

# DRUG UPDATE

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## WHICH STATIN?

There is considerable evidence that statins reduce cardiovascular events in people at increased risk of cardiovascular disease. This reduction in cardiovascular events appears linearly related to the achieved reduction in LDL cholesterol. Because of its low cost and the wealth of data indicating clinical effectiveness and safety, simvastatin, in a starting dose of 40 mg daily, is a rational and cost-effective first choice. Pravastatin is a useful but less potent alternative for patients at risk of drug interactions. More potent statins such as atorvastatin should be reserved for patients who fail to meet treatment targets on first-line therapy.

### What are they?

Statins inhibit cholesterol synthesis by blocking HMG CoA reductase. Currently, five statins are licensed in the UK for prevention of coronary heart disease (CHD) and/or treatment of hyperlipidaemia: simvastatin, atorvastatin, fluvastatin, pravastatin and rosuvastatin. The patents for simvastatin and pravastatin have already expired and those for fluvastatin and atorvastatin are expected to expire in August 2008 and November 2011 respectively.<sup>1</sup> This is particularly important considering the numbers of people who might benefit from these agents.

### Effects on plasma lipids

At present the evidence suggests that the statins' beneficial effects are mediated through lowering low density lipoprotein (LDL) cholesterol. A recent meta-analysis of 14 randomised trials (n=90,056) showed that statin therapy reduces the 5-year incidence of major coronary events, coronary revascularisation and stroke by one fifth per mmol/L reduction in LDL cholesterol.<sup>2</sup> The relationship between the absolute reductions in LDL cholesterol and the proportional reductions in the incidence of cardiovascular events is linear.<sup>2</sup> Small differences in effects on plasma high density lipoprotein (HDL) cholesterol and triglycerides (TGs) have been reported,<sup>3</sup> but there is currently no convincing evidence that these differences affect clinical outcomes over and above that associated with the reduction in LDL cholesterol. There is evidence that long-term simvastatin and atorvastatin induce plaque stability and regression, but these are surrogate endpoints and of uncertain clinical significance.<sup>4,5</sup>

### Current risk thresholds and targets

The National Service Framework for CHD states that patients with clinical evidence of CHD, occlusive arterial disease and a 10-year risk of a CHD event of greater than 30% should be considered for treatment with a statin (target serum cholesterol <5 mmol/L).<sup>6</sup> A consultative document from the National Institute for Clinical Excellence (NICE) suggests reducing this threshold to a 10-year cardiovascular disease (CVD) risk of  $\geq 20\%$  (which equates to a 10-year CHD risk of  $\geq 15\%$ ).<sup>7</sup> The Joint British Societies have recently revised their guidelines suggesting optimal targets of total cholesterol <4 mmol/L and LDL cholesterol <2 mmol/L.<sup>8</sup> Evidence from the Treating to New Targets study suggests that additional benefit may be gained by treating patients with clinically evident stable CHD more aggressively.<sup>9</sup> In this study, a high daily dose of atorvastatin (80 mg) was more effective at preventing cardiovascular events than a low dose (10 mg) in 10,001 patients with clinically evident CHD. However, there was no difference in overall mortality.

### Drug interactions

Simvastatin, fluvastatin and possibly rosuvastatin increase, whereas atorvastatin may reduce, the anticoagulant effect of warfarin.<sup>10</sup> This can often be managed by careful monitoring of the international normalised ratio (INR) during initiation of statins and any subsequent dose changes. Concurrent therapy of drugs that are potent inhibitors of cytochrome P450 (CYP3A4) with simvastatin or atorvastatin may increase the risk of dose-related side effects, including rhabdomyolysis.<sup>11</sup> The risk of serious myopathy is also increased when high doses of simvastatin are combined with less potent inhibitors of CYP3A4, including amiodarone, verapamil and diltiazem.<sup>11</sup> Grapefruit juice should be avoided when taking simvastatin.<sup>11</sup> Fluvastatin is metabolised by a different cytochrome P450 enzyme (CYP2C9), while pravastatin and rosuvastatin are not substantially metabolised by cytochrome P450,<sup>11</sup> and are not expected to be subject to these interactions.

### Choice of statin

#### Simvastatin

The UK-based Heart Protection Study (HPS) (n=20,536) confirmed that simvastatin 40 mg daily is a safe and effective first-choice statin, with benefit demonstrated in people with or at high risk of CVD, including the elderly (up to the age of 80 years at enrolment), women and diabetics.<sup>12</sup> It is the cheapest statin currently available and has been evaluated in many other clinical studies.

