NICE guidance on statins: Implications for primary care

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Article points

1. Updated National Institute for Health and Clinical Excellence (NICE) guidance on cardiovascular disease (CVD) prevention supports aggressive cholesterol management in high-risk patients.
2. This group includes the vast majority of people with diabetes.
3. The NICE guidance highlights the lack of validated CVD risk calculators for people with diabetes, older people and members of ethnic minorities, and recommends individual assessment of every case.
4. Lowering of the threshold for statin therapy to a 10-year CVD risk of ≥20% significantly increases the number of eligible patients in primary care.
5. There is no payment under the Quality and Outcomes Framework for statin use in primary prevention.

Key words

- Cholesterol targets
- Statins
- NICE guidance

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The NICE guidance on statin use in the prevention of cardiovascular disease (CVD; NICE, 2006) has now been published, within 2 months of publication of the second version of the well-respected Joint British Societies' guidelines (JBS 2, 2005). Together, these two guidelines not only set out best practice for prescribing of statins in today's NHS, but also provide a framework for determining cost-effectiveness and funding. Both follow the trend of ever-lowering targets for both total cholesterol and low-density lipoprotein-cholesterol in primary and secondary prevention of CVD. These guidelines have major implications for people with diabetes – one of the highest risk groups for CVD.

It is probably hard for the average primary care professional to imagine life without statins; yet it was less than 12 years ago that the Scandinavian Simvastatin Survival Study (4S), the first really major study of the effect of statins on cardiovascular mortality and morbidity, was published (4S Group, 1994).

Simvastatin, the statin concerned, is now off patent and one of the most commonly prescribed drugs in the country; since 2004 it has even been available without presciption for primary prevention of cardiovascular disease (CVD) in patients with a moderate coronary heart disease (CHD) risk (10-year CHD risk of 15–30%). Under the National Service Framework (NSF) for CHD, these patients were not eligible for statins on prescription (Department of Health [DoH], 2000).

The NSF for CHD recommended statins (in addition to lifestyle measures) for all patients requiring secondary prevention of CHD, and for primary prevention in those with a very high (>30%) 10-year risk of CHD (*Table 1*). Even at this stage, it was recognised that people with type 2 diabetes were at greatly increased risk of CVD events, and that their prognosis following a CVD event was worse than that for people who did not have diabetes (DoH, 2001).

Cholesterol: Moving targets

How have national recommendations for cholesterol targets changed over the years? The trend, outlined in *Table 2*, is clear – ever downward, with little or no sign of slowing its descent. The rapid change is based on a huge volume of emerging evidence which shows that, in both primary and secondary prevention, there is a linear correlation between low-density lipoprotein (LDL)-cholesterol levels and CVD morbidity and mortality (*Figure 1*; Ballantyne, 1998).

In 1998, both the European Atherosclerosis Society (EAS) and the first Joint British Societies' (JBS's) guidelines (Wood et al, 1998) recommended a total cholesterol target of <5 mmol/l, and an LDL-cholesterol target of

Table 1. Recommendations for statin use under the National Service Framework for coronary heart disease (Department of Health, 2000).

- **Secondary prevention** for patients with manifestation of an atherosclerotic event:
  - myocardial infarction
  - angina
  - coronary revascularisation
  - stroke
  - transient ischaemic attack
  - peripheral arterial disease
- **Primary prevention** in patients with 10-year coronary heart disease risk >30%

<3 mmol/l, for broadly similar groups to those outlined in *Table 1*.

By 2000, the NSF for CHD (DoH, 2000) had adopted the same figures, and the same target population, but stipulated that total cholesterol must be reduced to <5 mmol/l or by 25%, whichever reduction was the greater. Likewise, the LDL-cholesterol target remained at <3 mmol/l, but with the proviso that LDL-cholesterol must be reduced to this level or by 30%, whichever reduction was the greater. This ensured that patients with features of the metabolic syndrome (see *Table 3* for the International Diabetes Federation's 2005 definition) were not undertreated. These patients are at greatly increased risk of CVD events despite having fairly normal total and LDL-cholesterol levels (partly because of their low levels of cardioprotective high-density lipoprotein (HDL)-cholesterol).

In 2003, the EAS updated its guidance, lowering the recommended limits to <4.5 mmol/l for total cholesterol and <2.5 mmol/l for LDL-cholesterol (De Backer et al, 2003). Importantly, however, the EAS also recommended for the first time that people with type 2 diabetes should be treated as CHD risk equivalents – a concept now enshrined in cardiovascular risk assessment.

