Bandolier Extra

Evidence-based health care April 2004

Cholesterol and Statins

Cholesterol is an important lipid present in all cell membranes and is a precursor of steroid hormones and bile acids. In excess, it accumulates in deposits of atherosclerotic plaque on the walls of blood vessels, leading to restrictions and interruptions of the circulation that can result in angina, heart attacks, and death. Populations with low cholesterol levels have less coronary heart disease (CHD) than those with higher cholesterol levels, but individuals moving from a low level population to a high level population show increases in their cholesterol levels and rates of CHD.

Cholesterol is transported in the blood in particles made up of protein and lipid, called lipoproteins, of which there are four main classes:

- Low density lipoproteins (LDL): LDL-cholesterol accounts for 60-70% of total serum cholesterol. It is the most atherogenic lipoprotein, and is the major target of cholesterol lowering treatments. It is sometimes referred to as "bad" cholesterol.

- High density lipoproteins (HDL): HDL-cholesterol accounts for 20-30% of total serum cholesterol. Levels are inversely correlated with CHD risk, which may be due to a protective effect, or to the fact that low HDL-cholesterol levels are associated with other atherogenic factors. It is sometimes referred to as "good" cholesterol.

- Very low density lipoproteins (VLDL): These are rich in triglycerides, but account for 10-15% of total serum cholesterol. Partially degraded VLDL (VLDL remnants) are enriched with cholesterol, and seem to be atherogenic.

- Chylomicrons: These are rich in triglycerides, and partially degraded chylomicron remnants are probably atherogenic.

Total cholesterol is usually subdivided into either HDL-cholesterol and LDL-cholesterol, or HDL-cholesterol and non-HDL-cholesterol.

Atherosclerotic plaques

At low cholesterol levels lipoproteins travel throughout the circulatory system without problem, but at higher levels, LDL particles begin to stick to the vessel wall, creating a lesion. The particles become susceptible to oxidation or other modifications, and the permeability of the endothelium increases, allowing further accumulation of LDL. Macrophages then adhere to the lesion and accumulate cholesterol, forming a fatty streak. A plaque is formed when the fatty streak is overlaid with a layer of scar tissue.

HDL particles may intervene directly in this process by removing cholesterol from the engorged macrophages (reverse cholesterol transport), and possibly through antioxidant and anti-inflammatory effects, limiting the damage.

Vessels have some capacity to "remodel", maintaining the size of the lumen, but large plaques can limit flow at times of increased demand. Plaques become unstable and rupture, particularly in the presence of high levels of LDL, and it is this that causes most acute coronary events.

Lesions, fatty streaks and plaques form throughout the vasculature. The process may take many years, and the individual will be asymptomatic. Lowering LDL in early life (lifestyle changes may be sufficient) aims to prevent or slow down plaque formation. Once symptoms (e.g. angina) are experienced, the disease is already established. Treatment needs to be more aggressive (lifestyle changes and pharmacotherapy), aiming to stabilise plaques and prevent acute coronary events.

How do statins work?

The body can synthesise up to 1 g of cholesterol per day, while 20-40 mg per day is absorbed from food, and serum cholesterol levels correlate with saturated fat intake much more closely than with dietary cholesterol intake. Most cholesterol is synthesised in the liver, and statins work primarily by inhibiting an enzyme involved in its synthesis.

3-hydroxy-3-methyglutaryl coenzme A (HGM CoA) is converted into mevalonate, a precursor of cholesterol, in the presence of the enzyme HGM CoA reductase. This rate-limiting step in cholesterol biosynthesis is blocked by statins (HGM CoA reductase inhibitors).

Reduced cholesterol synthesis results in lower levels of hepatic cholesterol, and up-regulation of LDL receptor activity in the liver. There is greater uptake of serum LDL and other non-HDL particles by the LDL receptors, leading to lower levels of total and non-HDL cholesterol in the circulation.

Statins also raise HDL levels by about 5%, but the mechanism is unknown, and how much this contributes to the overall reduction in CHD risk is uncertain. Evidence is also

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accumulating for effects of statins that are independent of cholesterol lowering.

Non-lipid effects of statins

Statins are undeniably good at altering lipid profiles and reducing morbidity and mortality associated with unfavourable lipid levels. It takes four to six weeks of treatment for plasma lipid levels to show changes, and longer for tissue lipid levels. Some of the benefits seen during therapy occur too early to be the direct consequence of lipid changes. It was recognised in the late 1980s and early 1990s that statins improve endothelial function, but this was attributed directly to their lipid-lowering effects, and it was not until 1997 that they were shown to have direct effects on the endothelium. Endothelial dysfunction is an early critical component of organ injury after acute events such as myocardial infarction, ischaemic stroke and haemorrhage, and in chronic disease states such as diabetes and hypercholesterolaemia. It is a good prognostic indicator for cardiac events and mortality, so an important target for intervention.

Many studies, using animal and human cell lines and animal models, suggest a number of important effects of statins, mostly related to the bioavailability of nitric oxide (NO) in the vascular endothelium. For those who want to get involved in the detailed biochemistry, there are useful reviews [1, 2, 3, 4], but for the rest of us, the main effects include:

- Improved endothelial function through increased NO production, due to upregulation of endothelial nitric oxide synthase.
- Anti-inflammatory effects due to reduction of acute phase proteins, including C-reactive protein, inflammatory cytokines and cell adhesion molecules.
- Antioxidant effects due to scavenging of superoxide and inhibition of isoprenoids (superoxide generators).
- Antithrombotic effects due to a shift in the fibrinolytic balance towards fibrinolysis and reduced platelet aggreagation.
- Stabilisation of atherosclerotic plaque.
- Antiproliferative effects, due to inhibition of smooth muscle cell proliferation

Do these laboratory findings translate into clinical benefit?

- A number of clinical trials and observational studies have shown that treatment with statins immediately following an acute coronary event (eg MI, stent implantation) reduces the risk of recurrent events within a few weeks of starting treatment, compared to placebo or no treatment.
- Reduced myocardial ischaemia has been observed in patients treated with statins.
- Treatment with pravastatin for 12 weeks before endarterectomy showed changes such as reductions in lipid, macrophages and T-cells, and increases in collagen, in recovered atheromatous plaques. These changes are likely to help to stabilise plaques in vivo.
- Levels of inflammatory markers, including C-reactive protein, are reduced in the blood of hypercholesterolemic patients after four to twenty-four weeks of treatment.
- Platelet thrombus formation and aggregation are reduced, and fibrinolytic capacity increased, in patients treated with statins.
- Statins can reduce graft vessel disease following heart or kidney transplants, and reduce restenosis after vascular injury.

Some of these clinical benefits have been studied in small groups of patients, or in sub-groups of larger clinical trials. Further large, prospective, randomised trials are needed to confirm them and establish their clinical importance. It does seem, however, that statins have a number of potentially beneficial effects, some of which are independent of their cholesterol-lowering effect, and this could increase the number of circulatory disorders in which they could help.

Statin outcome trials update

Across all large outcome studies, irrespective of baseline risk, statins have an NNT of 19 (17-23) for prevention of death or nonfatal heart attack of stroke.

Cardiovascular disease is a leading cause of morbidity and mortality in the industrialised world. Observational studies have demonstrated a clear link between elevated serum LDL cholesterol concentrations and coronary heart disease, making hyperlipidaemia a significant modifiable risk factor that can be targeted. Early attempts to modify lipid profiles using diet and drugs had limited success, and made little impact on clinical outcomes. Statins reduce cellular cholesterol synthesis and were introduced in 1987. They rapidly became popular because they cause larger and clinically significant reductions in cholesterol levels, with few serious adverse effects, and are well tolerated by patients.

Efficacy

Evidence for the efficacy of statins is dominated by relatively few large randomised controlled trials (4,000 to 20,000 patients).

Coronary heart disease (CHD)

Five of the big trials have been combined in a meta-analysis [5]. The trials were all randomised, placebo-controlled and double-blind, with mean intervention durations of more than four years and primary end points of clinical disease or death [6-11]. A total of 30,817 patients were studied and the mean duration of treatment was 5.4 years with simvastatin, pravastatin or lovastatin. Three trials recruited patients with established coronary heart disease (secondary prevention) and two recruited patients with no history, signs or symptoms of coronary heart disease, but with at risk lipid profiles (primary prevention). Lipid changes were similar across the trials (Table 1).

Table 1: Mean lipid changes with statins

Lipid fraction	Reduction (%)	Increase (%)
Total cholesterol	20	
LDL cholesterol	28	5
HDL cholesterol		
Triglycerides	13	

Table 2: Major outcomes from meta-analysis [5]

Outcome	Relative risk (95% CI)	NNT (95% CI)
Major coronary event	0.73 (0.69-0.78)	28 (23-34)
Coronary death	0.73 (0.66-0.81)	75 (56-112)
Cardiovascular death	0.74 (0.67-0.82)	69 (52-103)
Data taken from LaRosa 1999		

There were no significant differences between primary and secondary prevention trials for all outcomes. Risk reduction and NNTs for various outcomes are shown in Table 2. There was no effect on non-cardiovascular mortality, and no difference in risk reduction between men and women or between those aged 65 years and more and less than 65 years.

Since then two reviews and two large trials have been published that add detail to the evidence.

The Prospective Pravastatin Pooling Project [12] evaluated three studies [7,8,11] using pravastatin at 40 mg/day in 19,768 patients, for at least 5 years. Risk reductions were similar for both men and women, younger and older patients (older patients were 65 years or more), smokers and non-smokers, and patients with or without diabetes or hypertension. The relative reduction in coronary risk was independent of baseline total cholesterol, HDL cholesterol, and triglyceride levels. For LDL cholesterol the risk reduction was reduced at the lowest baseline values (less than 3.2 mmol/L). This may have been due to chance alone, or may suggest a threshold below which there is a smaller or no risk reduction.

A second review [13] evaluated only trials in primary prevention [7, 10, 14] and found similar reductions in CHD events and mortality, but a non-significant effect on all cause mortality.

