Introduction
In the glamorous world of cardiology, with its emphasis on cutting edge procedures and new technology, it can be easy to forget the importance of risk factor management. Raised cholesterol levels are a key independent risk factor for cardiovascular death and lipid management plays a vital role in the secondary prevention of ischaemic heart disease. In this editorial, I will summarise current UK guidance on lipid management after acute coronary syndrome (ACS) and also provide an update on the latest trial about the new kids on the block – PCSK9 inhibitors.

Statin therapy
The cornerstone of lipid management is the use of hydroxymethyl glutaryl (HMG) coenzyme A reductase inhibitors, otherwise known as statins. This class of drug has played a key role in reducing morbidity and mortality in ischaemic heart disease. Their primary mode of action is by reversibly inhibiting HMG coenzyme A, which leads to increased expression of hepatic LDL receptors with a subsequent reduction in levels of circulating LDL cholesterol. A series of double blind, placebo-controlled trials in the early 1990s established that statin therapy successfully reduced low density lipoprotein (LDL) cholesterol levels and conferred a prognostic benefit in patients with ischaemic heart disease. These early trials focused mainly on simvastatin and pravastatin. The evidence for atorvastatin, a high intensity statin, comes mainly from the landmark PROVE-IT study. This large study of 4162 patients with recent ACS and total cholesterol <6.2mmol/L or 5.2mmol/L if already established on statin therapy compared the standard regime of pravastatin 40mg once daily (od) with atorvastatin 80mg od.

LDL cholesterol: How low should you go? Insights from ODYSSEY OUTCOMES trial.
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Take Home Messages

- Lipid management is vital in secondary prevention of ischaemic heart disease.
- Statins are the mainstay of therapy but are often poorly tolerated.
- PCSK9 inhibitors are a new class of lipid lowering drugs that show promise in reducing LDL cholesterol and cardiovascular events.
- Prognostic data on PCSK9 inhibitors to date have been disappointing.
- I agree with the conservative approach taken by NICE of restricting PCSK9 inhibitors to high risk patients.
This trial demonstrated a significant reduction in median LDL cholesterol as well as a significant reduction in the composite outcome of death, myocardial infarction and need for revascularisation in the atorvastatin group (6). The prognostic benefit of intensive lipid management was further elucidated in a meta-analysis of 26 trials of statin therapy demonstrating that a 10% reduction in all-cause mortality and a 20% reduction in cardiovascular mortality for each 1.0mmol/L reduction in LDL cholesterol (7).

Current National Institute for Health and Clinical Excellence (NICE) guidelines recommend high intensity statin therapy (such as atorvastatin 80mg once daily) after an acute coronary syndrome (ACS) with a view to reducing non-HDL cholesterol by 40% from baseline (8).

Despite the well proven benefits, there are many patients who are intolerant of statins. The most common side effects are musculoskeletal with rates of myopathy of 5-10% reported in the literature (9,10). Data from clinical trials shows that discontinuation of statin therapy is common with dropout rates of 25-42% reported in large trials (6,10). Rates of musculoskeletal side effects are consistent among different statins,(11) suggesting that this is a class effect rather than due to individual drugs. However, in clinical practice, it is usual to trial different statins in patients who suffer side effects. It is also recognised that a significant “nocebo” effect exists for statins, with patients aware that they are taking statins more likely to complain of side-effects (12).

**Ezetimibe**

Ezetimibe is a second line cholesterol lowering agent that is used for combating cholesterol levels. It targets the Niemann–Pick C1–like 1 (NPC1L1) protein, thereby reducing absorption of cholesterol from the intestine (13). The IMPROVE-IT trial demonstrated that addition of ezetimibe to simvastatin 40mg provided an incremental 24% reduction in LDL cholesterol. There was a significant reduction of vascular events (a composite of cardiovascular death, stroke or revascularisation) in the combined simvastatin and ezetimibe group.(10)

Current NICE guidance recommends the use of ezetimibe as monotherapy in patients who are intolerant of statin therapy or as combination therapy with statins in patients who have inadequate lipid control at the highest tolerated statin dose (14).

