British Cardiovascular Society
'Promoting excellence in cardiovascular care'

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

Ashwin Radhakrishnan

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.

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(1) 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 co-enzyme A, which leads to increased expression of hepatic LDL receptors with a subsequent reduction in levels of circulating LDL cholesterol (2). 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 (3–5). 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.

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

1. Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ [Internet]. 1991;303(6797):276–82. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1670480&tool=pmcentrez&rendertype=abstract

2. Stancu C, Sima A. Statins: mechanism of action and effects. J Cell Mol Med [Internet]. 2001 Oct 1;5(4):378–87. Available from: https://doi.org/10.1111/j.1582-4934.2001.tb00172.x

3. Group SSSS. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet [Internet]. 1994 Nov 19;344(8934):1383–9. Available from: https://doi.org/10.1016/S0140-6736(94)90566-5

4. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels. N Engl J Med [Internet]. 1996 Oct 3;335(14):1001–9. Available from: https://doi.org/10.1056/NEJM199610033351401

5. The long term intervention with pravastatin in ischaemic heart disease (LIPID) Study Group. Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. N Engl J Med [Internet]. 1998 Nov 5;339(19):1349–57. Available from: https://doi.org/10.1056/NEJM199811053391902

6. Cannon, Christopher P. Braunwald Eugene ME et al. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med [Internet]. 2004 Aug 12;351(7):714–7. Available from: https://doi.org/10.1056/NEJM200408123510719

7. Collaboration CTT (CTT), Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet (London, England) [Internet]. 2010 Nov 13;376(9753):1670–81. Available from: https://www.ncbi.nlm.nih.gov/pubmed/21067804

8. National Institute for Health and Care Excellence(NICE). Cardiovascular Disease: Risk Assessment and Reduction including lipid modification. CG181. 2014;(CG181):1–50. Available from: http://www.nice.org.uk/guidance/cg181/chapter/Introduction

9. Ihle P, Dippel FW, Schubert I. Statin-associated myopathy. Assessment of frequency based on data of all statutory health insurance funds in Germany. Pharmacol Res Perspect. 2018;6(3):1–9.

10. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med [Internet]. 2015 Jun 3;372(25):2387–97. Available from: https://doi.org/10.1056/NEJMoa1410489

11. Naci H, Brugts J, Ades T. Comparative tolerability and harms of individual statins : A study-level network meta-analysis of 246 955 participants from 135 randomized, controlled trials. Circ Cardiovasc Qual Outcomes. 2013;6(4):390–9.

12. Gupta A, Thompson D, Whitehouse A, Collier T, Dahlof B, Poulter N, et al. Adverse events associated with unblinded, but not with blinded, statin therapy in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA): a randomised double-blind placebo-controlled trial and its non-randomised non-blind extension phase. Lancet [Internet]. 2017 Jun 24;389(10088):2473–81. Available from: https://doi.org/10.1016/S0140-6736(17)31075-9

13. Sudhop T, Lutjohann D, Kodal A, Tribble DL, Shah S, Perevozskaya I, et al. Inhibition of intestinal cholesterol absorption by ezetimibe in humans. Circulation. 2002;106(15):1943–8.

14. NICE. Ezetimibe for treating primary hypercholesterolaemia. 2016;(February 2016). Available from: nice.org.uk/guidance/ta385

15. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence Variations in PCSK9, Low LDL, and Protection against Coronary Heart Disease. N Engl J Med [Internet]. 2006 Mar 23;354(12):1264–72. Available from: https://doi.org/10.1056/NEJMoa054013

16. Stein EA, Mellis S, Yancopoulos GD, Stahl N, Logan D, Smith WB, et al. Effect of a Monoclonal Antibody to PCSK9 on LDL Cholesterol. N Engl J Med [Internet]. 2012 Mar 21;366(12):1108–18. Available from: https://doi.org/10.1056/NEJMoa1105803

17. NICE - National Institute for Health and Care Excellence. Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. 2016;(June).

18. National Institute for Health and Care Excellence(NICE). Evolocumab for treating primary hypercholesterolaemia and mix mixeded dyslipidaemia. 2016;(June 2016).

19. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med [Internet]. 2018 Nov 7;379(22):2097–107. Available from: https://doi.org/10.1056/NEJMoa1801174

20. Papalia F. LDL-C reduction with PCSK9 inhibitors: An update on the latest evidence. BCS editorial 26/04/2017. Available from https://www.bcs.com/pages/news_full.asp?NewsID=19792589

21. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med [Internet]. 2017 Mar 17;376(18):1713–22. Available from: https://doi.org/10.1056/NEJMoa1615664