UCLH GUIDELINES ON STATIN PRESCRIBING

Simvastatin and atorvastatin are the current main UCLH statins. Simvastatin is now off-patent whereas atorvastatin retains its patent until November 2011.

Nationally, in 2004, statins accounted for 9.1% of NHS prescription costs, and prescriptions are growing exponentially by 30% per year. Atorvastatin and simvastatin and are the number 1 and 2 drug costs in England (£360 and £251 million respectively). However simvastatin is now up to 30 times cheaper than atorvastatin. This price fall will save more than £200million in England this year, but an equivalent or larger gain is available if patients on atorvastatin 10mg or 20mg are swapped to simvastatin 40mg. For UCLH, such a change will save approximately £80,000 pa. Given that prescribing practice at UCLH influences primary care and neighbouring Trusts, substantial PCT savings could be achieved.

The new NICE guidelines (January 2006) propose statins for secondary prevention of cardiovascular disease and primary prevention for individuals with ≥20% 10 year cardiovascular risk. They also state that the statin with the lowest acquisition cost be used. Initial estimates are the guidelines make 1 in 4 of the population aged 30 to 75 eligible.

Recommendations

First line therapy:

1. Simvastatin 40mg is the first choice.
2. Patients admitted on atorvastatin 10mg and 20mg will receive and be discharged on simvastatin 40mg
3. In patients intolerant*of simvastatin 20mg or 40mg:
   Pravastatin up to 40mg is the first alternative
   Simvastatin 10mg is the second alternative
4. Atorvastatin 10mg and 20mg will not be available from pharmacy.

Intensive lipid lowering therapy:

1. Caution is required to avoid drug interactions and side-effects
2. Monotherapy strategies are atorvastatin 40mg or 80mg
3. Combination therapies (ezetimibe/fish oils/fibrates + statins) may be considered on a case by case basis.

*intolerance is typically muscle or liver related: myalgia, CK or LFTs >3x normal

FAQS:

The different statins: do they work in the same way?

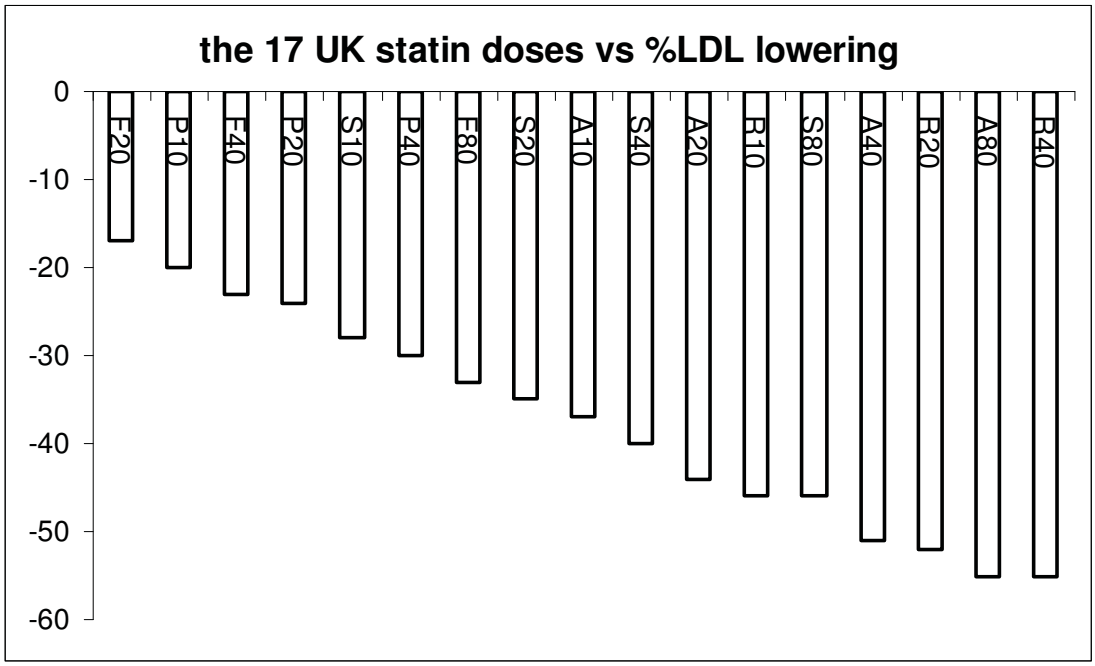
All statins work in essentially the same way. They are HMGCoA reductase inhibitors. The effects are (in order of clinical importance): to reduce LDL, increase HDL, reduce triglycerides and additional, more subtle effects, termed pleiotropic effects. Clinical trials suggest that the beneficial effects on morbidity and mortality relate to LDL lowering, but epidemiological data and fibrate studies suggests the raising HDL may also play a role. It is not clear whether statin effects on triglycerides or pleiotropic effects are clinically significant.

