Statins in primary care: bridging the treatment gap

Many patients with coronary heart disease do not have any, or adequate, lipid-lowering treatment. This article describes strategies to bridge the gap between potentially achievable targets and actual lipid levels.

Abstract

Audits of cholesterol management in patients with coronary heart disease (CHD) demonstrate that many patients do not achieve targets set out in national guidelines. Under-treatment is a component of the treatment gap and many patients are prescribed low-dose statins. The delivery of systematic care and adoption of more efficacious initial doses will increase the number of patients who achieve recommended low-density lipoprotein cholesterol (LDL-C) levels and maintain their LDL-C goals. Current studies indicate that rosuvastatin, atorvastatin and simvastatin are the most efficacious agents for lowering LDL-C and triglycerides. Compliance and persistence with statin treatment are poor and represent significant barriers to delivering mortality reductions in clinical practice. Efforts to improve concordance are necessary to ensure that treatment benefits are realised in clinical practice.

Key words: cholesterol, coronary heart disease, statins.

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Introduction

Despite the benefits of statin therapy, which have been demonstrated in large-scale clinical trials, recent secondary prevention audits show that cholesterol management remains suboptimal and that many patients treated with statins still do not achieve their recommended low-density lipoprotein cholesterol (LDL-C) goals.[1,2] In the EUROASPIRE II study, a total of 5,556 patients had their lipid levels reviewed following hospitalisation for coronary heart disease (CHD).[2] Only 61% of patients were receiving lipid-lowering therapy and, of these, 51% had total cholesterol levels below their treatment goals.[2] The Healthwise I study demonstrated that 44% of patients with CHD who had their cholesterol checked still had a total cholesterol greater than 5 mmol/L (mean cholesterol 5.9 mmol/L), while the proportion receiving statins was only 16%.[3] The Healthwise II study found that 48% of patients had their cholesterol measured, of whom 55% were taking a statin; only 53% of these had a total cholesterol below 5 mmol/L, and the mean cholesterol of patients on completion of the study was 4.8 mmol/L (± 1.1 mmol/L).[4]

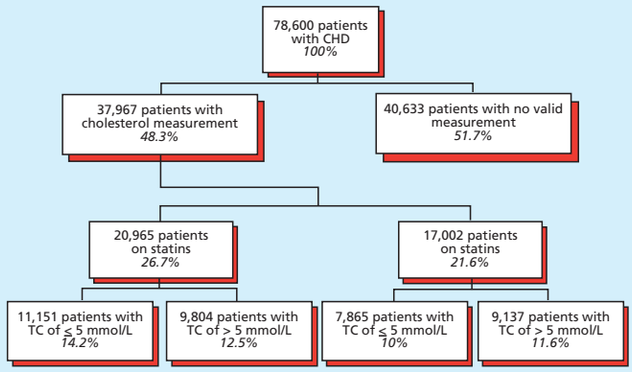
'The rule of halves applies to cholesterol management in patients with CHD'
Rubin Minhas

Valuable information can be gained from examining the largest published audit of cholesterol management in English general practice, which assessed the clinical records of 2.4 million people – approximately 4% of the UK population.[5] Among patients with CHD, the mean total cholesterol level in patients taking statins was 5.13 mmol/L, while in patients who were not taking statins the mean cholesterol level was only slightly higher, at 5.27 mmol/L. The study found that the 'rule of halves' applies to cholesterol management in patients with CHD – half had a record of cholesterol measurement, only half of these were receiving a statin, and only half of these had reached their cholesterol goal (figure 1). These and other studies point to a treatment gap in the current UK lipid management of patients with CHD; many patients are under-treated and others remain untreated. Ensuring the delivery of systematic care should address lack of treatment but the reasons and remedies for under-treatment warrant further examination.

Trends in prescribing

Suboptimal lipid management may be the result of several factors, including inappropriate choice of drug, the use of inadequate doses[1,6–8] and patients not adhering to the recommended treatment. Analysis of community prescription data across England during 2002 demonstrates that 41% and 65% of prescriptions dispensed for simvastatin and atorvastatin, respectively, were for the 10 mg dosage.[9] Moreover, statin

Figure 1. Cholesterol management in patients with CHD – the rule of halves[5]



Key: LDL-C = low-density lipoprotein cholesterol; CHD = coronary heart disease; TC = total cholesterol

dosages of 20 mg or below represented 85% of all prescriptions for simvastatin and 90% of all those for atorvastatin, suggesting that use of inadequate doses of statins may play a significant role in suboptimal lipid management in the UK.