In the past 2 years, both the British Hypertension Society (BHS; Williams et al, 2004) and the JBS (British Cardiac Society et al, 2005; JBS 2) have issued updated guidelines. In both cases, the recommended target for total cholesterol has been further lowered to <4 mmol/l, and for LDL-cholesterol to <2 mmol/l.

The groups recommended for targeting in the JBS 2 guidelines are given in *Table 4*. Of particular relevance to the treatment of diabetes in primary care are the following recommendations.

1 All people aged 40 or older with diabetes should be treated with cholesterol-reducing medication to targets of <4 mmol/l for total cholesterol and <2 mmol/l for LDL-cholesterol.

2 All people aged between 18 and 39 with diabetes and at least one other risk factor (treated hypertension, retinopathy, nephropathy, metabolic syndrome or high-risk family history) should be treated to the same targets as people with diabetes aged 40 or older.

Page points

1. The European Atherosclerosis Society recommended for the first time that people with type 2 diabetes should be treated as coronary heart disease risk equivalents.
2. In the past 2 years, both the British Hypertension Society and the Joint British Societies have issued updated guidelines.
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Table 2. Changes in recommended cholesterol targets between 1998 and 2005.

Guideline	Year published	LDL-cholesterol target (mmol/l)	Total cholesterol target (mmol/l)
JBS 1/EAS-1	1998	<3.0	<5.0
NSF for CHD	2000	<3.0 or 30% reduction	<5.0 or 25% reduction
EAS-2	2003	<2.5 in high risk	<4.5 in high risk
New GMS contract	2004	N/A	<5.0
BHS-IV	2004	<2.0 in high risk	<4.0 in high risk
JBS 2	2005	<2.0 in high risk	<4.0 in high risk

BHS, British Heart Society; EAS, European Atherosclerosis Society; JBS, Joint British Societies; GMS, General Medical Services; LDL, low-density lipoprotein; NSF for CHD, National Service Framework for coronary heart disease.

Page points

1. In January 2006, the National Institute for Health and Clinical Excellence (NICE; formerly the National Institute for Clinical Excellence) guidance on statin use was launched.
2. Perhaps the major cost and workload implication of the NICE guidance is the recommendation that, as under the the updated Joint British Societies' guidelines, in addition to all patients with existing evidence of cardiovascular disease (CVD), patients with a 10-year CVD risk ≥20 % should be treated with statins.
3. The guidance stops short of recommending that all patients with diabetes receive statins, but it does highlight the lack of validated risk calculators for patients with diabetes.
4. One of the major implications of the NICE guidance on statins is the increased number of eligible patients.