What is the cost and effectiveness of the statins available in England?

There are 5 statins and a total of 17 doses currently available in England, each with different doses, efficacy, costs and evidence base, but the market is dominated by simvastatin and atorvastatin.

LDL lowering:

The LDL lowering effects of the different statins/doses (from dosing studies) are below, figure 1.

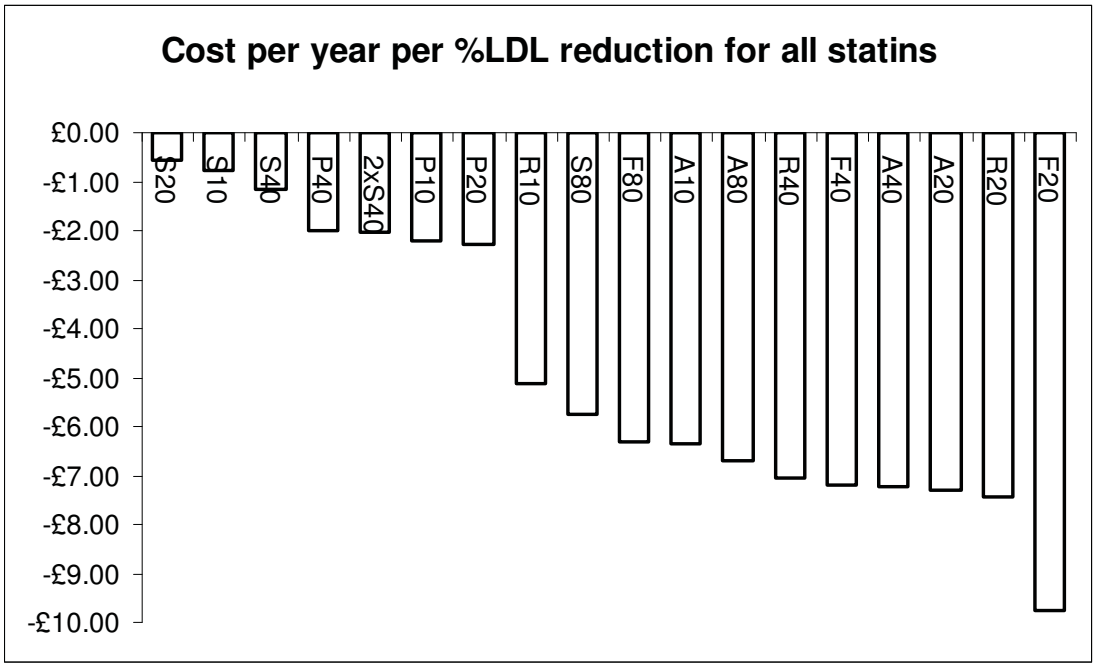


The most potent drugs are on the right hand side of this graph. (a=atorvastatin F=fluvastatin P=Pravastatin R=rosuvastatin S=simvastatin. Dose is included after the name letter).