The MRC/BHF Heart Protection Study [15] was a large RCT evaluating simvastatin 40 mg/day for 5 years in 20,536 patients with coronary disease, other occlusive arterial disease or diabetes. Significant reductions were seen for coronary mortality, non-fatal MI, stroke and revascularisation procedures, which combined to give an NNT of 33 (26-45) for major vascular events, that was independent of baseline lipids, prior disease category, age, sex, smoking status, hypertension or various co-therapies.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) [16] involved over 19,000 patients with hypertension and at least three other cardiovascular risk factors, who were randomised to one of two antihypertensive treatments. The lipid-lowering arm of the trial comprised 10,305 patients with non-fasting total cholesterol levels of 6.5 mmol/L or less, who were randomised to additional treatment with atorvastatin (10 mg daily) or placebo. Follow up was planned for five years, but the study was stopped after a median of 3.3 years. Results of MRC/BHF and ASCOT have been included in the results in Table 3.

Stroke

The effects of cholesterol lowering on stroke have been less well studied and are more controversial. Observational studies have demonstrated an increased risk of ischaemic stroke at high cholesterol levels (more than 6.2 mmol/L; 240 mg/dl) and an increased risk of haemorrhagic stroke at low cholesterol levels (less than 5.2 mmol/L; 200 mg/dl) [17, 18]. It is suggested that low cholesterol may predispose to haemorrhagic stroke by contributing to a weakening of the endothelium of small cerebral arteries. Many statin trials have focused on coronary events and total mortality, but others have prospectively collected data for stroke, and these have been subject to meta-analysis.

Warshafsky et al [19] analysed 13 trials involving 19,921 patients randomised to lovastatin, pravastatin or simvastatin. Baseline cholesterol levels varied from 5.2 to 7.0 mmol/L (200 to 272 mg/dl). Trial duration ranged from 0.5 to 5.4 years, with a weighted mean duration of 4.3 years. The total number of stroke events was low (404/19,921), and few trials showed a significant difference between statin and placebo. Pooled analysis showed a significant reduction for total stroke only in secondary prevention trials. Most studies did not report on the pathology of strokes.

The Pravastatin Pooling Project [12] (19,768 patients, 5 years or more) included two secondary prevention trials that were not included in the previous analysis [8, 10]. These trials again showed a reduction in total and non-fatal stroke, while the primary prevention trial showed a smaller non-significant reduction. The secondary prevention trials provided data on stroke pathology. There were 171 non-haemorrhagic, 19 haemorrhagic and 31 strokes of unknown type. Most of the effect of treatment was on nonfatal, non-haemorrhagic strokes, which comprised 70% of the total. There was no evidence for an effect on haemorrhagic strokes, but the numbers were small and on average cholesterol levels did not drop much below 5.2 mmol/L (200 mg/dl).

The MRC/BHF Heart Protection Study [15] (20,536 patients, simvastatin, five years, primary and secondary prevention) also demonstrated a significant reduction in non-fatal stroke, and a non-significant reduction in fatal stroke.

Combined outcomes

Most people are concerned with "all bad things happening", which combines death and non-fatal heart attacks and strokes. We have pulled together the large trials that provide data on fatal and non-fatal CHD and stroke in Table 3 and Figure 1, together with results for different outcomes.

Table 3: Pooled results from large statin outcome trials

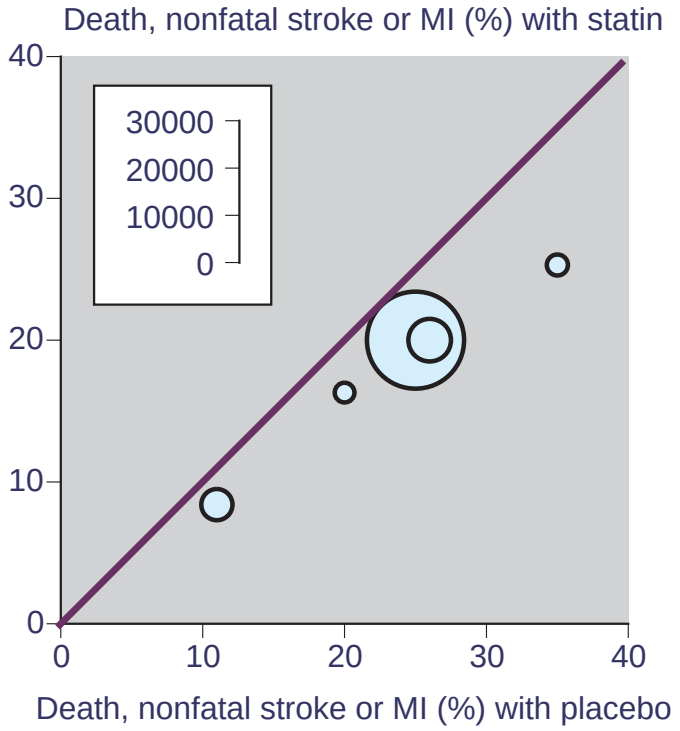
Event	Trials	Participants	Relative risk (95% CI)	NNT (95% CI)
All CHD	7	61658	0.73 (0.70-0.77)	33 (29-39)
Non-fatal CHD	6	51353	0.71 (0.66-0.76)	47 (39-58)
All stroke	6	55053	0.76 (0.70-0.83)	101 (77-149)
Non-fatal stroke	5	44748	0.74 (0.67-0.82)	95 (72-140)
All CHD and stroke	6	55053	0.74 (0.71-0.77)	26 (23-31)
All cause death	7	61658	0.85 (0.81-0.89)	67 (51-96)
All bad things	5	44748	0.78 (0.75-0.81)	19 (17-23)

Before the new trials were added, the NNTs for statins to prevent death or non-fatal stroke or MI compared with placebo were 35 in primary prevention and 11 in secondary prevention. This is well in accord with the new pooled outcome of 19 in Table 3. The question is which patient to treat, and what statin to use.

Special groups

"Which patient" is now usually defined as an individual having an absolute risk of coronary heart disease of 15% or more over 10 years (equivalent to a combined risk of CHD and stroke (cardiovascular risk of over 20% over the same period). In reality the goal is usually to treat all patients whose 10-year CHD risk is 30%. Other special groups deserve attention.

Figure 1: The outcome of "all bad things" in five RCTs



Statin use in diabetics

About 150 million people have diabetes worldwide, and the prevalence may double by 2025. Diabetics are at increased risk of cardiovascular morbidity and mortality, but as a group have not been targeted for lipid-lowering therapy, probably because their serum concentrations of total and LDL cholesterol are similar to those in the general population, although triglycerides may be raised and HDL cholesterol lowered in type 2 diabetes, and in type 1 diabetes with poor glycaemic control.

Observational studies have shown a direct association between stable total cholesterol levels and coronary heart disease rates, which is independent of baseline cholesterol level. The Multiple Risk Factor Intervention Trial [20] screened 360,000 middle-aged American men, and found that a 1.0 mmol/L lower level is associated with a 50% lower coronary disease risk. For the 5,000 diabetics included in the study, the absolute risk of coronary mortality was three to five times higher than for non-diabetics for each level of total cholesterol.

A meta-analysis of seven trials of cholesterol-lowering agents (mostly statins) found that treatment of diabetics for about five years resulted in a 25% (95% CI 7-39) reduction in the combined outcome of coronary heart disease death and non-fatal myocardial infarction [21]. Individual cardiovascular outcomes showed the same trend, but with wide confidence intervals, and were not statistically significant. Only 2,603 diabetics were included in these trials, representing 8% of the total trial population (2-25% in individual trials), so it is not surprising that numbers were too low to show significant differences.

Analysis of the MRC/BHF Heart Protection Study has clearly demonstrated the benefits of statin use in diabetics [15]. 5,963 adult diabetics (of whom about 2,000 had pre-existing coronary disease, 1,000 had other occlusive arterial disease, and 3,000 had no evidence of occlusive arterial disease) and 14,573 adults with arterial occlusive disease but no diabetes, were randomised to simvastatin (40 mg/day) or placebo, for five years. Changes in lipid profiles during treatment were substantial, and similar in diabetic and non diabetic patients (Table 4).

Table 4. Changes in lipid profile during treatment with simvastatin (40 mg/day for five years), compared to placebo, in diabetics and non-diabetics.

Lipid fraction	Diabetes (n=5,963)		No diabetes (n=14,573)	
	Baseline (mmol/L)	Mean change (mmol/L)	Baseline (mmol/L)	Mean change (mmol/L)
Total cholesterol	5.7	-1.1	5.9	-1.2
LDL cholesterol	3.2	-0.9	3.4	-1
HDL cholesterol	1.06	0.01	1.06	0.04
Triglycerides	2.3	-0.3	2	-0.3

Baseline values are mean values

The rate for the combined outcome of any major vascular event was reduced by about a quarter (Table 5), and this rate was similar for the individual outcomes of any major coronary event, stroke, and revascularisations. Importantly, the proportional risk reduction did not differ between diabetics and non-diabetics, or for various subgroups of diabetic patient based on duration, type or control of diabetes, sex, age, baseline cholesterol level, or established vascular disease at entry.

We might expect to see larger absolute risk reductions for diabetics since they have higher baseline risk levels than non-diabetics matched for age, cardiovascular disease and cholesterol. However, in this study the non-diabetics were generally older and more likely to have a history of occlusive arterial disease, which would account for the similar absolute risk reductions seen here.

After corrections for non-compliance in the study, the authors estimate that treatment of diabetics without established occlusive arterial disease with 40 mg/day of simvastatin for five years would prevent about 45 people per 1,000 from having one or more major vascular events (about 70 events in total). For diabetics with established occlusive arterial disease, about 90 people per 1,000 would benefit.

Treatment did not have any effect on glycaemic control or the incidence of newly diagnosed diabetes, and elevations of liver and muscle enzymes were rare and did not differ between treated and placebo groups. There may have been small beneficial effects on peripheral macrovascular complications and renal function.

Statin therapy can significantly reduce morbidity and mortality in diabetics. The decision to treat should be based on vascular risk and not initial cholesterol levels.

Statins in older people

A question that is begged to some extent is what constitutes an older person. One definition is someone a decade or so older that you, but here it is probably someone in their eighth or ninth decades. There is evidence from good trials that statins work as well in older as well as younger people.

