How aggressively should cholesterol targets be pursued?

Statins are universally acknowledged as one of the great successes of cardiovascular therapy in the last 25 years yet remain controversial in the popular media. Like many drugs they are under-prescribed and under-dosed in clinical practice. The statin controversy shows no sign of ending but at least it has now begun to rage over whether 'lower is better' when a high-dose statin is compared with a lower dose in prospective studies and in which groups of patients.

The epidemiology of hyperlipidaemia shows that cholesterol levels are associated with cardiovascular risk down to levels of 2.5 mmol/litre for total cholesterol (1.5 mmol/litre for low density lipoprotein-cholesterol (LDL-C) (Chen et al, 1991). The National Service Framework (NSF) for Coronary Heart Disease (Department of Health, 2000) and Quality Outcomes Framework have used a total cholesterol <5 mmol/litre (or 20% reduction) and a LDL-C of <3 mmol/litre (or 30% reduction) as a definition of adequate care. Moderate statin therapy achieves the current targets easily but at significant cost to the Exchequer (£1 billion) unless generic agents are used (Moon and Bogle, 2006, 2007; Minhas, 2007).

The Heart Protection Study (HPS) validated the use of simvastatin 40 mg in high-risk patients with established atherosclerosis (coronary heart disease, stroke, peripheral arterial disease) or those at high risk of developing occlusive arterial disease: patients with type 2 diabetes and a few with type 1 (Heart Protection Study Collaborative Group, 2002). The Cholesterol Treatment Triallists' pooled analysis (Baigent et al, 2005) showed a reduction of 12% in mortality and 20–25% in cardiovascular events, depending on the endpoint, per 1 mmol/litre cholesterol reduction.

An argument has raged between the Joint British Societies (JBS) and the UK government over the question of whether new lower targets (4 and 2 mmol/litre) are appropriate for cardiovascular disease or whether 5 and 3 mmol/litre are adequate. All groups agree that the minimum target (the JBS-2 audit standard and the NSF target) should be 5 and 3 mmol/litre. The answer seems to lie in the underlying cardiovascular risk of the patient.

Secondary prevention

Two trials – PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) and Aggrastat to Zocor (A-Z) have addressed the controversy of aggressive *vs* usual care for cholesterol in acute coronary syndromes by comparing intensive with usual care regimens. A lower LDL-C (1.75 mmol/litre) and a greater differential between study arms was associated with benefits in terms of reduced morbidity, especially in patients undergoing angioplasty, in both studies (Cannon et al, 2006).

Similarly in chronic coronary heart disease a 15% extra reduction in LDL-C from imputed baseline levels was associated with 22% relative risk reduction in coronary events although no effect was seen on the notably very low cardiovascular mortality rate in the Treatment to new Targets (TnT) and Incremental Decrease in Endpoints through Aggressive Lipid lowering (IDEAL) studies. The benefits were achieved at the price of a 3% rate of significant liver dysfunction (elevated transaminases). Thus there is a clinical justification for lower targets in secondary prevention.

Diabetes

Diabetes is primarily a cardiovascular disease in which statin therapy delivers substantial benefits (Eliasson et al, 2005). The HPS (Collins et al, 2003) followed by the Collaborative AtoRvastatin Diabetes Study (CARDS) study (Colhoun et al, 2004) showed that LDL-C reduction was effective in preventing cardiovascular events in diabetes. However, controversy still remains in some areas as results were less positive in some studies: the Anglo-Scandinavian Coronary Outcomes trial (ASCOT) diabetes subgroup (Sever et al, 2005) and the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN) study (Knopp et al, 2006). The meta-analysis of all patients with diabetes in the statin trials by the Cholesterol Treatment Trialists' is eagerly awaited and is likely to reinforce the necessity to treat LDL-C aggressively in patients with type 2 diabetes and consider them a cardiovascular risk equivalent population as recommended in the JBS-2 guidelines (British Cardiac Society et al, 2005).

Primary prevention

In primary prevention, too many patients are treated on the basis of cholesterol levels rather than calculated cardiovascular risk. All health systems limit treatment to patients at higher cardiovascular risk (20%/decade) on the basis of number needed to treat. Targets are controversial in this field (Wierzbicki, 2007). Statins show benefits in the ultra-low risk populations recruited for some recent studies.

Data from the ASCOT study in patients without diabetes showed benefits in the lower quartile of lower LDL-C in post-hoc analyses but implies a high number needed to treat even in patients with three or four cardiovascular risk factors (Sever et al, 2003). In the MEGA study pravastatin 10–20 mg reduced events by 33% in patients achieving a final LDL-C of 3.31 mmol/litre but with a number needed to treat of 119, an event rate of 0.5%/year and with benefits occurring mostly in men (Nakamura et al, 2006).