**The new kids on the block – PCSK9 inhibitors**

Given the high levels of statin intolerance in population and the importance of improved lipid control in patients after ACS, there was a need for a novel class of drugs to help combat cholesterol.
Proprotein convertase subtilisin/kexin type 9 serine proteases (PCSK9) are enzymes that bind to LDL receptors, leading to their accelerated degradation and increased LDL cholesterol levels. (15) Patients with nonsense mutations in the PCSK9 gene had lower LDL cholesterol levels and a significantly lower risk of ischaemic heart disease. (15) Monoclonal antibodies to PCSK9, inhibit the hepatic degradation of LDL receptors, and provide significant reductions in LDL cholesterol (16) to hitherto unseen levels.

There are two PCSK9 inhibitors available on the market at present; evolocumab (Repatha) and alirocumab (Praluent). Both are given as fortnightly subcutaneous injections. They were first used in the management of familial hypercholesterolaemia. Both agents are increasingly being used for patients with non-familial hypercholesterolaemia and inadequate cholesterol control despite statin therapy. Current NICE guidelines recommend the use of PCSK9 inhibitors in patients with high risk of cardiovascular disease who have LDL cholesterol persistently above 4mmol/L or for patients with very high risk of cardiovascular disease who have LDL cholesterol above 3.5mmol/L. (17,18)

Although there is no doubt that PCSK9 inhibitors reduce laboratory measures of LDL cholesterol significantly – difference in median LDL cholesterol after 24 week treatment with alirocumab compared with placebo was 62% (17) – data on long term cardiovascular outcomes for patients taking these medication are lacking.

**Insights from the ODYSSEY OUTCOMES trial**

The recently published ODYSSEY OUTCOMES trial (19) was designed to address the question of whether treatment with alirocumab reduced cardiovascular morbidity and mortality in patients with a recent ACS.

In total 18924 patients in 57 countries were included in the trial. Participants had been hospitalised with ACS within the last 12 months, had a baseline LDL cholesterol >1.8mmol/L and were on the highest tolerated dose of a high intensity statin (atorvastatin or rosuvastatin). Patients were randomised to alirocumab or placebo in a 1:1 basis. Alirocumab was started at 75mg fortnightly and increased under blinded conditions to 150mg fortnightly if needed to reduce LDL cholesterol to levels between 0.6-1.3 mmol/L.

Mean LDL level at 2 years in the alirocumab group was 1.7 mmol/L compared with 2.5 mmol/L in the placebo group. The trial showed a statistically significant reduction in the alirocumab group of the primary composite end point of death from coronary heart disease, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke or unstable angina requiring hospitalisation (HR 0.85, CI 0.78 – 0.93, p<0.001). When examining secondary outcomes, there was a significant
reduction in the composite endpoint of death from coronary heart disease, non-fatal MI, unstable angina requiring hospitalisation and repeat revascularisation (HR 0.88, CI0.81-0.95, p=0.001). However, when examined independently, there was no significant reduction in death from coronary heart disease. No significance testing was carried out for reductions in death from cardiovascular causes and all-cause mortality.

There are a number of limitations with the study. The use of composite endpoints makes it difficult to draw conclusions about the individual components of the endpoint. Ultimately, the trial did not show a definite mortality benefit with alirocumab therapy. The significance of the primary composite endpoint, which included death from coronary heart disease, was driven mainly by reductions in non-fatal myocardial infarction and unstable angina requiring hospitalisation. However, patients enrolled in this trial already had low levels of LDL cholesterol (mean LDL cholesterol at baseline 2.38 +/- 0.8 mmol/L) and this is a population with better lipid control than patients eligible for PCSK9 inhibitors in the UK. The benefit of alirocumab was greatest in patients who had a baseline LDL cholesterol >2.6mmol/L, so the trial may have found a mortality benefit in a more “real world” population with poorer lipid control. Secondly median follow up was only 2.8 years, so we still lack long term data on the efficacy and safety of alirocumab.

These findings are very similar to those from the FOURIER study (published in 2017) that was expertly reviewed in a previous BCS editorial.(20) FOURIER compared evolocumab with placebo and also demonstrated a significant reduction in LDL levels, rates of myocardial infarction and need for revascularisation but no mortality benefit (21).

**Conclusion**

PCSK9 inhibitors are undoubtedly a useful addition to the cardiologist’s armoury. While they cause a significant reduction in LDL cholesterol and reduce non fatal cardiovascular events, the data so far on their prognostic benefit have been somewhat disappointing. Given the high cost (annual cost of alirocumab is £4383 per patient) and the lack of long-term outcome data, I feel that the current conservative approach taken by NICE is warranted.
References


