therapies in the relatively healthy younger and asymptomatic patients with no history of cardiovascular disease.

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