General practitioners (GPs) must ensure delivery of their National Service Framework (NSF) targets and the recent new General Medical Service (GMS) contract also outlines a wide range of 'quality markers' with respect to service delivery, including measurement of the numbers of patients with CHD who have total cholesterol below 5.0 mmol/L. As raised plasma cholesterol (> 5.2 mmol/L) is reported to be a factor in 46% of patients with CHD,[10] the GMS contract could compound the treatment gap through being sensitive only to the prevalence of elevated cholesterol levels in CHD patients rather than focusing on the prevalence of treatment.

The identification of a treatment gap with an under-treatment component requires a reappraisal of existing lipid management policies in light of observed patterns of prescribing behaviour and current data on clinical efficacy. LDL-C is currently the primary target for treatment, although statins can also modify other components of the lipid profile such as high-density lipoprotein cholesterol (HDL-C) and triglycerides.[11] Low HDL-C and elevated triglycerides are common abnormalities (even in the absence of raised LDL-C)[12] and, as with LDL-C, the extent of the improvement is statin- and dose-dependent.[13,14]

Current statins: effect on LDL-C

A direct comparison of the lipid-modifying effects of five statins, the CURVES study,[15] was an eight-week multicentre, randomised, parallel-group study. The trial evaluated the dose efficacy of atorvastatin 10–80 mg compared with simvastatin 10–40 mg, pravastatin 10–40 mg, lovastatin 20–80 mg and fluvastatin 20–40 mg among 534 hypercholesterolaemic patients aged 18–80 years who had LDL-C concentrations ≥ 4.2 mmol/L and triglyceride concentrations ≤ 4.5 mmol/L. Atorvastatin produced significantly greater reductions in LDL-C than milligram-equivalent doses of the other statins tested, and atorvastatin 10 mg produced LDL-C reductions greater than simvastatin 10 mg, pravastatin 10 and 20 mg, lovastatin 20 and 40 mg, and fluvastatin 20 and 40 mg.[15] However, dose-to-dose comparisons were not prospectively planned or corrected for multiple comparisons and the study contained disproportionate sample sizes by drug and dosage level.

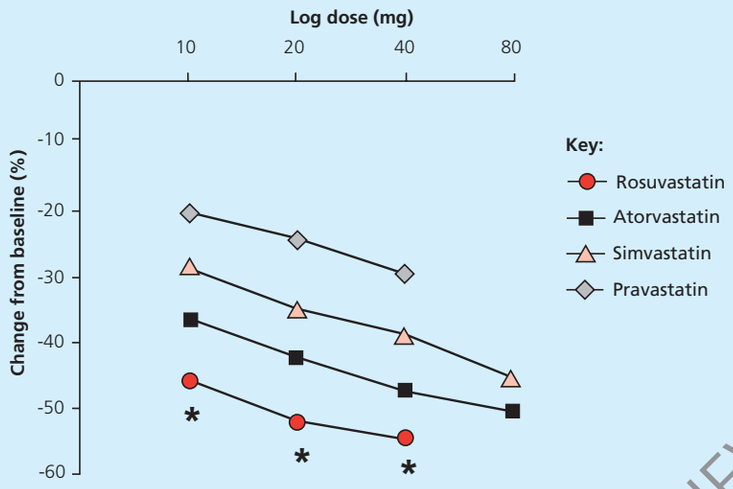
In the larger Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS), the effects of five statins over a 54-week period were compared in 3,916 patients with hypercholesterolaemia.[16] At the lowest recommended doses, atorvastatin produced the greatest reduction in LDL-C after six weeks, then simvastatin and lovastatin; pravastatin and fluvastatin produced similar reductions, which were smaller than that obtained with lovastatin. Since all patients were treated initially with the lowest recommended dose for each statin, dose-to-dose comparisons between statins across their dose ranges were not possible.

The STELLAR (Statin Therapies for Elevated Lipid Levels compared Across dose ranges to Rosuvastatin) study[17] was a six-week, open label, parallel group, multi-centre trial in which rosuvastatin was compared across recommended dose ranges with the three most widely prescribed statins, atorvastatin, simvastatin and pravastatin. A total of 2,431 adults with LDL-C levels ≥ 4.2 mmol/L and < 6.5 mmol/L and triglyceride levels < 4.5 mmol/L were studied. Rosuvastatin 10 mg was shown to be significantly more effective at reducing LDL-C than atorvastatin 10 mg, simvastatin 10–40 mg and pravastatin 10–40 mg (figure 2),[18] while maximal doses of atorvastatin (80 mg) and rosuvastatin (40 mg) produced statistically similar LDL-C reductions of 55% and 51%, respectively.