Data sources: dosing studies including STELLAR and CURVES; PCA cost data (correct august 2005) http://www.ppa.org.uk/ppa/edt_intro.htm

Cost per %LDL reduction:

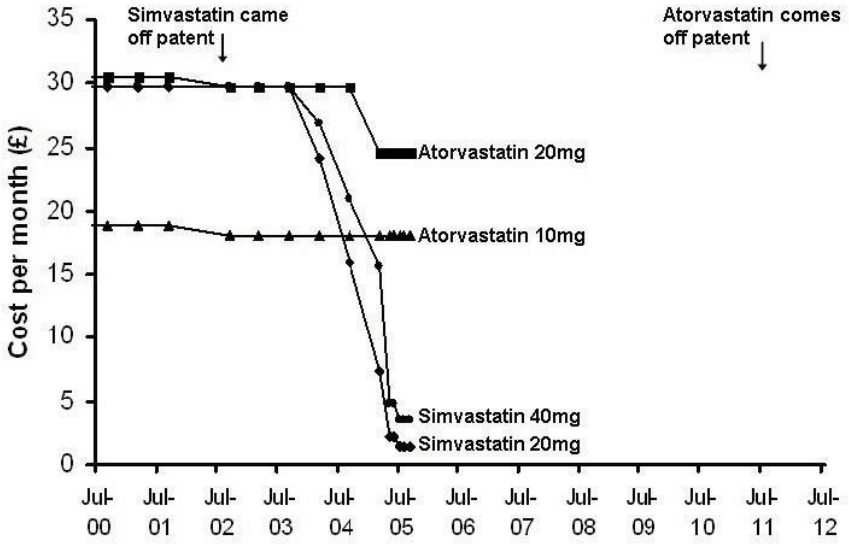
If the cost in incorporated, the graph is shown in figure 2: One additional column has been incorporated: that of simvastatin 80mg taken as 2 simvastatin 40mg tablets. It should be remembered that the trust-negotiated simvastatin 40mg price would make it the cheapest drug per %LDL lowering achieved.



Ideally, the drugs for first line use should be to the right of the first graph (potency) and to the left of the second graph (cheap for potency). Simvastatin 40mg fulfils these criteria.

Is this price fall really worth focusing on?

Yes. For several reasons. The price of simvastatin really has fallen spectacularly, beyond that usually associated with a drug coming off patent. Simvastatin is easy to manufacture – it is the de-acylated fermentation product of aspergillus growth, and the global market is large. With generics and price control since 1993, the NHS price has fallen by up to 30 times. At UCLH, we have negotiated a cost for simvastatin that is several times lower again. The result is that for 1 month of atorvastatin 20mg treatment, UCLH could treat 25 patients with simvastatin 40mg. Atorvastatin is the number 1 drug cost in England, and 85% of tablets are at 10mg or 20mg. Nationally, replacing atorvastatin 10/20mg with simvastatin 40mg would, based on the 2004 spend on atorvastatin 10mg and 20mg reduce costs from £290million to £47million per year.



Price changes over the last 5 years in the cost of a months drug supply. Note the atorvastatin price stability and the patent expiry date.

Why do these guidelines split into 2 dose ranges?

Over time, clinically used statin doses have been rising, and targets are becoming more aggressive. There is a limit however: the lipid lowering effect reaches a plateau, but side-effects/drug interactions increase.

First line therapy, appropriate for most patients (technically low/intermediate dose statin monotherapy) reduces LDL by 30-40%. This strategy is in line with most national guidelines (e.g. the US ATP III guidelines), and is safe, effective and evidence based. Drugs that will effect this LDL reduction include atorvastatin ≤20mg, simvastatin 20/40mg and pravastatin 40mg.

Intensive lipid lowering therapy (high dose statin monotherapy or combination therapy), reduce LDL by up to 55% and are reserved for patients who fail to reach target, have very high initial cholesterol or progressive disease despite initial lipid lowering strategies, or following recent acute coronary syndrome.

Why not supply intensive lipid lowering therapy for everyone?

Several reasons.