Table 5. Main outcome events for diabetic and non-diabetic patients.

Event	Simvastatin (n=10,269)	Placebo (n=10,267)	Absolute Risk Reduction	Relative Risk Reduction (95% CI)
Major coronary event				
Diabetes	279 (9.4%)	377 (12.6%)	3.2%	
No diabetes	619 (8.5%)	835 (11.5%)	3.0%	
All patients	898 (8.7%)	1212 (11.8%)	3.1%	27% (21-33)
Stroke				
Diabetes	149 (5.0%)	193 (6.5%)	1.5%	
No diabetes	295 (4.0%)	392 (5.4%)	1.4%	
All patients	444 (4.3%)	585 (5.7%)	1.4%	25% (15-34)
Revascularisations				
Diabetes	260 (8.7%)	309 (10.4%)	1.7%	
No diabetes	679 (9.3%)	896 (12.3%)	3.0%	
All patients	939 (9.1%)	1205 (11.7%)	2.6%	24% (17-30)
All major vascular events				
Diabetes	601 (20.2%)	748 (25.1%)	4.9%	
No diabetes	1432 (19.6%)	1837 (25.2%)	5.6%	
All patients	2033 (19.8%)	2585 (25.2%)	5.4%	24% (19-28)

Systematic review [1]

This examined five large randomised studies (4S, WOSCOPS, CARE, AFCAPS and LIPID) with just under 31,000 participants, where statin had been compared with placebo, and published up to the end of 1998. Statins used were simvastatin and lovastatin on one each, and pravastatin in three.

The main outcome for analysis was major coronary events, which included coronary death, nonfatal myocardial infarction, silent infarction, or resuscitated cardiac arrest, as well as unstable angina in one trial. Participants older than 65 years were included in four of the trials (not WOSCOPS).

Risk was reduced by an average of 32% by statins in participants older than 65 years (Table 6), and was similar to the risk reduction in participants younger than 65 years (31%). A similar degree of risk reduction was seen in studies with high and low rates of previous myocardial infarction. The number of older people needed to be treated with statins for at least five years to prevent one major coronary event was 23 (95% CI 17 to 33).

Heart Protection Study [15]

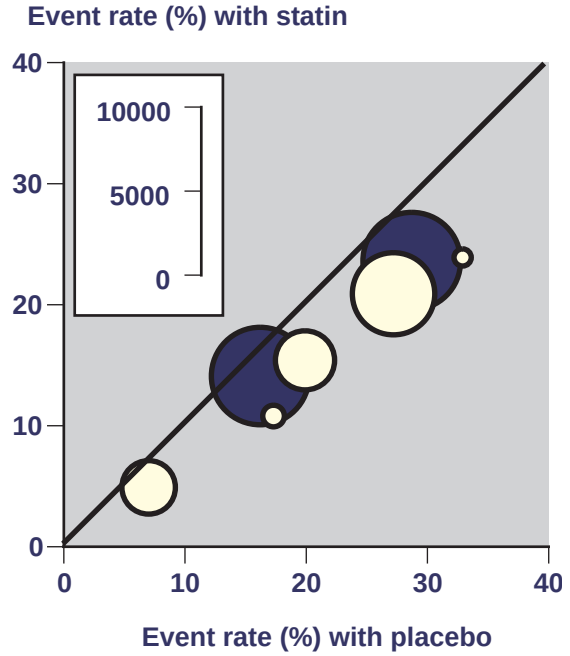
HPS randomised 20,536 people aged 40-80 years with coronary disease, occlusive arterial disease or diabetes to 40 mg simvastatin or placebo for five years. The outcome for subgroup analysis by age with about 10,000 people over 65 years was first major coronary event (nonfatal myocardial infarction or coronary mortality).

The results were reported by different age ranges of 65 to 70 years, and over 70 years (Table 6). Risk was reduced with statin by 23% and 18% respectively, and the number needed to treat for five years compared with placebo was 16 and 20 respectively (Table 6).

PROSPER [22]

This trial randomised 5,800 men and women aged 70 to 82 years with a history of, or risk factors for, vascular disease, to pravastatin 40 mg daily or placebo for a mean of 3.2 years. The primary endpoint was fatal or nonfatal heart attack or stroke.

Figure 2: Event rates in statin trials in people over 65 years (light symbols) and over 70 years (dark symbols)



Risk was reduced by an average of 15% (Table 6). The number of people needed to be treated for three years to prevent an event in one of them was 47 (25 to 358).

Comment

What we have here is a lot of information about statins in people older than 65 years. Over 25,000 have been included in well done clinical trials, and nearly half of them were over 70 years. There was a consistency of response over all the studies, irrespective of the statin and dose use, the duration, or the outcomes reported (Figure 2), and whether these older people were younger or older than 70 years.

Statins are effective in older people, and just as effective as in people aged under 65 or over 70 years.

Reading the HPS and PROSPER papers is interesting, because both examine effectiveness by stratification, and show that low levels of HDL cholesterol increase the risk of events. Statins were particularly effective in people with low HDL cholesterol levels.

Table 6: Effects of statins in older people. Note that event rates for the systematic review are approximate, and that somewhat different outcomes were used in different trials

Study/Review	Age in analysis (years)	Duration (years)	Number in analysis	Event rate (%)		Risk reduction (%, 95%CI)	NNT (95%CI)
				Statin	Placebo		
4S, CARE, AFCAPS, LIPID	65 or older	4.9-6.1	8998	12.0	16.4	32 (26 to 35)	23 (17 to 33)
Heart Protection Study	65 to 70	5	4891	20.9	27.2	23 (15 to 30)	16 (12 to 26)
Heart Protection Study	Over 70	5	5806	23.6	28.7	18 (11 to 25)	20 (14 to 35)
PROSPER	70 to 82	3.2	5804	14.1	16.2	15 (3 to 26)	47 (25 to 358)
Combined data			**25499**	**16.8**	**21.2**	**21 (17 to 25)**	**23 (17 to 29)**

Statins and intermittent claudication

Intermittent claudication is caused by peripheral arterial disease in the lower limbs. It limits walking distance, causes pain, reduces quality of life, and has a mortality rate of 3 to 5% per year. Patients are at high risk of coronary heart disease and cerebrovascular disease, and most will fall within current guidelines for treatment with statins to reduce this risk.

In the Scandinavian Simvastatin Survival Study (4S), patients with a history of myocardial infarction or angina, with raised total cholesterol levels, were treated with simvastatin (20 to 40 mg/day) or placebo for five years [6]. Analysis of adverse experiences likely to be caused by atherosclerotic disease shows a reduction in the risk of new or worsening intermittent claudication from 3.6% on placebo to 2.3% on simvastatin (relative risk reduction of 38%) [23].

The study was randomised and double-blinded, but this outcome was based on patients' reports of symptoms (subjective) and clinical examination (possible interobserver bias), with no systematically applied objective measurement of atherosclerosis. It does, however, strongly suggest that simvastatin has effects on the arterial vasculature beyond the coronary and cerebral circulations, with clinically significant effects on ischaemic symptoms.

In another double-blind, placebo-controlled study, 86 patients with peripheral arterial disease (Fontaine stage II), intermittent claudication, and total cholesterol greater than 5.7 mmol/L (220 mg/dL) were randomised to treatment with simvastatin (40 mg/day) or placebo for six months [24]. Pain-free and total walking distance, resting and postexercise ankle-brachial indexes, self-assessment questionnaire scores and lipid profiles were determined at 0, 3 and 6 months.

Measures of walking distance and ankle-brachial index improved significantly more in the simvastatin group than the placebo group (Table 7). Intermediate values were recorded at three months.

The self-assessment questionnaire asked patients to estimate on a 10-step scale:

- walking distance
- intensity of leg pain
- recovery time after claudication
- feeling of physical limitation

All parameters improved in the simvastatin group compared to placebo at three months, and improvement was maintained or increased at six months.

Expected reductions were seen in the simvastatin group for total and LDL cholesterol. There were no significant changes in HDL cholesterol, triglycerides, aminotransferases or creatinine kinase in either group.

The authors suggest that these observed improvements with simvastatin are not due primarily to reduction in size of peripheral atherosclerotic plaques, since the change in ankle-brachial index is small compared to increase in walking distance. It is more likely that functional effects such as plaque stabilisation and improved endothelial function are responsible.

Another randomised, double-blinded study compared lovastatin (20 mg/day) with policosanol (10 mg/day) for 20 weeks in patients with moderately severe intermittent claudication [25]. There was no placebo group. Measurements of walking distance, ankle-brachial index and quality of life improved with policosanol, but not lovastatin. It may be that lovastatin is not effective, at least at this dose, but since there were only 14 patients in each group, the results are not robust.

Comment

It seems reasonable to expect that statins will affect the entire vascular system, not just the coronary and cerebral circulations, and not unreasonable to hope that that they might bring about clinical improvement in symptoms of peripheral ischaemic disease. Results from one large and one small randomised controlled trial suggest that 40 mg/day of simvastatin can reduce symptoms of intermittent claudication. Larger randomised controlled trials with blinded objective outcome assessments are needed to confirm this, compare simvastatin with other statins/therapies, and understand the mechanisms involved. One trial involving 350 patients with symptomatic intermittent claudication treated with atorvastatin or placebo is underway. Meanwhile most patients with intermittent claudication should be taking a statin to reduce risk of CHD or stroke anyway.

Table 7: Effect of simvastatin (40 mg/day) on walking distance and ankle-brachial index.

	Baseline		6 Months	
Measurement	S (n=43)	P (n=43)	S (n=43)	P (n=43)
Pain-free walking (metres)	72 ± 13	74 ± 15	190 ± 38	100 ± 34
Total walking (metres)	96 ± 18	93 ± 13	230 ± 45	104 ± 29
Ankle-brachial index at rest	0.53 ± 0.06	0.55 ± 0.06	0.65 ± 0.08	0.56 ± 0.10
and after exercise	0.35 ± 0.11	0.39 ± 0.07	0.55 ± 0.12	0.36 ± 0.13

Results are expressed as Mean ± SD; S = simvastatin; P = placebo

Statins in heart failure

Heart failure is a progressive disease for which the underlying aetiology, at least in the western world, is most often coronary heart disease (CHD). Patients with symptomatic heart failure were either excluded or under represented in the major statin outcome trials, but subgroup analyses of 4S and CARE have shown reductions of around 20% in the incidence of new chronic heart failure for patients treated with statin compared to placebo [26, 27].

