

## Therapeutic options

# Lipid management: Does the evidence support treatment to lower targets?

### Introduction

An important concept to grasp when determining how best to use statin drugs is that we are not talking so much about the management of hyperlipidaemia as about modifying the risks caused by our modern, westernised diet characterised by an excess of saturated fats. Nearly all individuals from adolescence onwards show some degree of damage because of this diet with signs of fatty deposits in blood vessels: atherosclerosis. The average total cholesterol in adults in the UK is around 5.8mmol/L.<sup>1</sup> Cardiovascular disease (CVD) is the main cause of death and 208,000 people die each year from the condition in the UK; about one in three of us will die from it.<sup>1</sup> The main forms of CVD are coronary heart disease (CHD) and stroke. In 2005, 31% of premature deaths (those before age 75 years) in men and 23% of premature deaths in women were from CHD.<sup>1</sup> Contrary to popular belief as many women die of CHD as men, but they do so at a later age.

In recent years, evidence from randomised controlled trials and meta-analyses has enabled the development of therapeutic and treatment strategies to reduce the risk of developing CHD and major atherosclerotic disease in general. A whole series of randomised-controlled studies from the 1990s clearly showed that statins were safe and effective in preventing cardiovascular (CV) events in people with established disease (secondary prevention) and in those without established CV disease, but who were at high risk (primary prevention).

### Treat to target or 'fire and forget'?

Studies published in the last decade have reinforced this evidence and some, more recent, studies have suggested that higher dose therapy may give added advantage in people who have recently had an acute coronary event, but this is at the risk of

greater adverse effects. Astonishingly, very few studies have adopted a target chasing approach. However, there is a powerful lobby to do this, partly fuelled by the drug industry. Most studies have used a single dose approach. There is considerable and heated debate between the 'standard dose' or 'fire and forget' fraternity and those that advocate 'the lower the better' target chasing.

### What do NICE say?

NICE currently advise that all people with established atherosclerotic CVD (CHD, stroke, TIA or peripheral vascular disease) should be considered for statin therapy, and all people with a 10-year risk of CVD event estimated to be above 20%.<sup>2</sup> This is the case in a very high proportion of the UK adult population — maybe as many as 20%. Thankfully, the price of generic statins has



© Amanda Robidet istockphoto

reduced considerably so this is just about affordable if a drug like simvastatin is used.

Despite telling us who to use them on NICE does not say how we should go about using statins. For several years a further set of guidance has been awaited from NICE: the lipid modification guidance, which hopefully may help to resolve some of the arguments about whether we should use

cholesterol targets, and if so which ones. These have been delayed until later in 2008 while a consultation takes place on whether a new type of risk calculator is adopted in England and Wales — the QRISK calculator (see <http://www.qrisk.org/>). This is based on a UK population, unlike the Framingham calculators, which are based on US patients and are now rather 'long in the tooth'.

In previous guidance, in the English 2000 *National Service Framework (NSF) for Coronary Heart Disease* (and followed by a Welsh version) the target set was: 'Statin therapy should aim to lower cholesterol below 5.0mmol/L or to reduce total serum cholesterol by 20–25%, whichever would result in the lowest level. Equivalent figures for LDL [low density lipoprotein] cholesterol would be 3.0mmol/L or by 30% reduction, whichever results in the lowest level'.<sup>3</sup> Until NICE publish their updated guidance, this remains the national policy in England and Wales. The quality and outcome framework of the general practitioners' contract, starting in April 2004, rewards practices according to the proportion of patients with vascular disease or diabetes, with total cholesterol concentrations below 5mmol/L.<sup>4</sup>

### Joint British Societies' set challenging targets

The updated *Joint British Societies' Guidelines (JBS2)* in December 2005 proposed more challenging targets for both primary and secondary prevention. They recommend to lower total cholesterol to less than 4mmol/L or a 25% reduction, or to lower LDL-cholesterol to less than 2mmol/L or a 30% reduction, whichever gets the person to the lowest absolute value.<sup>5</sup> JBS2 acknowledge a lack of evidence for their approach: 'There are no clinical trials which have evaluated the relative and absolute benefits of cholesterol lowering to different total and