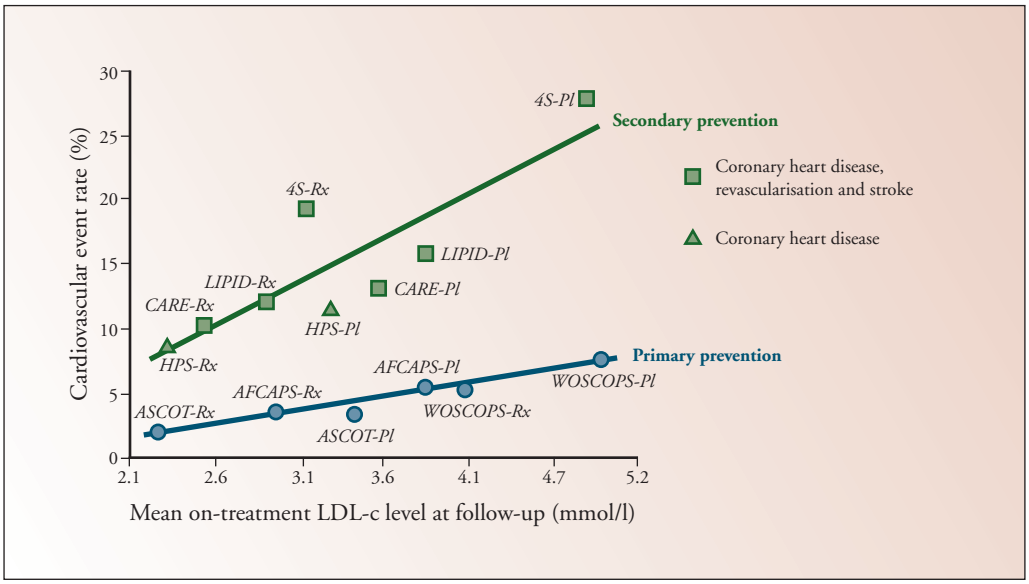

Figure 1. Relationship between cardiovascular event rate and low-density lipoprotein-cholesterol level (adapted from Ballantyne, 1998). 4S, Scandinavian Simvastatin Survival Study; AFCAPS, Air Force/ Texas Coronary Atherosclerosis Prevention Study; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CARE, Cholesterol And Recurrent Events study; HPS, Heart Protection Study; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease; Pl, placebo arm; Rx, treatment arm; WOSCOPS, West Of Scotland COronary Prevention Study.

3 Patients with an HDL-to-total cholesterol ratio of ≥6 should be considered high risk. This lipid profile is particularly common in patients with metabolic syndrome (*Table 3*).

NICE guidance

In January 2006, the National Institute for Health and Clinical Excellence (NICE; formerly the National Institute for Clinical Excellence) guidance on statin use was launched (NICE, 2006; *Table 5*). This latest Technology Appraisal is of major significance for prescribing – not least because, as of 1 January 2006, primary care organisations have been required to prove that they have set aside the funding necessary to implement Technology Appraisals.

Perhaps the major cost and workload implication of the NICE guidance is the recommendation that, as under the JBS 2 guidelines, in addition to all patients with existing evidence of CVD, patients with a 10-year CVD risk ≥20 % should be treated with statins. The guidance stops short of recommending that all patients with diabetes receive statins, but it does highlight the lack of validated risk calculators for patients with diabetes, and recommends that each patient's case should be considered individually.

Table 3. International Diabetes Federation criteria for metabolic syndrome (IDF, 2005).

- Central obesity (defined based on ethnic group)
- Together with at least two of the following:
  - raised triglyceride levels (≥1.7 mmol/l) or treatment for this
  - reduced high-density lipoprotein-cholesterol (<1.03 mmol/l in males and <1.29 mmol/l in females) or treatment for this
  - raised blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg) or treatment of previously diagnosed hypertension
  - raised fasting plasma glucose (≥5.6 mmol/l) or previously diagnosed type 2 diabetes.

Implementing the NICE guidance

One of the major implications of the NICE guidance on statins is the increased number of eligible patients: it is estimated that under these guidelines, 3.3 million patients will be eligible for statin therapy. For statin use in primary prevention, there is no payment under the Quality and Outcomes Framework (QOF), but publication of the NICE guidance should

Table 4. Summary of the JBS 2 recommendations (British Cardiac Society et al, 2005).

- Consider risk in terms of 10-year risk of cardiovascular disease (CVD) rather than coronary heart disease (CHD).
- Consider opportunistic screening of all adults aged 40–80 years.
- Screen patients under 40 with a family history of premature atherosclerotic disease (cardiovascular event in a first-degree male family relative under 55 years, or a first-degree female relative under 60 years).
- All screening lipid profiles should include an assessment of high-density lipoprotein cholesterol.
- The total cholesterol target is <4 mmol/l.
- The low-density lipoprotein-cholesterol target <2 mmol/l.
- Statin therapy should be initiated immediately following a cardiovascular event.
- Measure the full lipid profile of all patients on cholesterol-lowering medication at least annually.

The following groups of patients should be treated

- All patients with manifestation of an atherosclerotic event:
  - myocardial infarction
  - angina
  - coronary revascularisation
  - stroke
  - transient ischaemic attack
  - peripheral arterial disease
- All patients with a 10-year CVD risk ≥20% (a 10-year CHD risk of approximately 15%)
- All patients aged 40 or older with diabetes
- All patients aged between 18 and 39 with diabetes and at least one other risk factor, including:
  - treated hypertension
  - retinopathy
  - nephropathy
  - features of the metabolic syndrome
  - high-risk family history

Page points

1. Most patients with a history of cardiovascular disease or diabetes should already be on a statin.
2. The Quality and Outcomes Framework payment for cholesterol reduction in these patients combined with highlighting of their risks in both the National Institute for Health and Clinical Excellence (NICE) guidance and the updated Joint British Societies' guidelines should help to ensure maximal coverage.
3. The NICE guidance recommends that therapy should be initiated with a drug at lowest acquisition cost, which for statins is simvastatin.

ensure that resources to cover the cost of statin therapy for this group are made available.