There is concern around treating patients with heart failure with statins.

Observational studies have suggested that low plasma cholesterol and lipoprotein levels are independent predictors of poor outcome in chronic heart failure [28, 29]. It is suggested that lipoproteins rich in cholesterol and triglycerides can bind and detoxify endotoxins (bacterial lipopolysaccharides), whose production is increased in heart failure [30]. Endotoxins stimulate release of proinflammatory cytokines, which are associated with progression of the disease. There may be a level below which it is unsafe to reduce cholesterol levels, at least in symptomatic heart failure.

Plasma levels of ubiquinone (coenzyme Q10) are reduced during treatment with statins. Ubiquinone is a coenzyme in mitochondrial respiration, and depletion could in theory adversely affect the cardiac muscle. Studies investigating dietary ubiquinone supplementation have produced mixed results for improving exercise tolerance in heart failure [31, 32].

Acute coronary events cause injury to the myocardium and can lead to progression of heart failure. Statins are effective in preventing acute coronary events. In the CARE study [27], left ventricular ejection fraction (LVEF) was recorded, and pravastatin was equally effective in reducing coronary events in patients with LVEF between 25% and 40% as in patients with LVEF greater than 40%. Patients with severe heart failure (LVEF less than 25%) were excluded.

Recently statins have been shown to have beneficial effects on the vasculature that are independent of their lipid lowering effects. Potential benefits include improvement of endothelial function and reduced production of inflammatory components. Both endothelial dysfunction and inflammation are significant components of heart failure, irrespective of underlying etiology.

Three recent studies support a role for statins in heart failure.

- In 63 patients with symptomatic, non-ischaemic dilated cardiomyopathy, those randomised to simvastatin for 14 weeks showed improvements in cardiac function, neurohormonal imbalance and markers of inflammation, compared to placebo. These changes correlated with improved symptoms [33].
- In a cohort of 551 patients with ischaemic and non-ischaemic heart failure (LVEF 40% or less), statin use was associated with improved survival without the necessity for urgent heart transplantation [34].
- A retrospective, analysis of all surviving patients from the OPTIMAAL study (which compared losartan and captopril), showed that initiation of beta-blocker and statin treatment early after MI complicated by heart failure was associated with reduced morbidity and mortality [35]. The effects of the two treatments were additive. These findings are limited by the retrospective and non-randomised design.

Recent outcome trials in systolic heart failure have reported baseline rates of lipid-lowering therapies of between 11% and 45%, indicating that these agents are becoming widely used in patients with heart failure, presumably because of underlying CHD. If statins benefit patients with heart failure, then it could be considered unethical to not treat them all, but if they are harmful, then the patients in these trials and others like them should not be receiving them.

A prospective randomised trial has been called for. In practice, if current guidelines are funded and followed, the vast majority of patients who are at risk of developing heart failure will in the future be taking a statin anyway, because of their risk of CHD. The decision will then be whether to stop treatment if they progress to heart failure. The hope is that many fewer will.

Which patient to treat with statin?

Statins, NNTs and risk

Using British National Formulary (BNF) definitions of cardiovascular risk and extrapolated 10-year efficacy, the NNT of statins is 6 and below for risks of 40% and above, and 11 falling to 6 at risks of 20-40%.

The evidence is that statins are effective in reducing heart attacks and stroke, both fatal and non-fatal. This reduction occurred consistently in large randomised trials with event rates for the combined outcome of fatal or nonfatal heart attack or stroke over five years of 10 to 35%. This corresponds to a 10-year risk of 20 to 70%.

If we are able to assume a consistent degree of risk reduction at different levels of risk, then we can calculate what the number needed to treat should be at all levels of risk. The importance of this is to help determine which patients to treat.

Assumptions

In the calculations below, we made the following assumptions:

- That the effect of statins was the same at all levels of risk (that is, the relative risk and the relative risk reduction would the same).
- That the five-year benefit found in statin trials could be extrapolated to double the effect for a 10-year benefit.
- That the levels of risk found in the trials were of the same nature as the levels of risk used in calculating cardio-

vascular and coronary heart disease risk in, for instance, the British National Formulary.

Results

The results are shown in Table 8 and Figure 3 using the relative risk of 0.78 for statins for the outcome of "all bad things", encompassing all death, and nonfatal heart attacks and strokes. Using BNF definitions of cardiovascular risk and extrapolated 10-year efficacy, the NNT of statins is 6 and below for risks of 40% and above, and 11 falling to 6 at risks of 20-40%.

The results in Table 9 use the relative risk of 0.75 for statins for the outcome of fatal and nonfatal heart attacks and strokes. Using BNF definitions of cardiovascular risk and extrapolated 10-year efficacy, the NNT of statins is 5 and below for risks of 40% and above, and 10 falling to 5 at risks of 20-40%.

Comment

These calculations show just how effective statins can be in high risk individuals, if taken correctly over long periods. The assumptions made in these calculations are probably justified. The difficult part is determining at what level of risk treatment should start.

Health economics of statin

The cost-effectiveness of statins is dependent on the baseline level of risk at which treatment starts. At a 10-year risk of 30% the overall costs are bearable, but by 15% 10-year risk the costs are huge. Atorvastatin, rosuvastatin, and simvastatin seem the best buys.

The health economics of statins are usually addressed in two ways, the absolute cost in terms of life saved, and comparative costs for different statins.

Establishing the cost of statins for a quality-adjusted life year (QALY) or year of life saved (YLS)

Here the issues are the cost of drug acquisition (essentially the price of the drug), and the level of risk in the target population. Results of some studies in this area are shown in Table 10 on page 11.

We know that the higher the level of risk, the more effective the statin will be, for instance in terms of the NNT for preventing a bad outcome like fatal or non-fatal heart attack or stroke. With five years of statin treatment NNTs fall from 91 at a 10-year risk of 5% to 9 with a 10-year risk of 50%. And clearly a statin that cost £100 a day would be less cost-effective than one that cost £0.01 per day.

Many of these analyses are based on the results of the large outcomes studies with statins, often with evidence brought in from other areas to bolster arguments. A typical review [36] concluded that the cost of statin treatment for secondary prevention and primary prevention for people with

Figure 3: NNTs for preventing any death, or nonfatal heart attack of stroke at different levels of baseline cardiovascular disease risk

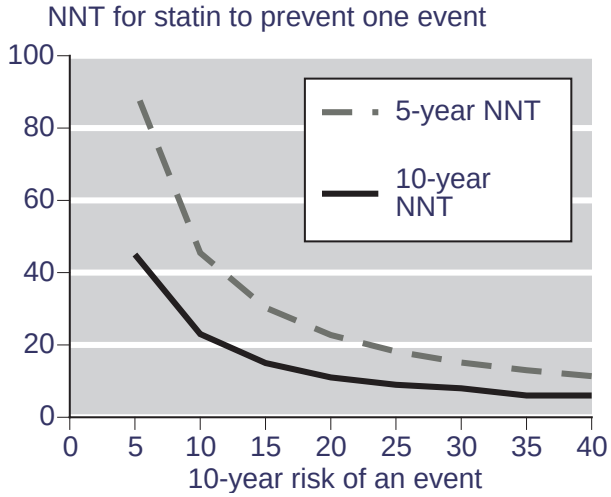


Table 8: NNTs for preventing any death, or nonfatal heart attack or stroke at different levels of baseline cardiovascular disease risk

10-year risk of CHD event (percent)	NNT usng 5-year statin efficacy	NNT extrapolated to 10 years
5	91	45
10	45	23
15	30	15
20	23	11
25	18	9
30	15	8
35	13	6
40	11	6

BNF says that high risk individuals are defined as those whose 10-year CHD risk exceeds 15% (equivalent to a cardiovascular risk of 20% over the same period). At a minimum those with the highest risk (over 30% CHD risk) should be targeted and treated now, and as resources allow others with risks above 15% should be progressively targeted.

Table 9: NNTs for fatal or nonfatal heart attacks or strokes at different levels of baseline cardiovascular disease risk

10-year risk of CHD event (percent)	NNT usng 5-year statin efficacy	NNT extrapolated to 10 years
5	77	38
10	38	19
15	26	13
20	19	10
25	15	8
30	13	6
35	11	5
40	10	5

higher risk, was about $45,000 per life saved, in the same range as other typical healthcare interventions. A good Dutch study [37] took a slightly different view, putting a ceiling of Euro 18,000 as an acceptable cost-effectiveness figure for year of life saved, and concluded that people with a 10-year risk of about 20% or more should be targeted. There were interesting age-related differences, with lower risk perhaps being treated in younger people, and higher risk in older people.

The most useful economic analysis from a UK perspective was an HTA review [38]. This extensive systematic review and economic model confirmed that the two major effects on cost were the initial risk, and the cost of the statin. It gives estimates of cost per life year gained as gross, or net of other interventions prevented, and discounted or undiscounted. The net discounted costs of statin treatment at different levels of risk are shown in Figure 4. At a 30% 10-year risk of mortality it was £4,727.

Yeo & Yeo [39] actually worked out the costs of implementing the National Service Framework (NSF) for coronary heart disease (CHD) in general practice in the UK. This was based on a survey of risk in 8,000 Scottish adults, of whom 3,251 were aged 35 to 64 years and were not taking lipid-lowering therapy. Of these:

- 555 (17%) had serum cholesterol below 5 mmol/L
- 217 (7%) had cholesterol above 5 mmol/L and a doctor's diagnosis of heart attack, angina, stroke or peripheral vascular disease, and were candidates for secondary prevention.
- 2,479 (76%) had cholesterol above 5 mmol/L who were candidates for primary prevention (and who had individual risk calculated). Of these candidates for primary prevention, 56 (2%) had a 10-year risk of 30% or more, 360 (11%) had a 10-year risk of 15% or more, and 1,216 (37%) had a 10-year risk of 6% or more. Figures for men and women differed (Figure 5 for 30% 10-year risk or more, and Figure 6 for 15% 10-year risk or more).