LDL-cholesterol targets in relation to clinical events. Therefore, targets defined by guidelines are a matter of judgement set in the context of the total CVD risk of trial populations and using, where available, pre-specified and post hoc analyses of total and LDL-cholesterol concentrations achieved'. Alongside the debate that these targets are not based on evidence, some have argued that these targets are too demanding and that the NHS in the UK cannot afford them.<sup>6</sup>

### So what is the current policy advice?

In the absence of strong evidence-base for this approach it is important to have a clear national policy. As far as cholesterol targets are concerned we are in a decision-making vacuum until the NICE lipid-modification guideline appears. To help with this indecision and concerns about the lack of an evidence-based approach, a message has gone out in England and Wales. A letter from the National Director for Heart Disease was sent to primary care trusts in England in November 2006, 'issued because some parts of the NHS have the impression that the *JBS2 Guideline* is now national policy.<sup>7</sup> The letter went on to state: 'The present situation is therefore absolutely clear. National policy currently accepts 5mmol/L for total cholesterol and 3mmol/L for LDL-cholesterol as targets for therapy as per the *NSF for CHD*. This will only be revised by any amendment that arises from the NICE guideline'. The same letter was sent out in Wales in 2007. It can be argued that this is inadequate, because recent studies, described below, suggest that all people at high risk of CVD will benefit from treatment, irrespective of their cholesterol level.

### Early evidence from the 1990s

Early, non-statin, lipid lowering trials did not give clear answers as to whether LDL-cholesterol reduction would decrease CVD mortality. The fibrate drugs continue to have a question mark over their effectiveness and the MHRA have recently reviewed their use and given them a 'thumbs down'.<sup>8</sup> The greater efficacy of statins in reducing LDL-cholesterol compared with previous treatments allowed studies to be carried out in

high risk populations with established CHD (such as the Scandinavian simvastatin survival study<sup>9</sup> trial in 1994) and in high-risk patients without CHD (such as the west of Scotland coronary prevention study<sup>10</sup> in 1995). These showed clearly that statins can reduce CHD events and mortality.

### The heart protection study

Published in July 2002, the UK heart protection study (HPS) is the largest statin trial to date. The HPS was a double-blind randomised controlled trial (RCT) of simvastatin 40mg daily versus placebo.<sup>11</sup> Of the 20,536 participants, 5,082 were female and 5,806 were at aged least 70 years (range 40–80 years). Patients had a non-fasting total cholesterol level of at least 3.5mmol/L and were at high-risk of a major vascular event occurring. The researchers included patients with: a previous myocardial infarct (MI) or angina; peripheral vascular disease without CHD; previous stroke or transient ischaemic attack (TIA) without CHD; diabetes mellitus (type 1 or 2); or treated



hypertension with additional risk factors (only 1% were included because of hypertension alone).<sup>11</sup>

After five years of follow-up and despite differences in baseline risk, the benefit of simvastatin 40mg daily was similar across all groups.<sup>11</sup> Overall, simvastatin was associated with a significant 24% (95% CI 19%–28%) relative reduction in the occurrence of major vascular events (coronary event, stroke, or revascularisation) compared with placebo (19.8% vs. 25.2%,  $P < 0.0001$ , number needed to treat [NNT] 19). All cause mortality was also reduced significantly versus placebo (12.9% vs.

Evidence from high dose statin trials suggest that if aggressive treatments were used in primary prevention, or in 'lower risk' people with established CVD, they have a potential for harm but with little prospect of added benefit. The evidence clearly shows that statins are beneficial, whatever the cholesterol level, in those where risk of CVD is high.

14.7%,  $P = 0.0003$ ). Simvastatin was well tolerated, with an average compliance rate of 85%. It showed a good safety profile with reports of muscle weakness similar to placebo, and an annual excess risk of myopathy of 0.01%.