Where patients taking simvastatin 40 mg at night fail to achieve total cholesterol  $\leq 5$  mmol/L, 80 mg can be considered, but this dose is only recommended in patients with severe hypercholesterolaemia and high risk cardiovascular complications, as the risk of rhabdomyolysis and myopathy is increased.<sup>13</sup>

#### Atorvastatin

If simvastatin is either not tolerated or ineffective, further cholesterol lowering may be achieved by switching to atorvastatin 40 mg and then if necessary increasing the dose to 80 mg. Average cholesterol lowering with atorvastatin 40 mg daily is greater than with simvastatin 40 mg daily.<sup>14</sup> However, this approach is substantially more expensive. The recent IDEAL study compared atorvastatin 80 mg/day with simvastatin 20 - 40 mg/day in 8,888 patients with previous myocardial infarction (MI).<sup>15</sup> It failed to demonstrate a difference in the primary end point (incidence of major coronary events). Differences in some secondary end points were documented, the clinical relevance of these is uncertain because of the low dose of simvastatin (20

mg/day in 77% of patients) used as a comparator.<sup>15</sup>

### Pravastatin

There is robust evidence of pravastatin's efficacy in primary and secondary prevention of CVD.<sup>3</sup> It is, however, less potent at lowering LDL cholesterol than simvastatin.<sup>14</sup> It may be an appropriate choice for patients at risk of drug interactions.

### Other statins

There is less clinical trial evidence of benefit with fluvastatin than simvastatin or pravastatin and no data on effects of rosuvastatin on clinical end points.<sup>1</sup> While rosuvastatin is potent, the lack of outcome and long-term safety data suggest it should be reserved for specialist use in patients with severe hyperlipidaemia who cannot be managed with other agents. It is not licensed for secondary prevention of CVD.

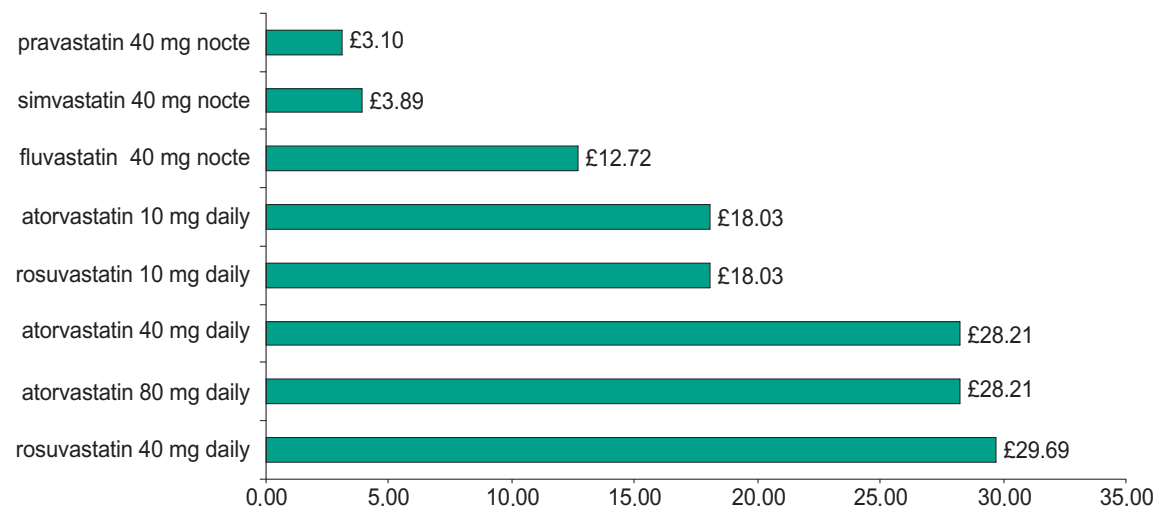
### Special patient groups

#### Mixed hyperlipidaemia

Simvastatin, atorvastatin and fluvastatin are licensed for use in mixed hyperlipidaemia. They are the treatment of choice

### How much does it cost?

Cost for 28 days' treatment (prices from Drug Tariff January 2006)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, CT - controlled trial, G - guidelines, R - review, MA - meta-analysis

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