Thus about 8% of the adult population between 35 and 65 years would need statin treatment to implement the NSF. The approximate costs for a typical GP practice with about 1,000 people aged between 35 and 64 years would be about £35,000 to treat those at 30% risk or more, £70,000 for those whose risk was 15% or more over 10 years, and about £170,000 for those at a 10-year risk of 6% or more.

Comparative costs of statins

Here the issues are simpler, because in the end it all comes down to the cost of effective statin doses. The arguments used here include percentage reduction in LDL cholesterol, though a major problem is the paucity of quality data from large numbers of randomised patients, and information is often quoted selectively. Two studies [40, 41], used randomised trials of statins with dose escalation built in to reach target LDL cholesterol levels, and then calculated the one-year cost of reaching the target based on drug costs and doctors office visits. Another [42] examined the maintenance costs after targets had been reached.

Figure 4: Net discounted costs of statin treatment at different levels of risk

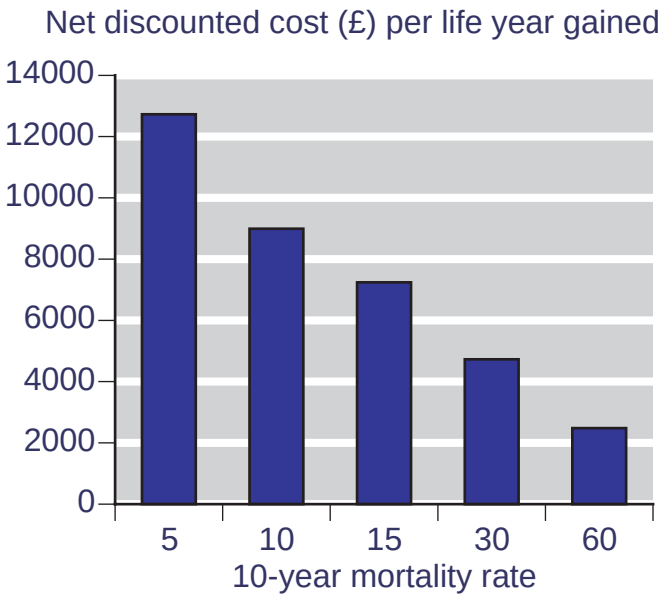


Figure 5: 30% 10-year risk or more

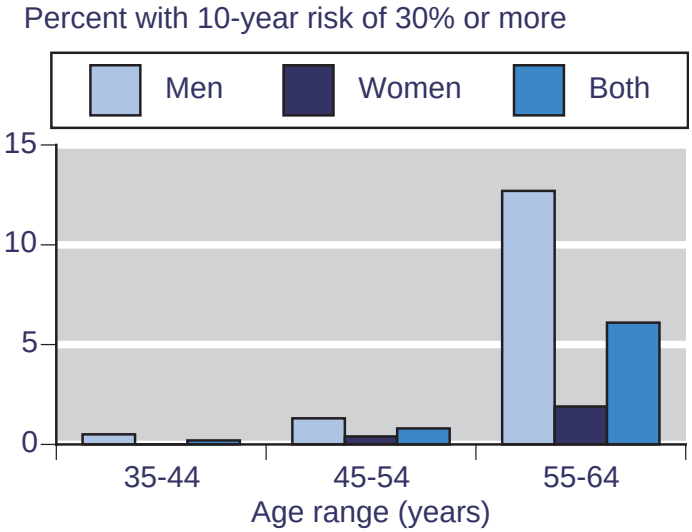


Figure 6: 15% 10-year risk or more

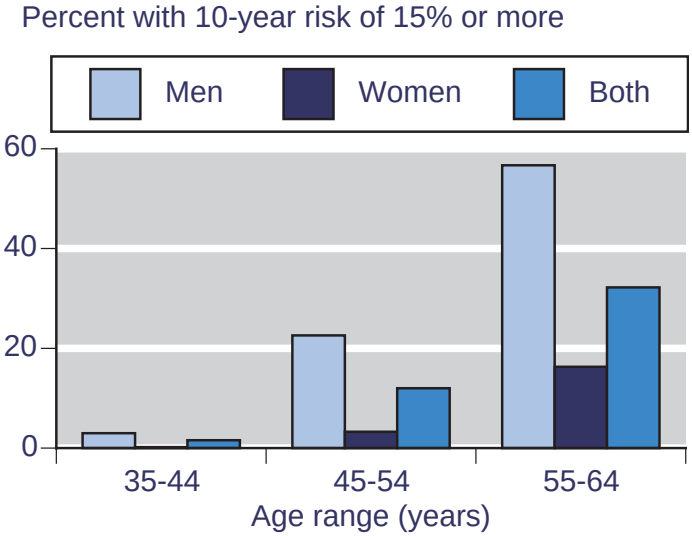


Table 10: Health economic studies of statins

Reference	Type of study	Main findings	Sponsorship
Cost effectiveness of statins			
Jacobson et al, 1998	Literature review examining effectiveness and costs of statins, with estimate of cost per year of life saved	Concluded that, compared with other interventions, statin use in secondary prevention is cost effective, and in some groups in primary prevention.	Sponsored by manufacturer of a statin
Ebrahim et al, 1999	Literature review examining cholesterol lowering, including statins, with cost analysis	Cost of life-year gained at different levels of risk, and of different statins. At 10-year risk of 30%, range of costs was £3,100 to £6,200, depening on whether discounter or not, or gross or net costs.	No sponsorship
Yeo & Yeo 2000	Estimate of costs associated with implementation of National Service Framework in UK	Using a GP list of 2,000 patients, with 1,00 0 aged 35-64 years, cost of statins drugs would be up to £37,000 a year to implement a policy of treating all with 10-year risk of 30% or more	No sponsorship
van Hout & Simoons, 2001	Modelling exercise for Holland, based on literature review and initial risk of new coronary heart disease events	Based on an arbitrary threshold of a cost effectiveness of Euro 18,000 per year of life saved, treatment should be targeted to those with a 19-26% 10-year CHD risk. This is affected by age, varying from 11% under age 30 to 41% over age 80 years.	No sponsorship
Comparison of costs of different statins			
Koren et al, 1998	Cost of achieving LDL-cholesterol target based on RCT of four statins in USA over one year	Atorvastatin and simvastatin had lowest cost, and lower than fluvastatin and pravastatin over one year, and more patients (90%) achieved target LDL-C. Based on cost of drugs and doctors office visits.	Sponsored by manufacturers of atorvastatin
Smith et al, 1998	Cost of achieving LDL-cholesterol target based on RCT of four statins in Europe, over one year	Atorvastatin and simvastatin had lowest cost, and lower than fluvastatin and pravastatin over one year, and more patients (90%) achieved target LDL-C. Based on cost of drugs and doctors office visits.	Sponsored by manufacturers of atorvastatin
Attanasio et al, 2000	Cost of maintenance on statin therapy after target LDL-C reached	Cost minimisation analysis of simvastatin versus atorvastatin based on results of final statin doses in Smith et al, 1998. Concluded simvastatin cheaper by 7-40%, depending on prices in different countries.	Sponsored by manufacturer of simvastatin
Huse et al, 1998	Cost effectiveness of different statins and doses based on cholesterol reduction in a US setting	Concluded atorvastatin cheaper than simvastatin cheaper than other statins.	Sponsored by manufacturers of atorvastatin
Russell et al, 2001	Cost effectiveness of different statins and doses based on cholesterol reduction in a Canadian setting. Virtual duplicate of Huse et al.	Concluded atorvastatin cheaper than simvastatin cheaper than other statins.	Sponsored by manufacturers of atorvastatin
Maclaine & Patel, 2001	Dose escalation comparison of statins to achieve a target LDL-C based on cholesterol reduction	Concluded atorvastatin cheaper than simvastatin cheaper than other statins.	Sponsored by manufacturers of atorvastatin

Sponsored in this table is taken to mean an explicit acknowledgement of sponsorship, or an author from a pharmaceutical company, or both

Each of this type of study [40-45] concluded that the cheapest option was the statin from the sponsoring company. Where several statins were studied, two, simvastatin and atorvastatin, generally were more cost-effective, with usually more patients hitting LDL cholesterol targets, and fewer dropping out.

Comment

None of these studies is perfect. Practical issues are often overlooked, particularly withdrawal from treatment that could limit any possible success on a population if not an individual basis. There has been at least one attempt to examine models used in predicting future events in cost-effectiveness work [46]. It concluded that in the UK situation more attention should be placed on achieving the goal of the ratio of total to HDL cholesterol, since that was what targets were based upon.

The bottom line is that statins are certainly cost-effective for those with a 10-year CHD risk of 30% or more, but that costs would limit a lower treatment threshold. Many individuals with a 10-year risk of lower than 15% and with a total cholesterol above 5 mmol/L or a total to HDL cholesterol above 5 might also judge that buying their own statin would be a personally sensible cost-effective purchase. As the public become more educated about risk, the level at which the state pays and at which the individual pays will become a hot potato.

Statins: whom should we treat?

Different guidelines apply to variable proportions of patients, and produce different numbers of patients who should be treated with lipid lowering drugs.

National guidelines for the prevention of coronary heart disease identify modification of lipid profiles, and particularly reduction of low density lipoprotein cholesterol (LDL-C), as a major target. These guidelines should help doctors to decide which patients should start treatment. In the UK doctors probably turn first to the Joint British Societies recommendations [47], but in Europe the Joint European Societies recommendations [48] and in the USA the National Cholesterol Education Program (NCEP) [49] are used. There are others.

The guidelines all agree that attempts to reduce the incidence of CHD should start with education and therapeutic lifestyle changes, including stopping smoking, stress reduction, increased physical activity, weight reduction and dietary modification. Comorbid conditions, such as hypertension and diabetes, should be controlled appropriately.