1. The evidence for this approach in all-comers is promising but not clear. The 'treat to new targets' study - atorvastatin 80mg (%LDL -55%) vs. atorvastatin 10mg (%LDL -37%) reduced risk of non-fatal MI and stroke (2.1% absolute risk reduction; NNT=48 over 5 years) but not mortality. Similarly, the 'IDEAL' study - atorvastatin 80mg (%LDL -55%) compared with simvastatin 20mg (%LDL -35%) failed to reach the primary pre-specified endpoint with no mortality benefit. The prove-it TIMI 22 trial compared atorvastatin 80mg (%LDL -55) with Pravastatin 40mg (% LDL -30%). This reduced 30 day events (3.0% vs 4.2%, p=0.046), and the 6 month event rate from 13% to 9.6% (p=0.003). Our recommended statin, simvastatin 40mg (% LDL -40) is more effective than the low dose control arms employed in all three of these trials.
2. Intensive lipid lowering therapy results in higher discontinuation rates, adverse effects, more drug interactions and requires robust monitoring.
3. The incremental lipid lowering comes at significant additional cost.
4. Other measures to reduce cardiovascular risk include aspirin, and good blood pressure control, which may be more cost-effective options than using high dose statin therapy to achieve small incremental reductions in cholesterol.

LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–35.

Pedersen TR, Faergeman O, Kastelein JJ et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after MI: the IDEAL study: a randomized controlled trial. JAMA. 2005;294:2437-45.

Why simvastatin 80mg as the preferred aggressive lipid lowering high dose statin?

These guidelines take into account the balance between LDL lowering and costs hence the recommendation of simvastatin 80mg (2x40mg tablets) as first line. However, there are concerns about evidence and safety of simvastatin 80mg, so the guidelines are much less prescriptive than for first-line therapy. Most of the studies are with atorvastatin 80mg rather than simvastatin 80mg, so in this instance atorvastatin at doses of 40-80mg are options.

Is atorvastatin more potent than simvastatin?

For the same LDL lowering effect, the clinically prescribed dose of atorvastatin is a little more than 2 times lower than simvastatin, mainly because of a longer half-life. However, it is not the dose used or name of the drug that is important, but lipid effects and clinical endpoint data.

Lipid effects

From dosing studies, simvastatin 40mg lowers LDL by 3% more than atorvastatin 10mg and 4% less than atorvastatin 20mg, figure 3. However simvastatin 40mg has a larger HDL raising effect than any atorvastatin dose (10-80mg), figure 4(and 6). Atorvastatin demonstrates a negative dose response curve for HDL – higher doses of atorvastatin are progressively worse.