HPS demonstrates that simvastatin 40mg daily is effective in reducing the incidence of major vascular events in a wider population than had previously been shown to benefit. It provides evidence for benefit in:

- all people with atherosclerotic vascular disease (stroke or PVD), but without diagnosed coronary disease
- people up to 80 years of age
- people with diabetes
- women, where direct evidence was previously lacking.

Risk reductions were in addition to those of other treatments (aspirin, beta-blockers and ACE inhibitors). A major finding was that benefits appeared to be independent of the baseline total cholesterol or LDL-cholesterol.<sup>11</sup> A similar finding was subsequently reported in the collaborative atorvastatin diabetes study (CARDS) study in type-2 diabetes with the use of atorvastatin 10mg daily.<sup>12</sup>

### Greater benefit from higher doses of statin?

Recent evidence suggests that there may be harms attributed to the more intensive lipid-lowering proposed by the JSB2, and that this treatment may not be well

## Therapeutic options

tolerated. These high dose studies are varied and some show benefit over 'standard dose' therapy. They have looked at high dose statins (mainly atorvastatin 80mg daily) in high risk patients, such as those with acute coronary syndrome or listed for percutaneous intervention, although none used a 'target chasing' approach. These show some additional benefit compared with standard dose therapy but at the expense of harm related to myopathy and liver disorder, and patient drop-outs. If this more aggressive therapy is applied to lower risk people, such as the primary prevention population, potential for harm or poor compliance could exceed benefit.

### What are the main high dose statin studies?

This worry of harm exceeding benefit is, in part, supported by recent evidence from the incremental decrease in end points through aggressive lipid lowering (IDEAL) study.<sup>13</sup> This compared simvastatin 20mg–40mg daily with atorvastatin 80mg daily in 8,888 patients with a history of MI. The primary endpoint of major coronary event was not significantly reduced by atorvastatin 80mg daily; HR 0.89 (95% CI 0.78–1.01),  $P=0.07$ . The incidences of adverse events resulting in discontinuation (9.6% vs. 4.2%,  $P<0.001$ ) and raised liver enzyme levels (for example, alanine aminotransferase of  $>3$  times the upper limit of normal 0.97% vs. 0.11%,  $P<0.001$ ) were significantly greater with atorvastatin than with simvastatin. Medication adherence was also lower with atorvastatin (89% vs. 95%).

IDEAL does not provide compelling evidence that high-dose atorvastatin should be used ahead of simvastatin (20mg and 40mg) as part of a general management strategy for secondary prevention of cardiovascular events, let alone in primary prevention. Looking at the mean LDL-cholesterol levels throughout the study: 2.1mmol/l with atorvastatin vs. 2.7mmol/l with simvastatin,<sup>13</sup> suggests that even with high dose potent statin therapy at least 50% of people will not obtain the targets proposed by JBS2.

Another study was also negative. This

**Table 1. Average percentage reductions in LDL-cholesterol compared with pre-treatment levels, after a short course of treatment with statins**

Statin	Dose (per day)				
	5 mg	10 mg	20 mg	40 mg	80 mg
Atorvastatin		37	43	49	55
Fluvastatin			21	27	33
Pravastatin		20	24	29	
Rosuvastatin	38	43	48	53	
Simvastatin		27	32	37	42

Derived from: Law MR, Wald NJ, Rudnicka AR. *BMJ* 2003; **326**: 1423–29.

was the Aggrastat to Zocor (A to Z) study, which compared simvastatin at high dose (40mg for one month then 80mg daily) versus low dose (placebo for four months then simvastatin 20mg daily) in 4,497 patients with acute coronary syndromes (median age 61 years); 24% were women.<sup>14</sup> At a median of around two years, the treatments did not differ significantly in the primary composite endpoint of cardiovascular death, MI, readmission for acute coronary syndrome or stroke (14.4% of patients with high-dose vs. 16.7% with low-dose therapy).

