Hyperlipidaemia: clinical outcome data for evolocumab

A large randomised controlled trial (the FOURIER study) found that evolocumab reduced the risk of a composite cardiovascular outcome when added to maximal tolerated lipid-lowering therapy in people with established cardiovascular disease at high risk of further events. No benefit was seen on the risk of death from cardiovascular causes but the median follow up was only 2.2 years. This limits the available information on any possible long-term adverse effects of evolocumab or of controlling cholesterol to very low levels. This new evidence supports the NICE technology appraisal guidance that recommends evolocumab as an option in specified circumstances.

Overview and current advice

Alirocumab and evolocumab are lipid-modifying monoclonal antibodies (PCSK9 inhibitors) administered by subcutaneous injection. They are recommended for use in specified circumstances (more narrowly defined than their marketing authorisations) in NICE technology appraisal guidance on alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia and evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. The technology appraisals recommend them as options for these conditions, only if:

- Low-density lipoprotein cholesterol (LDL-C) levels are persistently above the thresholds specified (see below) despite maximal tolerated lipid-lowering therapy. That is, either the maximum dose has been reached or further titration is limited by intolerance (clinically significant adverse effects that represent an unacceptable risk to the patient or that may reduce compliance with therapy).
- The dosage of evolocumab is 140 mg every 2 weeks (it is also licensed at a dosage of 420 mg once monthly; doses are clinically equivalent).
- The companies provide them with the discounts agreed in the patient access schemes.

Subject to the other conditions in the technology appraisals, they are options for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in people who have cardiovascular (CV) disease (a history of acute coronary syndrome, coronary or other arterial revascularisation, chronic heart disease, ischaemic stroke, or peripheral arterial disease), only if their LDL-C level is:

- persistently above 4.0 mmol/l despite maximal tolerated lipid-lowering therapy, or
- persistently above 3.5 mmol/l despite maximal tolerated lipid-lowering therapy and the person has had recurrent CV events or CV events in more than 1 vascular bed (polyvascular disease).

Alirocumab and evolocumab are not recommended by NICE for treating primary non-familial hypercholesterolaemia or mixed dyslipidaemia in people who do not have established CV disease.
Subject to the other conditions in the technology appraisals, alirocumab and evolocumab are recommended as options for treating primary heterozygous-familial hypercholesterolaemia only if the person’s LDL-C level is:

- persistently above 3.5 mmol/l despite maximal tolerated lipid-lowering therapy if they have established CV disease, or
- persistently above 5.0 mmol/l despite maximal tolerated lipid-lowering therapy if they do not have established CV disease.

Evolocumab is also licensed for treating homozygous familial hypercholesterolaemia in adults and young people aged 12 years and over. This indication was outside the scope of the NICE technology appraisal.

The study summarised in this evidence commentary had not been published at the time of publication of the NICE technology appraisal guidance. A cardiovascular outcomes trial of alirocumab in people with a history of acute coronary syndrome in the past year, ODYSSEY OUTCOMES, is ongoing and is expected to be completed in early 2018.

The NICE Pathway: cardiovascular disease prevention brings together all related NICE guidance and associated products on the condition in a set of interactive flow charts. NICE has also produced a Key Therapeutic Topic on lipid-modifying drugs.

**New evidence**

The FOURIER study (Sabatine et al. 2017), was a double blind multinational RCT of evolocumab in 27,564 people (mean age 63 years, 76% male) with clinically evident atherosclerotic CV disease plus other factors that placed them at higher CV risk, such as having diabetes, being a current smoker or being aged over 65 years at randomisation. The proportion of participants with familial or non-familial hypercholesterolaemia was not reported.

All participants had a fasting LDL-C level of 1.8 mmol/l or higher (median 2.4 mmol/l) or a non-HDL-C of 2.6 mmol/l or higher (median 3.2 mmol/l) while taking atorvastatin 20 mg/day or higher, or equivalent (this would be defined as high intensity statin in the NICE guideline on lipid modification), with or without ezetimibe. During the study, 10% of the participants had changes to their background lipid modification therapy. About 92% of participants were taking aspirin, a P2Y12 inhibitor (such as clopidogrel) or both; 76% were taking a beta-blocker and 78% were taking an ACE inhibitor (ACE-I) or angiotensin receptor blocker (ARB), or an aldosterone antagonist, or both an ACE-I or ARB plus an aldosterone antagonist.

Participants were randomised to receive evolocumab (140 mg every 2 weeks or 420 mg every month, according to participant preference) or placebo. Allocation was concealed. The median duration of follow-up was 26 months (interquartile range 22 to 30 months).

Compared with placebo, evolocumab reduced the risk of the primary endpoint: a composite of death from cardiovascular causes, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation. This endpoint occurred in 9.8% of the evolocumab group compared with 11.3% of the placebo group (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.79 to 0.92, p<0.001, absolute risk reduction 1.5%, number needed to treat 67 over 26 months). However, when the outcome components were analysed individually, evolocumab was not found to reduce the risk of death from cardiovascular causes (or any cause) or hospitalisation for unstable angina. Evolocumab reduced median LDL-C levels from baseline by 59% at 48 weeks of treatment, to a median of 0.8 mmol/l, and median non-HDL-C levels from baseline by 52%. The authors state that the effect of
evolocumab on the risk of major coronary events, stroke and urgent coronary revascularisation was largely consistent with the effect of statins in terms of benefit per mmol/l reduction in LDL-C.

The numbers of participants with any adverse effects (77%) or serious adverse effects (25%) were similar in both groups, the only statistically significant difference being in the number of injection site reactions, which occurred more often in the evolocumab group (2.1% compared with 1.6% in the placebo group, p<0.001).

**Commentary**

**Commentary provided by Dr Paul Flynn, Consultant Physician, Addenbrooke’s Hospital, Cambridge**

In the FOURIER trial LDL-C was lowered using evolocumab, one of two monoclonal antibodies that bind and inhibit PCSK9 that have recently been approved by NICE for use in certain groups of people at high cardiovascular risk. The FOURIER study adds to the considerable literature showing that reducing LDL-C reduces cardiovascular risk, and that it matters less how that is achieved than by how much (with the exception of some of the CETP inhibitors whose effects on lipids are not primarily to reduce LDL-C). It is encouraging that reducing LDL-C to the levels seen in this trial did not cause harm, though this was a relatively short-term study. Two caveats about the widespread use of alirocumab and evolocumab remain: firstly, we do not know the long term consequences of using monoclonal antibodies directed against a protein whose physiological function is unknown; and secondly, there needs to be a full cost-benefit analysis of these agents in wider patient groups than currently recommended by NICE. A ‘law of diminishing returns’ applies here as in other conditions: in absolute terms the incremental absolute benefits from additional treatments diminish as more are added.

Clinicians and patients will need to weigh up the possible benefits from treatment with PCSK9 inhibitors against the risk of adverse effects, including those that may only emerge when more people have been treated with these drugs and for longer than at present. The results of the FOURIER trial suggest that these agents may offer particular benefit for some people with high LDL-C levels despite optimised standard lipid lowering therapy. For all patients, a careful review of current treatment, including adherence, and informed, shared decision-making are essential.

Declaration of interests:
Paul Flynn declared no competing interests.

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**References**

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