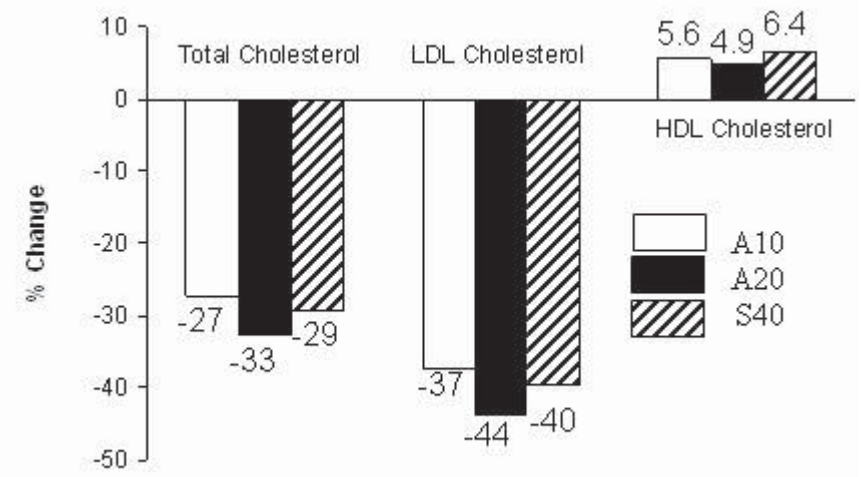


*Figure 3. Lipid effects of atorvastatin 10/20mg and simvastatin 40mg.**

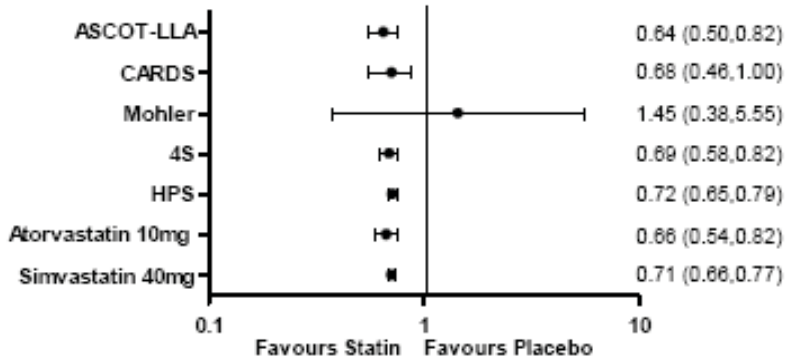
**results are from dosing studies - STELLAR and CURVES combined*

Jones P, Kafonek S, Laurora I ET AL. Comparative dose efficacy study of atorvastatin versus simvastatin, pravastatin, lovastatin, and fluvastatin in patients with hypercholesterolemia (the CURVES study) Am J Cardiol. 1998;81:582-7.

Jones PH, Davidson MH, Stein EA et al., STELLAR Study Group. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and Pravastatin across doses (STELLAR Trial). Am J Cardiol. 2003;92:152-60.*

Clinical trial data

Evidence is strong for atorvastatin 10mg (ASCOT-LLA, CARDS) and simvastatin up to 40mg (HPS, 4S) but not for atorvastatin 20mg – the only study (4D -in diabetics on haemodialysis) was negative. The one study comparing atorvastatin and simvastatin was underpowered but negative (3T). A meta-analysis of simvastatin 40mg vs atorvastatin 10mg (conducted in-house) shows no differences in mortality, CHD death or stroke.



Meta-Analysis showing CHD death/non fatal MI comparing atorvastatin 10mg and simvastatin 40mg trials (conducted in house).

Why do these guidelines give pravastatin up to 40mg and simvastatin 10mg as the alternative to simvastatin 20mg/40mg?

Pravastatin up to 40mg is a good second-line alternative because unlike atorvastatin and simvastatin, it is not metabolised via P450 CyP3A4 (so no interaction with amiodarone, macrolides,

diltiazem, verapamil, anti-retrovirals etc.). Unlike simvastatin and atorvastatin, it is hydrophilic rather than lipophilic. It has a good evidence base (WOSCOPS, LIPID and CARE), and is cheap; monthly cost: £3.41 to 4.59. The LDL lowering effect of simvastatin 10mg is substantial (%LDL reduction 28%) may be achieved without causing adverse effects.

Can simvastatin 40mg treat to target?

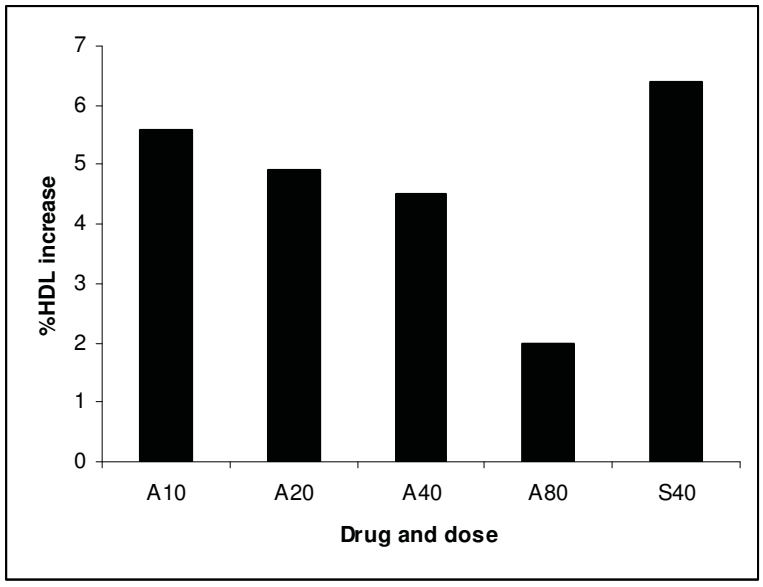
For most people, yes, but clearly there is a limit, depending on the target and initial lipids. From a lipid perspective, simvastatin 40mg is essentially going to achieve target as well as atorvastatin 10/20mg. In primary care, simvastatin is as likely as atorvastatin to reach target and compliance is similar. The American National Cholesterol Education Program update recommends using a statin for intermediate and high-risk patients which lowers LDL cholesterol by 30-40%. Simvastatin 40mg lowers LDL cholesterol by 40%. On average, current statin prescribing reduces LDL cholesterol by 37% in England (in-house data).