Several other studies are more supportive of a high dose approach. In the treating to new targets (TNT) trial, 15,464 patients with stable CHD entered a 'run in' for eight weeks with atorvastatin 10mg daily; they were then excluded if their LDL-cholesterol concentration had not fallen below 3.4mmol/L, or if they did not adhere to, or tolerate, the medication.<sup>15</sup> The remaining 10,001 patients (65%; mean age around 61 years) were then randomised to atorvastatin 80mg or 10mg daily; 19% were women. At a median of 4.9 years, fewer patients taking atorvastatin 80mg daily had reached the primary composite endpoint of CHD death, MI, resuscitated cardiac arrest or stroke (8.7% vs. 10.9%,  $P<0.001$ ). This study, oddly, given its name, did not use a 'target chasing approach' but used a set dose of high dose atorvastatin.

Another positive study, the pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction (PROVE IT-TIMI) trial compared atorvastatin 80mg daily with pravastatin 40mg daily in 4,162 patients (mean

age 58 years) admitted to hospital with acute coronary syndromes; 22% were women.<sup>16</sup> At a mean of two years, fewer patients taking high-dose therapy had reached the primary composite endpoint of death, MI, hospitalisation for unstable angina, revascularisation or stroke (22.4% vs. 26.3%,  $P=0.005$ ).

### The right comparisons?

Apart from the TNT study, the 'standard' therapy used in these trials (pravastatin 40mg or simvastatin 20mg daily) produced less LDL-cholesterol lowering than would have occurred with simvastatin 40mg daily (perhaps a fairer 'standard' comparison). However, there is now a case for using high dose statin, such as atorvastatin 80mg daily in patients admitted to hospital with 'high risk' acute coronary syndrome. Whether the dose should be stepped down after a few months when patients become stable, is yet to be determined, but this the policy in some areas.

### How low can one go?

There seems to be a practical limit of approximately 55% LDL-cholesterol reduction that can be achieved safely with any statin, including atorvastatin (maximum dose 80mg daily) and rosuvastatin (maximum dose 40mg daily)<sup>17</sup> — see Table 1. In people with very high cholesterol (for example more than 8mmol/L) or the 'true' hyperlipidaemia seen in inherited familial hyperlipidaemia, additional therapies to reduce LDL-cholesterol further may be considered. Bile acid sequestrants (BAS) and the cholesterol absorption inhibitor ezetimibe can reduce LDL-cholesterol by a further 10–25% but are limited by side-effects.

Outcome investigations are underway for ezetimibe and ezetimibe/simvastatin combination therapy in these patients and more widely in the higher risk population. The recent adverse publicity surrounding the ENHANCE study in familial hyperlipidaemia suggests that intensive lipid-lowering with this combination may not be as effective as it sounds.<sup>18</sup>

### Statins and safety

Statins are generally safe and indeed their safety profile at 'standard dose' is probably much better than that of aspirin. The common side-effects are a generally transient gastrointestinal disturbance seen in all lipid lowering agents to date, liver function test disturbance (usually reversible) and a spectrum of muscle-related side-effects ranging from myalgia (common) through muscle inflammation (myositis) to rhabdomyolysis, which is very rare when used at standard doses.

### So, can we see a solution?

Do we have to use cholesterol targets? There are other ways. One approach would be to ensure that all those with atherosclerotic cardiovascular disease, or who are at high risk of disease (diabetes or greater than 20% 10-year risk indicated by NICE), get an evidence-based dose of statin: simvastatin 40mg daily has an excellent evidence base and is affordable.