Most patients with a history of CVD or diabetes should already be on a statin, but the combined stimuli of QOF payment for cholesterol reduction in these patients and the highlighting of their risks under both the NICE guidance and the JBS 2 guidelines should offer an additional incentive for audit to ensure maximal coverage.

Which statin when?

The NICE guidance does not give a target for total cholesterol or LDL-cholesterol level, but the JBS 2 guidance provides persuasive evidence for a target of <4 mmol/l for total cholesterol and <2 mmol/l for LDL-cholesterol. The NICE guidance recommends that therapy should be initiated with a drug at lowest acquisition cost, which for statins is simvastatin (NICE, 2006).

Simvastatin is licensed at a starting dose of up to 40 mg nocte, and a maximum dose of 80 mg nocte. However, side effects, including myopathy and deranged liver function tests, increase significantly between doses of 40 mg and 80 mg (Brewer, 2003); also, as with all statins, doubling the dose accrues only approximately an extra 6% LDL-cholesterol reduction (Law et al, 2003). In addition, the relatively flat pricing structure for generic simvastatin 10–40 mg does not apply to the 80 mg dose; thus, an 80 mg dose represents

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Scandinavian Simvastatin Survival Study Group (1994) Randomised trial of cholesterol lowering in 4,444 patients with CHD. *Lancet* **344**: 1383–9

Williams B, Poulter NR, Brown MJ et al (2004) British Hypertension Society guidelines. *Journal of Human Hypertension* **18**: 139–85

Wood A, Durrington P, Poulter N et al (1998) Joint British recommendations on prevention of coronary heart disease in clinical practice. *Heart* **80**: S1–29

Table 5. Key recommendations of the National Institute for Health and Clinical Excellence (2006) guidance on statins.

- Consider risk in terms of 10-year risk of cardiovascular disease (CVD) rather than coronary heart disease (CHD).
- Treat all patients with a history of an atherosclerotic event, and all patients with a 10-year CVD risk ≥20 % (a 10-year CHD risk of approximately 15 %).
- Statins should be included as part of general CVD prevention strategy.
- Statin therapy should be initiated with the drug with the lowest acquisition cost.
- If there is clinical justification for selecting another drug (such as failure to reach target cholesterol levels), the most cost-effective drug should be initiated.
- All statins exhibit a similar tolerability profile.
- Local audit is essential.
- Be aware that there are no validated risk calculators for patients in the following categories (CVD risk should be estimated using clinical assessment in these patients):
  – people with diabetes
  – older people (over 70 years)
  – people from an ethnic background (particularly South Asian).

significant increased cost and incidence of side effects with relatively little gain, compared with the 40 mg dose. Some clinicians may therefore consider that simvastatin should be used at a maximum dose of 40 mg. At this level, simvastatin will reduce LDL-cholesterol by approximately 37 % (Law et al, 2003) – not enough to reach target if the pretreatment LDL-cholesterol is >2.8 mmol/l.

Switching statins

So, which statin should be used if simvastatin is not adequate? The NICE guidance recommends that if there is clinical justification for selecting another drug (such as failure to reach target cholesterol levels), then the most cost-effective drug should be initiated.

Rosuvastatin is the most effective of the statins at reducing LDL-cholesterol (Law et al, 2003) and does so at the same cost as atorvastatin; it is therefore the most cost-effective (Joint Formulary Committee, 2005). Indeed, the NICE (2006) guidance states that:

> *'The Assessment Group's surrogate endpoint analysis, used to assess the cost-effectiveness of rosuvastatin in primary CHD prevention, generated lower cost per [quality-adjusted life year] estimates compared with the base case results.'*

The NICE guidance confirms that all statins exhibit a similar tolerability profile.

Conclusion

The NICE guidance on statins, and the JBS 2 guidelines on prevention of CVD, have far-reaching implications for prescribing in primary care. They use a persuasive evidence base to validate the ever-increasing emphasis on aggressive cholesterol management in high-risk patients.

The NICE guidance highlights the lack of validated risk calculators for patients with diabetes, and recommends individual assessment of the CVD risk of every person with the disease (as well as of older people and members of ethnic minorities). The JBS 2 guidance recommends cholesterol-lowering medication for the vast majority of patients with diabetes. In addition, the lowering of the threshold for statin therapy to a 10-year CVD risk of ≥20 % will significantly increase the number of eligible patients in primary care. ■

Conflict of interest
Sarah Jarvis has received honoraria for lecturing for, and sitting on advisory boards for, AstraZeneca and Sanofi-Aventis.