Nearly all patients with established CHD will be eligible for lipid-lowering drug therapy. For primary prevention things are more complicated. First we need a form of risk assessment, and then we need recommendations on the level of risk at which drug treatment should be started.

A recent study has compared the current guidelines for primary prevention of CHD to determine whether they agree or differ in their assessments of CHD risk and their recommendations for lipid-lowering therapy [50]. The guidelines compared were:

- Framingham risk equation [51];
- National Cholesterol Education Program (Adult Treatment Panel III) (NCEP ATP III) [49];
- Joint European Societies guidelines [48];
- Joint British guidelines [47];
- Revised Sheffield table [52];
- Munster Heart Study calculator (PROCAM) [53].

Participants were 100 consecutive patients without clinical evidence of cardiovascular disease who attended a University outpatient lipid and diabetes clinic. Data were collected for age, sex, blood pressure, smoking, diabetes, family history of premature CHD, LVH on ECG, total, HDL and LDL cholesterol (T-C, HDL-C, LDL-C), and trigyceride levels.

Risk Assessment

PROCAM guidelines are based on data from the Munster Heart Study, while the others are based on data from the Framingham Heart Study. For this reason, the authors chose to use the risk calculated using the Framingham equation as a gold standard to which risks calculated using the other guidelines were compared (Table 11).

Recommendations

Four of the available guidelines make recommendations concerning lipid-lowering therapy (Table 12).

Comment

The analysis used data from a relatively small number of 100 patients from a specialised segment of the population, but is in agreement with two previous studies [54, 55].

The algorithms for risk assessment were not applicable to all patients. In this study Framingham, NCEP, Joint European and Revised Sheffield could be applied to at least four out of every five patients, and Joint British to seven out of every ten, while PROCAM was inappropriate for any population other than middle-aged men (less than one in five of this population). To be useful, algorithms need to be widely applicable.

The algorithms also provided different estimates of risk. A patient at significant risk according to one guideline could be low-risk according to another; Joint British was in best agreement with the Framingham equation in this study.

Finally, those guidelines that make recommendations for initiation of lipid-lowering therapy use differing criteria, which result in different, but overlapping, sets of patients who are considered eligible. This reflects different priorities and constraints rather than disagreement, but may contribute to confusion about whom to treat. The greater number of patients identified for treatment by the NCEP ATP III guidelines probably reflects the fact that these guidelines have been most recently updated, incorporating the growing evidence of benefit in a wider range of patients.

Table 11. Level of agreement between guidelines on CHD risk.

	Framingham	NCEP ATP III	Joint European	Joint British	Revised Sheffield	PROCAM
Total patients studied	100	100	100	100	100	100
Patients included in guidelines	87	93	81	72	95	22
	All guidelines applicable to a total of 62 patients					
CHD risk 20% or more over next 10 years	21	33*	16**	20**		
CHD risk 15% or more over next 5 years	8				3	
CHD risk 20% or more over next 10 years	10 (of 22)					3
Agreement (kappa)		Fair (0.22)	Good (0.64)	Very good (0.81)	Poor (less than 0.2)	not calculated

* only 19 of 21 patients identified by Framingham were identified by NCEP ATP III; ** all included in 21 patients identified by Framingham

Table 12. Comparison of guidelines for recommendation of lipid-lowering therapy

	NCEP ATP III	Joint European	Joint British	Revised Sheffield
Criteria for recommending lipid-lowering therapy	dependent on LDL-C, CHD risk and number of risk factors	CHD risk over 20% over 10 years,T-C over 190 mg/dL and/or LDL-C over 115 mg/dL	CHD risk over 15% over 10 years and T-C over 5 mmol/L	CHD risk over 3% per year
Number recommended for treatment	32	16*	22**	3

* only 11 included in NCEP ATP III recommendations; ** only 14 included in NCEP ATP III recommendations

This is all rather confusing, but we must remember that guidelines, estimates and recommendations are not intended to give a definitive answer to treat or otherwise, but to help in the process of making a decision about an individual patient within the limits of available resources.

Dose-response of statins in short-term trials

All statins show a dose response in trials of two to six weeks' duration. Different statins are prescribed at different doses. The evidence [56] quantified the average reduction in LDL cholesterol in short term (2-6 week) trials.

Randomised trials of statins used in a fixed dose were chosen, including rosuvastatin but omitting cerivastatin. Several electronic databases were searched, including the Cochrane Library. All double blind studies were included, irrespective of age or disease states in patients. Excluded were trials without placebo groups, trials that lasted for less than two weeks, used dose titration, or used cholesterol-lowering drugs in combination. Also excluded were trials in patients with renal failure or after organ transplantation.

There were 164 trials with 24,000 patients on statins and 14,000 on placebo. Participants in most trials were healthy with above average lipid concentrations, and in some trials they had high blood pressure, ischaemic heart disease or diabetes.

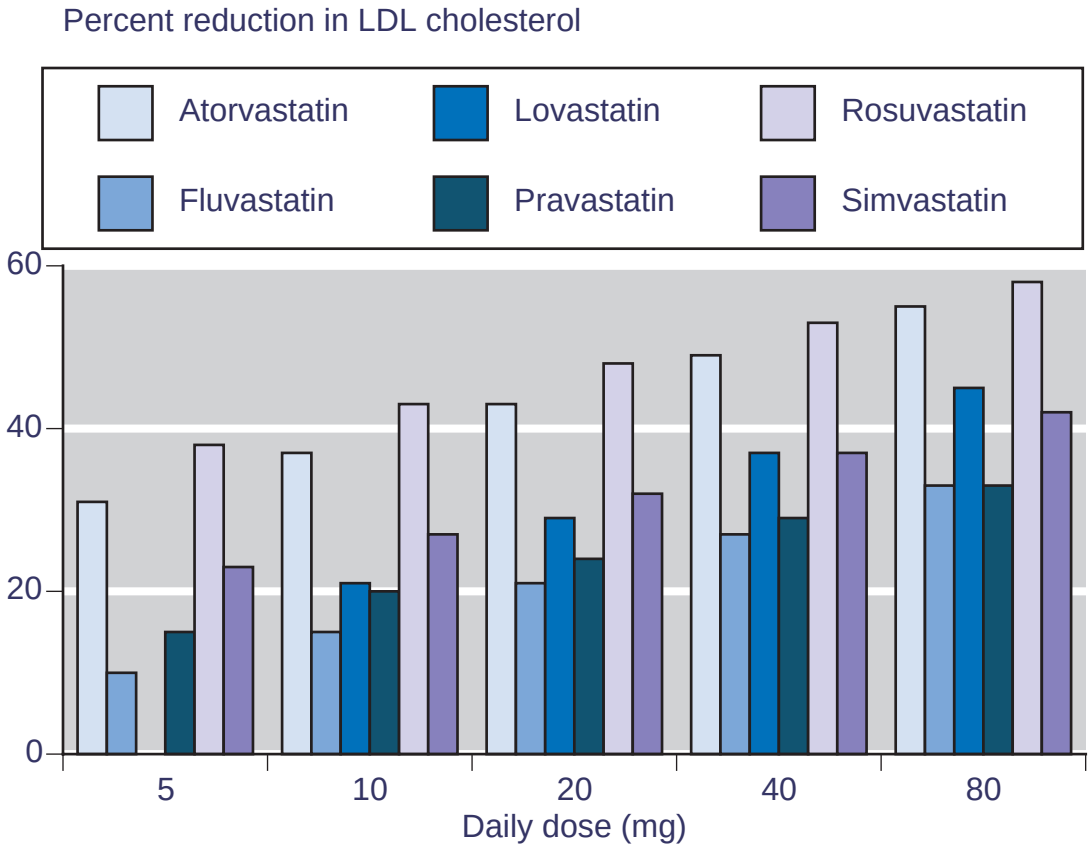
All the statins had a dose response (Figure 7) over the range of 5 mg to 80 mg daily. Rosuvastatin 5 mg/day, atorvastatin 10 mg/day, and lovastatin or simvastatin 40 mg/day reduced LDL cholesterol concentrations by about 35% (or about 1.8 mmol/L).

Atorvastatin and rosuvastatin were taken in the morning, and other statins in the evening. Three randomised trials reported an average greater reduction of 0.2 mmol/L (95% confidence interval 0.05 to 0.44 mmol/L) with evening dose. There was an average increase in LDL cholesterol of 0.07 mmol/L (0.06 to 0.08 mmol/L).

The comparison of guidelines [50] needs to be read in full. It pulls together much information. The possible limitation of this part of it relating to dose-response is that it examines only studies over two to six weeks, when people taking statins should be taking it life long.

The implications are particularly interesting for making decisions about individuals. For example, the Joint British Societies coronary risk protection charts suggest that a man aged 55 to 64 years, a non-smoker, and with a systolic blood pressure of 120 mmHg would just creep in to a 15% risk with a total cholesterol of about 5.5 mmol/L and HDL cholesterol of 0.85 mmol/L (TC:HDL of 6.5). Using an effective dose of statin would, on average, change the figures to 4.0 mmol/L and 0.92 mmol/L respectively, bringing the ratio down to 4.3, and a much lower risk.

Figure 7: Dose response for statins - percentage reduction in LDL cholesterol in trials over 2-6 weeks



When there are suggestions that statins may become available from pharmacists without prescription, this brings potential for reduced risk even to people whose risk, at face value, is not high.

Dose-response of statins in long-term trials

What about knowing which dose gives best lipid lowering in long-term trials. A new systematic review [57] gives the answer. Searching for randomised, double-blind controlled trials assessing the effect of statins on cholesterol in patients with hypercholesterolaemia was to September 2001 using the Cochrane Library and PubMed. Pharmaceutical companies known to manufacture statins were contacted for references. Reference lists of retrieved trials and reviews were checked to identify other studies.

Included trials were both randomised and double blind, had at least two treatment groups (placebo, different doses of the same statin, or different treatments), had a mean total cholesterol of at least 5.0 mmol/L at baseline (with or without dispersion), and provided baseline and outcome data for total cholesterol, LDL, HDL and triglycerides. Because trials of less than three months duration are unlikely to adequately inform about sustainable effects in terms of lipid lowering with statins, only those of at least three months were included.