Current statins: effect on HDL-C

Low HDL-C levels are recognised to be a marker for increased coronary risk,[11,19] although European and British guidelines do not yet specify HDL-C as a target for treatment. Niacin and fibrates are the most effective drugs available at increasing HDL-C levels but they produce only modest LDL-C lowering[20] and the incidence of troublesome side effects can limit their usefulness although newer formulations offer improved tolerability. Statins have moderately beneficial effects on HDL-C levels but they differ in their ability to modify

Figure 2. Percentage change from baseline in LDL-C across dose ranges for, atorvastatin, pravastatin, rosuvastatin and simvastatin[17]



*p<0.001 versus mg-equivalent doses (p values <0.002 are statistically significant)

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this component of the lipid profile and a predictable dose-response relationship is not consistently observed.[20]

In the CURVES study, maximal effects on HDL-C for each statin were + 5.5% (atorvastatin 10 mg), + 9.6% (simvastatin 40 mg), + 9.9% (pravastatin 10 mg), + 8.0% (lovastatin 80 mg), and + 0.9% (fluvastatin 20 mg). In this study, atorvastatin produced greater reductions in LDL-C than the other statins whereas increases in HDL-C levels were greater with most of the other statins tested. Increasing doses of atorvastatin were associated with progressively smaller increases in HDL-C, indicating a negative dose response. Effects on HDL-C were not significantly different between atorvastatin and the other statins at milligram-equivalent doses except at the 40 mg dose, when simvastatin produced greater elevations in HDL-C than atorvastatin.[15]

The ACCESS investigators reported increases in HDL-C of 4–6% in all treatment groups after six weeks of therapy with the lowest recommended dose of the statins investigated.[16] The mean increase was significantly greater in the atorvastatin 10 mg and simvastatin 10 mg groups than in the pravastatin 10 mg or fluvastatin 20 mg groups.

In the STELLAR study, rosuvastatin 10–40 mg increased HDL-C by 7.6–9.6%, compared with 2.1–5.7% for atorvastatin 10–80 mg, 5.2–6.8% for simvastatin 10–80 mg, and 3.3–5.5% for pravastatin 10–40 mg, again, increasing doses of atorvastatin produced progressively smaller increases in HDL-C levels.[17]

Current statins: effect on triglycerides

The ability of statins to lower triglyceride levels has received greater attention as evidence accumulates that serum triglycerides may be an independent risk factor for CHD.[21,22] Trial data indicate that statin therapy decreases triglycerides to a greater extent in patients with elevated levels than in those with lower levels.[22] The ability of a statin to lower triglycerides appears to be related to its LDL-lowering potency.[22]

The CURVES study[15] was not powered to detect differences in effects on triglycerides and statistically greater reductions in triglycerides were only observed with 40 mg atorvastatin. Atorvastatin was the most effective statin at reducing triglyceride levels in ACCESS, with an 18% decrease after six weeks of treatment with the 10 mg dose.[16] In the STELLAR study, rosuvastatin reduced triglyceride levels to a greater extent than simvastatin or pravastatin across the dose range studied but similar reductions in triglycerides were observed with both rosuvastatin 10–40 mg (20–26%) and atorvastatin 10–80 mg (20–28%).[16]

From evidence to practice

The primary aim of treatment with statins is to reduce LDL-C to levels advocated in evidence-based guidelines.[11,23] Several studies have assessed the ability of statin therapy to help patients achieve guideline LDL-C levels, and have demonstrated that more efficacious statins enable more patients to achieve their goals.[24–26] Rosuvastatin, atorvastatin and then simvastatin are the most efficacious agents for lowering LDL-C at usual starting doses although lipid-lowering efficacy does not appear to be significantly different between rosuvastatin and atorvastatin at maximal doses. Rosuvastatin and simvastatin also appear to provide the greatest improvements in HDL-C, while the effect of statins on triglyceride levels is related to their efficacy for lowering LDL-C. In addition to examining known differences in efficacy, clinicians must always ensure that primary importance is attached to drug safety considerations in addition to clinical and cost effectiveness data when selecting the appropriate therapy.

Although a population approach to lipid management in patients with CHD is not current practice, a number of studies have found that most patients who begin treatment with a statin remain at the initial dose,[6-8] a finding reflected by prescription cost analysis data. In practice, clinicians may fail to increase doses after initiating therapy and patients may also be lost to follow-up when attempts are made to reassess treatment. Consequently lipid management strategies that reduce the need for dose titrations offer considerable advantages.