Another way, highlighted by a recent large review of the subject, the cholesterol treatment trialists' (CTT) collaborators meta-analysis, is to ensure a reasonable reduction in LDL-cholesterol in all treated individuals.<sup>19</sup> The CTT analysis demonstrates that the benefit from statins is proportionally related to the absolute reduction in LDL-cholesterol, across trials for up to five years of treatment, largely irrespective of the initial lipid profile or other presenting characteristics. The CTT collaborators indicated that full compliance with available statin regimens (for example, simvastatin 40mg daily) can reduce LDL-cholesterol by at least 1.5mmol/L in most patients, and hence should reduce the incidence of major vascular events by about one third.<sup>19</sup>

### Summary and conclusion

The evidence from high dose statin trials (which generally do not employ target-chasing methodology) suggest that if aggressive treatments were to be used in primary prevention, or in 'lower risk' people with established CVD, they have a potential for harm but with little prospect of added benefit. The evidence clearly shows that statins are beneficial, whatever the cholesterol level, in those where risk of CVD is high. This is an important point and even such people with a pre-treatment total cholesterol level at or below 5mmol/L should still get a statin. Current best evidence suggests that most should be given a standard dose of statin and simvastatin 40mg daily is the most cost-effective at present. For these reasons it would be more helpful (and better based on evidence) if the general practitioner Quality and Outcome Framework target was based on the proportion of eligible patients treated with an evidence-based dose of statin (such as simvastatin 40mg/day). This strategy has been variously described as 'standard dose'

therapy or 'fire and forget'. If cholesterol targets are to be set they should aim to lower LDL-cholesterol by 1mmol/L to 1.5 mmol/L in each person treated. This is achieved in many simply by using simvastatin 40mg daily. ❀

### Declaration of competing interests

The author declares he has no competing interests.

**Martin Duerden**, General Practitioner and Medical Director, Conwy Local Health Board and honorary senior lecturer in therapeutics, Cardiff University.

### Series editors:

**Jonathan Underhill**, National Prescribing Centre, Liverpool, UK

**Scott Pegler**, principal pharmacist, medicines information manager, Morrision Hospital, Swansea NHS Trust, UK

**John Bane**, medicine information/clinical trial pharmacist, Pharmacy Dept, Sheffield Childrens NHS Foundation Trust, Sheffield, UK

### References

- Allender S, Peto V, Scarborough P *et al*. Coronary heart disease statistics July 2007. British Heart Foundation. From: [www.heartstats.org](http://www.heartstats.org) (accessed 24 February 2008).
- National Institute for Health and Clinical Excellence. *Statins for the prevention of cardiovascular events*. Technology appraisal 94 and related costing template and report. January 2006. From [www.nice.org.uk](http://www.nice.org.uk) (accessed 24 February 2008).
- Boyle R. Letter: DoH explains thinking behind national service framework for coronary heart disease. *BMJ* 2000; **321**: 1083.
- British Medical Association. *New GMS contract. Investing in general practice*. London: BMA, 2003.
- British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, The Stroke Association. JBS 2: Joint British Societies' Guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 2005; **91**(Suppl V): v1-v52.
- Minhas R. Statin utilisation — recognising the role of the invisible hand. *Int J Clin Pract* 2007; **61**: 3-6.
- Boyle R. Letter to NHS in England clarifying cholesterol targets, 7 November 2006. Available from: <http://www.networks.nhs.uk/news.php?nid=1149> (Accessed 24 February 2008).
- MHRA and CHM. Fibrates: new prescribing advice. *Drug Safety Update* November 2007; **1**(Issue 4): 2-3. (Available from <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm> Accessed February 27 2008).
- Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994; **344**: 1383-9.
- Shepherd J *et al*. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995; **333**: 1301-7.
- Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**: 7-22.
- Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004; **364**: 685-96.
- Pedersen TR, Faergeman O, Kastelein JJP *et al*. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction. *JAMA* 2005; **294**: 2437-45.
- De Lemos JA, Blazing MA, Wiviott SD *et al*. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA* 2004; **292**: 1307-16.
- La Rosa JC, Grundy SM, Waters DD *et al* for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352**: 1425-35.
- Cannon CP, Braunwald E, McCabe CH *et al*. for the Pravastatin or Atorvastatin Evaluation and Infection Therapy — Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495-504.
- Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003; **326**: 1423-9.
- Lenzer J. Unreported cholesterol drug data released by company *BMJ* 2008; **336**: 180-1.
- Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267-78.