In the patients with calculated Framingham risk <10% recruited to the Measuring Effects on intima media Thickness: an Evaluation Of Rosuvastatin (METEOR) study, aggressive therapy with rosuvastatin 40 mg achieving an LDL-C of 2.02 mmol/litre reduced the progression of carotid intima media thickness – a well-accepted surrogate of atherosclerosis (Crouse et al, 2007). Thus although there is evidence for 5 and 3 mmol/litre targets,

there is less for 4 and 2 mmol/litre. In addition there is justification for a 'fire and forget' strategy of prescribing an adequate dose of statin (e.g. simvastatin 40 mg) and not bothering with targets. The consequent 1 mmol/litre reduction will reduce cardiovascular events by 20–25% at minimal cost (Baigent et al, 2005). This approach has been adopted by the Scottish Intercollegiate Guidelines Network (2007). One accidental consequence of the financially-orientated statin-switch strategies is that it is driving the review of patient records and also encouraging repeat attendance for assessment and thus may also improve the standard of care as inadequate doses are recognized and titrated.

The future

There are better prospects on the horizon. The high tolerability of ezetimibe and the cost effectiveness of the combination of statin-ezetimibe compared to switch/titrate strategies suggests that a simple second stage addition may be all that is required to optimize lipid control in 90% of patients (Daskalopoulou and Mikhailidis, 2006). Once ezetimibe-statin is generic the fire and forget strategy will be very tempting to health payment organizations. It may do away with the need for LDL-C targets in both primary and secondary prevention as the vast majority of patients will achieve good lipid control with hopefully a single tablet. BJHM

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Baigent C, Keech A, Kearney PM et al (2005) Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* **366**(9493): 1267–78

British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, and The Stroke Association (2005) JBS 2: the Joint British Societies' guidelines for prevention of cardiovascular disease in clinical practice. *Heart* **91**(suppl V): v1–v52

Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E (2006) Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. *J Am Coll Cardiol* **48(3)**: 438–45

Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W (1991) Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. *BMJ* **303**(6797): 276–82

Colhoun HM, Betteridge DJ, Durrington PN et al (2004) Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* **364**: 685–96

Collins R, Armitage J, Parish S, Sleigh P, Peto R (2003) MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* **361**(9374): 2005–16

Crouse JR III, Raichlen JS, Riley WA et al (2007) Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. *JAMA* **297**(12): 1344–53

Daskalopoulou SS, Mikhailidis DP (2006) Reaching goal in hypercholesterolaemia: dual inhibition of cholesterol synthesis and absorption with simvastatin plus ezetimibe. *Curr Med Res Opin* **22**(3): 511–28

Department of Health (2000) *National Service Framework for Coronary Heart Disease.* Stationery Office, London

Eliasson B, Cederholm J, Nilsson P, Gudbjornsdottir S (2005) The gap between guidelines and reality: Type 2 diabetes in a National Diabetes Register 1996-2003. *Diabet Med* **22**(10): 1420–6

Heart Protection Study Collaborative Group (2002) MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* **360**(9326): 7–22

Knopp RH, d'Emden M, Smilde JG, Pocock SJ (2006) Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (ASPEN). *Diabetes Care* **29**(7): 1478–85

Minhas R (2007) Statin utilisation--recognising the role of the invisible hand. *Int J Clin Pract* **61**(1): 3–6

Moon JC, Bogle RG (2006) Switching statins. *BMJ* **332**(7554): 1344–5

Moon JC, Bogle RG (2007) How to lose a billion pounds. *Int J Clin Pract* **61(1):** 2–3

Nakamura H, Arakawa K, Itakura H et al (2006) Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. *Lancet* **368**(9542): 1155–63

Scottish Intercollegiate Guidelines Network (2007) *Risk estimation and the prevention of cardiovascular disease: a national clinical guideline.* Scottish Intercollegiate Guidelines Network, Edinburgh

Sever PS, Dahlof B, Poulter NR et al (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* **361**(9364): 1149–58

Sever PS, Poulter NR, Dahlof B et al (2005) Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial--lipid-lowering arm (ASCOT-LLA). *Diabetes Care* **28**(5): 1151–7

Wierzbicki AS (2007) Newer, lower, better? Lipid drugs and cardiovascular disease- the continuing story. *Int J Clin Pract* (in press)

KEY POINTS

- Statin therapy is first line for all at-risk cardiovascular disease.
- Higher risk patients should be treated more aggressively.
- Targets for patients with established atherosclerosis should be total cholesterol <4 mmol/litre and low density lipoprotein-cholesterol <2 mmol/litre.
- Targets for patients with diabetes should be total cholesterol <4 mmol/litre and low density lipoprotein-cholesterol <2 mmol/litre.

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If you would like to comment on any of the articles in the *British Journal of Hospital Medicine*, or any issues which are relevant to our readers, please write in no more than 250 words to:

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