National Cholesterol Education Program Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 2004http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3full.pdf

Valdez CA, Ulrich H. Similar medication compliance and control of dyslipidemia with simvastatin or atorvastatin in a staff-model HMO medical clinic. J Manag Care Pharm. 2005:11:499-504.

Atorvastatin is said to increase HDL cholesterol. Is this an advantage?

This is incorrect. Simvastatin 40mg is better than any dose of atorvastatin. Atorvastatin exhibits a negative dose response curve for HDL. This is shown in dosing studies (STELLAR and CURVES combined, below), and confirmed by at least 2 other studies.



Crouse JR III, Frohlich J, Ose L et al. Effects of high doses of simvastatin and atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I. Am J Cardiol 1999;83;1476 –1477.
Kastelein JJ, Isaacsohn JL, Ose L et al. Comparison of effects of simvastatin versus atorvastatin on high-density lipoprotein cholesterol and apolipoprotein A-I levels. Am J Cardiol. 2000;86:221-3.

Doesn't atorvastatin have better evidence for patients with diabetes?

Not since the publication of the HPS study in 2003. More people were studied with diabetes in the Heart Protection Study (HPS, simvastatin 40mg, 5963 diabetic patients) than were in CARDS (atorvastatin 10mg, 2828 patients), with similar risk reductions (HPS CVD events were reduced from 13.5% (placebo) to 9.3% with simvastatin 40mg daily; CARDS 9.0% (placebo) to 5.8%).

Collins R, Armitage J, Parish S et al. Heart Protection Study Collaborative Group MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet. 2003;361:2005-16.

Colhoun HM, Betteridge DJ, Durrington PN et al.; CARDS investigators. 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.

Does atorvastatin have an advantage in renal impairment?
No. Neither atorvastatin nor simvastatin require dosage adjustment in renal impairment, unless the patient is in severe renal failure i.e. GFR < 10mls/min when a small dose of simvastatin may suffice e.g. 10mg daily. In dialysis-dependent renal failure, one study of 1255 diabetics on haemodialysis, demonstrated no effect of atorvastatin to reduce the incidence of the composite of cardiac death, nonfatal myocardial infarction, and stroke. There was an increase (2.03 [95 percent confidence interval, 1.05 to 3.93] P=0.04) in fatal strokes in individuals taking atorvastatin.

Wanner C, Krane V, Marz W, et al., German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis N Engl J Med. 2005:353:238-48.

Atorvastatin has fewer drug interactions; is this important?
Simvastatin and atorvastatin are both metabolised by CYP3A4, therefore both have the potential for the same, numerous drug-drug interactions. Most interactions will elevate the blood levels of simvastatin/atorvastatin. There are no hard data, but if a patient is already on atorvastatin 10/20mg, because of the similar metabolic pathways involved, swapping to simvastatin 40mg is unlikely to be an issue.

