Prescribing....

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Ezetimibe

- The new IMPROVE-IT study, found that adding ezetimibe to simvastatin 40 mg after ACS reduced cardiac events more than simvastatin 40 to 80 mg alone.
- However the reduction in LDL cholesterol achieved was less than what we might expect with a high intensity statin such as atorvastatin 20 mg to 80 mg daily.
- The Number Needed to Treat or NNT in the trial participants,to prevent one event, was 50 over 7 years.
- Ezetimibe is extremely expensive, costing £27 per patient per month and £73,000 in the Bailiwick in the past 12 months.

What is the background to this ?

Ezetimibe is licensed for the treatment of primary (heterozygous-familial and non-familial) hypercholesterolaemia. The NICE guidance on the topic is being updated and publication is expected in February 2016. Existing guidance 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%; atorvastatin is the only statin specifically named in the guideline. Rosuvastatin is not of low acquisition cost. 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 three months of treatment, aiming for a greater than 40% reduction in non-HDL cholesterol. If this reduction is not achieved NICE recommends

- Discussing adherence and the timing of the dose
- Optimising adherence to diet and lifestyle mesaures
- **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.

Generic atorvastatin 80mg now costs £2.73 per month. Ezetimibe is an extremely expensive treatment, costing £27.48 per item. In the twelve months ending May 2015 there were 2,800 prescriptions dispensed on the islands at a cost of £73,959. This represented a reduction of 13% in items and cost on the previous year.

What is the new evidence ?

The IMPROVE-IT study was a large randomised controlled trial (RCT) conducted in 1147 centres which 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. 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** The absolute risk reduction of 2.0 percentage points was equivalent to a number needed to treat of 50 over 7 years.

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,

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.

So what ?

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 in the NEJM 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.

Conclusion

- Numerous studies have been conducted on ezetimibe and this is the only one that has shown an improvement in hard outcomes for patients.
- The magnitude of the benefit, even in these very high risk ACS patients, was very small.
- Adding ezetimibe did not improve tolerability or reduce rates of drop-out.
- There are more effective treatments e.g. generic atorvastatin which are far better value.
- Clinicians are earnestly requested to review patients on ezetimibe and to consider whether or not the benefits obtained justify the very high cost.

References : NICE Medicines and Evidence Commentary July 2015

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