Studies without baseline data were excluded, as were those with fewer than 20 patients per treatment group. Also excluded were trials with mean baseline concentration of total cholesterol below 5.0 mmol/L, combinations of a statin plus another drug, trials examining patients with familial hypercholesterolaemia, diabetes mellitus, renal or hepatic pathology, or trials in which patients were randomised to statin treatment within 24 hours of procedures such as angioplasty or cardiac surgery.

The main outcomes sought were mean change (absolute or percent) from baseline during double blind treatment for total cholesterol, LDL, HDL and triglycerides or data allowing their calculation.

Results

Forty-two reviews and 509 reports regarded as potential randomised trials were retrieved, and 418 were excluded, mostly because they were shorter than 12 weeks, were not double blind, had fewer than 20 patients per group, or were duplicates. Ninety-one trials met the inclusion criteria and contributed to the analysis, with 43,404 patients on statins and 25,081 on placebo. In most trials initial average concentration of total cholesterol was between 6.5 and 7.8 mmol/L.

Most patient information was available for lovastatin, pravastatin and simvastatin, mainly because of the publication of large, long-term trials, with far less information available for atorvastatin, cerivastatin, fluvastatin and rosuvastatin. The most commonly used doses were atorvastatin 10 mg, fluvastatin 40 mg, lovastatin 40 mg, pravastatin 40 mg and simvastatin 40 mg. Information for both 5 mg and 10 mg of rosuvastatin was used since patient numbers were almost identical.

Duration of study beyond 12 weeks, initial concentration of cholesterol, use of placebo or active controls, and the inclusion or exclusion of major trials had no effect on lipid-altering capacity. The cholesterol-lowering capacity of statins was generally unaffected by dose used, and by use of fixed dose or dose-titration. Figure 8 shows this for the statin with the largest amount of information, simvastatin.

The cholesterol-lowering capacity of the most commonly used fixed doses was different between statins. Figure 9 shows the mean percentage reductions for total cholesterol, and Figure 10 for LDL-cholesterol. In both cases the rank order was the same, with 5 and 10 mg of rosuvastatin giving the largest reduction, followed by the two most prescribed statins ahead of the other statins.

The all cause discontinuation rate was about 10% and discontinuation because of adverse events was about 4% in these trials, with no major difference between statins.

Comment

So what are the take-home messages? One is that in the UK, and probably world wide, prescribing of statins has been rather evidence-based, since the most frequently used (atorvastatin 10 mg and simvastatin 40 mg) are the established statins with the most cholesterol-lowering impact. That is encouraging. Rosuvastatin, with less information, seems to have even more punch at 5 mg and 10 mg. This might help costing exercises based on local pricing regimes, though arguments about effects of statins beyond those of cholesterol lowering will probably continue.

Figure 8: Percentage change in LDL-cholesterol from baseline with different simvastatin doses

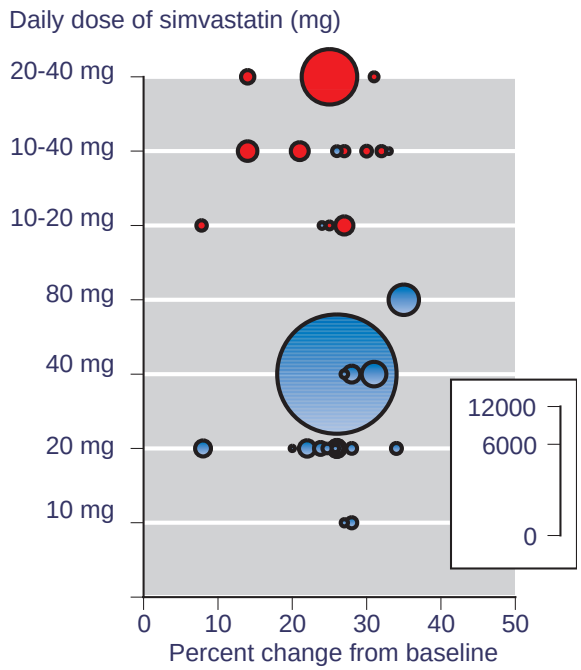


Figure 9: Percentage change in total cholesterol from baseline (number of subjects)

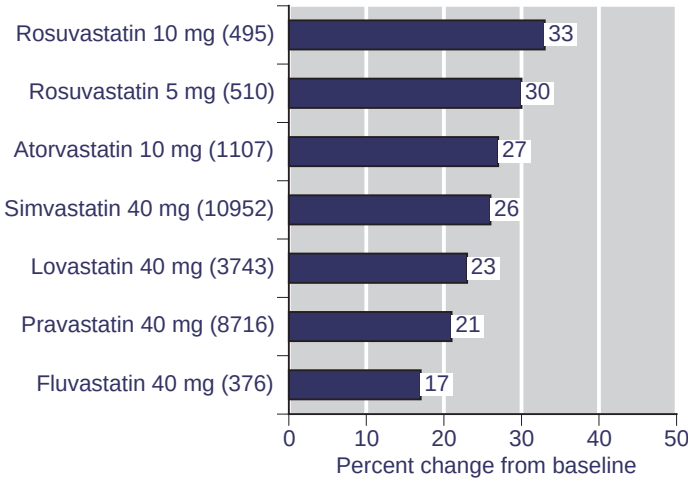
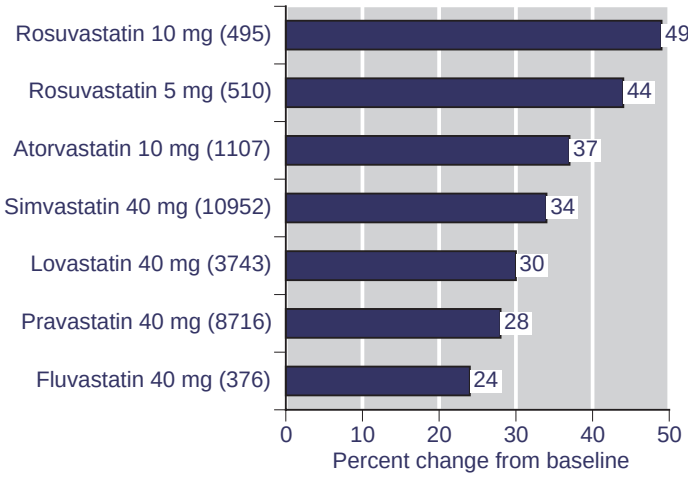


Figure 10: Percentage change in LDL-cholesterol from baseline (number of subjects)



Even so, it was surprising that there was only information on about 1,000 patients for atorvastatin and rosuvastatin, compared with 11,000 for simvastatin. The cholesterol-lowering effect for atorvastatin in the large ASCOT study [16] is in line with the effect found in the meta-analysis.

Perhaps the most surprising thing was the lack of dose response in these longer term studies. Law and colleagues [56] analysed trials of two to six weeks duration by drug and dose in 25,000 patients on statins and found good dose-response for all statins. This meta-analysis [57] had data from 68,000 patients but in trials lasting at least 12 weeks, compared with the 2-6 weeks in the other review of dose-response [56]. This may reflect better the long term use of statins, and if so may open a question about how long people should be on a statin before dose or drug change is considered. ***Bandolier*** could find no papers that looked at how long it took for the maximum reduction in cholesterol to be achieved.

Duration and extent of cholesterol reduction and risk reduction

Reduction in risk of fatal and non-fatal cardiac death depends on both the duration and extent of cholesterol reduction use. The greatest reduction in risk was associated with LDL reduction of at least 1.5 mmol/L for more than two years [56].

Statins to reduce total cholesterol and low density lipoprotein cholesterol have been available for a decade or more, and are now much used. The evidence here [56] examined reduction of risk against the extent and duration of cholesterol reduction.

Randomised trials of cholesterol reduction by any means were sought, excluding those in which risk factors other than cholesterol were changed, fewer than five ischaemic heart disease events occurred, or in which there was no untreated control group. Ischaemic heart disease events were IHD death or non-fatal myocardial infarction (and excluding silent infarcts).

There were 58 trials with 76,000 treated patients and 72,000 controls, with 5,440 and 7,102 respective events, with treatments including fibrates, resins, niacin, statins or dietary change). Results from trials were standardised to a 1 mmol/L reduction in LDL cholesterol by raising the observed odds ratio to the power of 1.0 divided by the observed LDL cholesterol reduction. Figure 11 shows the effects of duration alone. Full protection depended upon cholesterol reduction for at least two years.

Table 13 shows the effects of duration together with the extent of LDL cholesterol reduction. Greater LDL reduction and longer duration of cholesterol reduction yielded larger reductions in risk.

Very useful information, showing that for full benefit, cholesterol reduction has to be large and sustained.

Figure 11: Effect of duration of cholesterol reduction on risk of IHD

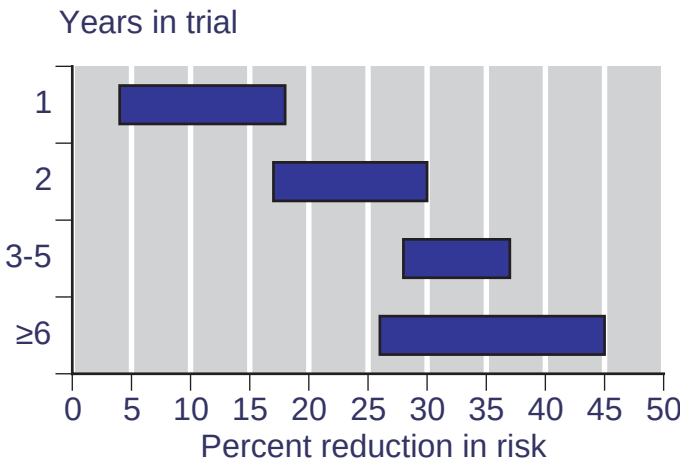


Table 13: Effect of duration and extent of cholesterol reduction on percentage risk reduction for IHD

	LDL cholesterol reduction (mmol/L)		
Years in trials	0.2-0.7	0.8-1.4	≥1.5
1 and 2	6	19	33
3-5	19	31	50
6 or more	21	30	52

Physician Compliance with Published Guidelines on Lipid-Lowering

Many studies show that the use of lipid-lowering treatments falls a long way short of recommendations set out in the various published guidelines for prevention of coronary heart disease. These studies vary in design and include chart review of selected groups [58-62], national surveys [63-65], and analysis of the General Practice Research Database (GPRD) [66]. The studies were conducted in the USA and Europe, and the most of the selected groups were secondary prevention groups. Despite the differing populations and study methods, each with their own potential biases, the studies are consistent in reporting poor physician compliance with guidelines for their own region, in terms of identifying patients eligible for treatment, initiating treatment, and achieving treatment goals (cholesterol levels).