From HPS to A–Z

The Heart Protection Study (HPS), in which more than 20,000 high-risk individuals were treated with simvastatin,[27] has been an important influence on clinical practice. On the basis of this study, there is an increasing trend among clinicians to adopt a starting dose for simvastatin of 40 mg, thus removing the need for initial dose titration and ensuring greater efficacy at initial statin dose. The HPS study design included an eight-week pre-randomisation run-in period that could have affected the eventual estimation of drug tolerability. However, the tolerability profile of a 40 mg dose of simvastatin has also been extensively demonstrated in long-term clinical trials[28,29] and through 11 years of worldwide post-marketing surveillance experience.

The recent A-Z study[30] provides further welcome short-term safety and tolerability data for patients who were titrated immediately onto 40 mg simvastatin for one month (before the dose was increased to 80 mg simvastatin). No cases of myopathy were reported among the patients who were titrated immediately onto 40 mg simvastatin but nine cases of myopathy were detected in patients subsequently receiving simvastatin 80 mg. There were three cases of rhabdomyolysis reported in patients receiving 80 mg simvastatin and this was consistent with the data obtained from larger studies such as HPS[27] and 4S.[28]

Hence assuming acceptability of a 40 mg dose of simvastatin, data from the STELLAR study demonstrate that rosuvastatin 10 mg (79%), simvastatin 40 mg (63%) and atorvastatin 10 mg (52%) are the most effective initial doses for reducing cholesterol below European targets.[31]

In the US, the Food and Drug Administration has approved the use of simvastatin 40 mg/day as a starting dose in patients who require large reductions (> 45%) in LDL-C concentrations. The publication of data from studies such as NASDAC (New Atorvastatin Starting Doses: A Comparison) may further highlight the potential advantages of starting patients on higher initial doses of statins.

Recent reports of rhabdomyolysis occurring in patients who were titrated to doses of rosuvastatin which are higher than recommended for this drug reinforce the importance of acknowledging evidence of safety prior to selecting starting doses of statin therapy.

Key messages

- There remains a significant treatment gap in the current lipid management of patients with CHD, despite the existence of effective therapies
- The majority of patients who are prescribed statins are taking low-dose statins
- Implementation of lipid-lowering strategies that reduce the need for dose titrations and use of higher initial doses of statin will help to reduce the treatment gap
- Improvements in concordance, compliance and persistence are necessary to help to bridge the treatment gap

Cost implications

The 78% increase in the prescribing of statins since the publication of the NSF for CHD, together with the increasing number of patients who are eligible for statin therapy, has resulted in a dramatic rise in the cost of statin therapy to the NHS. This highlights an urgent need for an appraisal of cost-effective lipid management strategies – the National Institute for Clinical Excellence (NICE) is expected to publish national guidance in April 2005.

> ***'Poor adherence to statin treatment occurs in practice'***

Several studies have demonstrated that the most efficacious statins are the most cost-effective in terms of patients achieving their recommended LDL-C goals.[31,32] Use of more efficacious doses may result in cost savings through fewer GP visits and a reduction in laboratory costs. In ACCESS, the extent of LDL-C reduction at the initial dose of statin treatment correlated strongly with the proportion of patients who maintained LDL-C goals,[16] suggesting that a greater margin between recommended LDL-C goal and the achieved LDL-C concentration enhances the likelihood of maintaining LDL-C below target levels. The long-term nature of preventative care means that analysis of cost savings is sensitive to changes in future drug acquisition costs – an important consideration given the availability of generic simvastatin.

Persistence in practice

Bridging the treatment gap requires more than just an increase in the prescribing of statins and a reduction in dose titration steps that minimise the risk of a loss of continuity of care.

Despite adherence rates of 80–90% reported in the large statin trials, the observation that poor adherence to statin treatment occurs in practice is supported by reports that, in real life, persistence falls to around 50% after six months and 30–40% after one year.[33] Studies in elderly patients have reported five-year persistence rates of only 25%, regardless of whether patients paid for treatment.[34] Analysis of these data has led to the identification of independent predictors of poor long-term compliance that include non-white race, lower income, older age, less cardiovascular morbidity at initiation of treatment, depression, dementia and occurrence of CHD events after starting treatment.[34]

One of the underlying reasons for poor persistence is likely to be a lack of concordance between patients and prescribers regarding the importance of treatment. In an era that is increasingly characterised by target-driven activity, the challenge for primary care is to ensure the delivery of CHD care in addition to treatment so that concordance, satisfactory compliance and persistence are achieved. Unless these issues are also addressed, the current goals and targets may seem elusive and the mortality reductions seen in clinical trials will remain theoretical.

Conflict of interest

None declared.

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