The SEARCH study (ongoing - data from company) has found that the incidence of myopathy with simvastatin 80mg plus amiodarone to be about 6% (versus no increased risk with a 20mg dose. The 40mg dose was not evaluated). As a result of this, the simvastatin SPC no longer recommends doses over 20mg of simvastatin for patients on amiodarone (exact mechanism of interaction unknown). In addition, due to CSM reports of myopathy for patients on simvastatin and either diltiazem or verapamil, the SPC also recommends a maximum dose of 20mg simvastatin if these agents are used concomitantly. Pfizer's (atorvastatin) review of 44 trials demonstrated no problems with concurrent amiodarone or verapamil. The company therefore have not amended their SPC with respect to any recommended dosage changes. Therefore, simvastatin can still be prescribed with these agents as long as the necessary dosage adjustments are made.

Are there differences between the drugs in their safety profile at low/intermediate dose?
For low/intermediate dose (atorvastatin 10/20mg, simvastatin 40mg), no. From trials, simvastatin and atorvastatin at moderate doses have minimal adverse effects. Adverse effects increase with dose, but it is not clear whether this is related to dose taken or lipid lowering effect. The withdrawn drug cerivastatin aside, no clinically important differences in major adverse effects have been described among available statins.

Pasternak RC, Smith SC Jr, Bairey-Merz CN et al., American College of Cardiology; American Heart Association; National Heart, Lung and Blood Institute. ACC/AHA/NHLBI clinical advisory on the use and safety of statins. J Am Coll Cardiol. 2002;40:567-72.

Atorvastatin is more likely to cause myalgia, and hepatic disturbance than is simvastatin. The incidence of serious muscle disease with both drugs at low/intermediate dose is low; in HPS, the incidence of myositis on simvastatin was 0.13% and 0.07% on placebo. In CARDS, the incidence of

myositis with atorvastatin was 0.1%. There were no reports of rhabdomyolysis (i.e. severe myositis and renal impairment). In one recent review, the incidence of rhabdomyolysis with atorvastatin and simvastatin is similar; 0.44 cases per 10,000 person years of treatment. For therapeutic substitution of simvastatin 40 for atorvastatin 10mg or 20mg, INR monitoring is advised.

Abourjaily HM, Alsheikh-Ali AA and Karas RH. Comparison of the frequency of adverse events in patients treated with atorvastatin or simvastatin. Am J Cardiol 2003;91:999-1002.
Graham DJ et al. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004; 292:2585-90.

Are there differences between the drugs in their safety profile for high dose statins?
Adverse effects increase with dose, so simvastatin 80mg should be compared with atorvastatin 40 or 80mg. The major concern is serious skeletal muscle problems including rhabdomyolysis. This led to the withdrawal of cerivastatin, which had a high incidence of rhabdomyolysis, mainly when co-prescribed with a fibrate. For high dose statins, great care is needed to avoid co-prescribing of drug that affect Cyp3A4, and that monitoring follow manufacturer guidelines. For new prescriptions of any high dose statin, careful INR monitoring advised.

There is some evidence that simvastatin 80mg is associated with a higher rate of myositis than high dose atorvastatin, but it does not yet appear clear.

Why do these guidelines not discuss fluvastatin or rosuvastatin?
Fluvastatin, even at maximal dose, is less effective at LDL lowering than either simvastatin 20/40mg or atorvastatin 10mg/20mg, and is expensive for the LDL lowering obtained.
Rosuvastatin is very effective at LDL lowering, and unlike high dose atorvastatin, raises HDL effectively. Rosuvastatin 10mg compares favourably to simvastatin 80mg (but not 2xsimvastatin 40mg) for cost per LDL lowering achieved. However, there are no clinical end-point data for rosuvastatin at present. These, together with its greater cost, mean that it is not recommended in these guidelines.

Who contributed to these guidelines?
Dr James Moon a Consultant Cardiologist; Dr Anthony Grosso a Clinical Pharmacist; and Prof Raymond MacAllister & Prof Aroon Hingorani, both Consultant Clinical Pharmacologists, drafted these guidelines which were approved by the multidisciplinary Use of Medicines Committee (Drugs and Therapeutics Committee).