The main findings from two studies [59, 64] are presented in Tables 14 and 15, as examples.

Of 149 patients who survived myocardial infarction [59], 101 (68%) were discharged from hospital taking a statin, but 63% of these were on a dose below that shown to reduce cardiovascular events in clinical trials.

In a study of patients on stable lipid-lowering treatments, which assessed success in achieving National Cholesterol Education Program LDL-C goals, drug therapy was better than non-drug therapy, and statins were better than other drug therapies [68]. However, only 40% of those receiving a statin as monotherapy achieved LDL-C target levels. The investigators found that patient non-compliance could not account for the high rates of failure, and that high doses of drugs were seldom used. They suggest that more aggressive treatment is required if treatment goals are to be met.

A study using the GPRD has found large differences between practices in the use of statins in a primary care setting [66], and also large differences in the age and sex of patients given statins. Only about 10% of the differences could be accounted for by variation in the prevalence of ischaemic heart disease.

Smith et al [58] found that differences in quality of lipid-lowering therapy for CHD patients attending either a cardiology clinic or cardiology private practice were accounted for by variation in individual physician prescribing habits, rather than any patient characteristics. Another study has shown that the likelihood of being prescribed a statin is associated with a number of patient characteristics [65], which are shown in Table 16.

Table 14: Results from a national cross sectional survey [64]

Patient Group	Number	%
Total	13,586	
With valid cholesterol measurement	10,569	
T-C 5 mmol/L or more	7133	68
T-C:HDL-C 5 or more	2804	27
Taking lipid-lowering drug	237	2.2
Age 16-75 with CHD and eligible for drug treatment*	385	
Taking lipid-lowering drug	114	30
T-C less than 5 mmol/L	50	44 **
No CHD but 10 year risk above 30% and T-C 5 mmol/L or more***	122	
Taking lipid-lowering drug	4	3
T-C less than 5 mmol/L	5****	4

* using Joint British recommendations [67]
** among those taking lipid-lowering drug
*** of 6304 patients without CHD who provided sufficient data for calculation
**** none of these patients were taking lipid-lowering drug
CHD=coronary heart disease; T-C=total cholesterol; HDL-C=high density lipoprotein cholesterol

Table 15: Results from an analysis of patients admitted to a coronary care unit with acute myocardial infarction [59]

Patient Group	Number	%
Total	177	
Mean age (years)	66	
Male/Female	114/63	
History of hyperlipidaemia	17	10
T-C above 5 mmol/L	98*	58
Recorded history of CHD	62	35
With CHD and taking lipid-lowering drug	12	19

*of 168 patients in whom lipid profile was measured

Table 16. Patient characteristics for which there was significant variation in prescribing of statins [65]

Patient characteristic	Odds ratio* (95%CI)
less than 65 years old	1.0 [reference]
65-74 years old	0.57 (0.38-0.85)
75 years old or more	0.11 (0.06-0.21)
non smoker	1.0 [reference]
smoker	0.49 (0.29-0.84)
Myocardial infarction	1.0 [reference]
angina	0.62 (0.42-0.91)

* adjusted for age and sex (sex only for age variable)

Other characteristics for which no significant variation was found include sex, family history of cardiovascular disease, diabetes, hypertension, obesity, and a number of social measures.

We know that statin prescribing is increasing, and the data for some of these studies were collected four to five years ago, so we might expect that the situation is improving as physicians become more familiar with guidelines and confident about the benefit and harm of statin therapy. The study from Smith et al [58] found improvement between 1994 and 1998. The changes to the NCEP guidelines in 2001 have altered the treatment-eligible population, targeting more younger and elderly subjects, requiring more detailed assessment of risk, and bringing more individuals into the category requiring aggressive treatment [69]. This may have the effect of making physician compliance in the USA appear worse until they catch up with the new recommendations.

Older people

Of particular concern is the apparent under use of statins in elderly patients. This is probably because earlier statin trials did not enrol patients over 75 years old. More recently, in the HPS [15] 28% of patients were 70 years or more at study entry, and PROSPER [22] studied only patients aged 70-82 years. Both trials demonstrated efficacy in these elderly patients, who are at high risk of cardiovascular events.

Ownership

An interesting study of general practitioners in Lothian, Scotland, an area with high rates of CHD, has looked at how doctors use evidence to make decisions about prescribing statins [70]. It showed that doctors were reasonably clear about the benefits and social and economic issues relating to statin use in secondary prevention, but not primary prevention. They rarely read and appraised clinical trials, and trial data were incorporated in to clinical practice only when they were confirmed by other sources (e.g. postgraduate meetings, hospital consultants, the media, and local prescribing advisors), and after a local consensus had emerged. Local guidelines were more widely trusted and used than national guidelines, while pharmaceutical company guidelines were distrusted and rejected. The authors suggested that strategies to maximise the use of clinical evidence in practice should build on local consensus.

Other suggestions to improve physician compliance have concentrated on enabling strategies (e.g. prompts attached to patients' notes), reinforcing strategies (e.g. feedback through routine audit), development of standardised treatment plans, and tracking and follow-up of missed appointments.

Comment

Many different types of studies from different parts of the world have demonstrated that physicians are not initiating appropriate lipid-lowering therapy in the majority of "at risk" individuals, according to current guidelines. There is variation between doctors in their willingness to assess patients for risk, to use drug therapy, and to use effective doses or combinations of drugs to achieve therapeutic goals.

Patient Compliance with statins

Cohort studies of patients prescribed statins show variable but disappointingly high rates of discontinuation of therapy and poor adherence to drug regimens [71-75], and failure to reach targets for cholesterol reduction in those who continue with therapy [76].

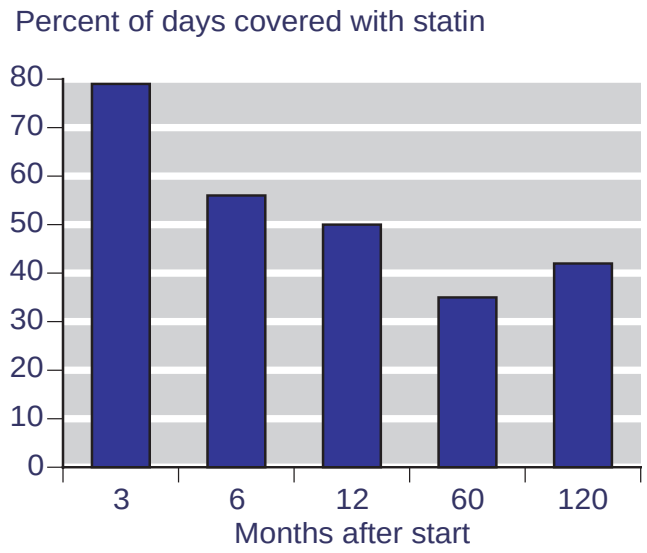
Discontinuation of therapy

Discontinuation rates at five years in clinical trials range from 6-30%, but in clinical practice the rates are much higher. Studies show that the number of patients continuing therapy falls sharply in the first few months of treatment, followed by a more gradual decline. In the USA it is estimated that only about 50% of patients continue at six months, and 30-40% at one year [77]. Similar rates have been found in Australia [74], and the same problem exists in the UK [78].

Failure to reach cholesterol target levels

This may in part be due to prescribing of insufficient doses of the statin, and at an individual patient level, there may be some who are less responsive to statins than the average. However poor response to treatment seems primarily to be due to patients not taking the drug as prescribed (e.g. intermittent use, reduced dosage).

Figure 12: Proportion of days covered by drug therapy in different treatment periods



Benner et al [72] used prescription records to study patterns of use in a cohort of 34,501 elderly (65 years or more) patients using statins. They measured the proportion of days covered by drug therapy (Figure 12), and the proportion of patients judged to be "adherent" (taking at least 80% of prescribed drug), "partially adherent" (20-79% of prescribed drug), or "non-adherent" (less than 20% of prescribed drug), in each six-month period for a total of 10 years after initiation of therapy (Table 17).

Patients could move between adherence groups in different time periods. Most patients lost from the partially adherent group moved into the non-adherent group. Of those who became non-adherent, only 4% had a prescription for another lipid-lowering drug dispensed, and adherence to that drug was also poor. Adverse effects rates are low and could account for only a small amount of the non-adherence. Although this study involved elderly patients from one geographical area (New Jersey), it is in broad agreement with other studies [71, 73, 74].

We do not know how much adherence is required to achieve some, if not maximum, benefit from statin therapy, or the effects of intermittent adherence, or "drug holidays". In

Table 17: Proportion of patients with different levels of adherence to their prescribed drugs in different treatment periods.

Duration of treatment (months)	Adherent (%)	Partially adherent (%)	Non-adherent (%)
3	60	40	0
6	43	29	29
60	26	18	56
120	32	18	50

WOSCOPS, however, patients who took at least 75% of their prescribed dose of pravastatin had significantly lower rates of non-fatal MI, revascularisation procedures, death from any cause, and cardiovascular death, compared to those who took less than 75% of their prescribed dose [7]. Patients taking statins for secondary prevention following MI had reduced risk of recurrent MI or death if they took 80% or more of their prescribed medication over the study period (maximum follow up 6 years) [79]. Other studies have shown that withdrawal of statins [80] or sudden reduction of dose [81] can increase the rate of thrombotic events.

There is no single cause of failure to comply with prescribed medication, and the problem is not restricted to statins. Some general predictors of compliance with medications for prevention of coronary heart disease have emerged and are summarised below.

Poor Compliance

- Female
- Age under 45 years
- Age over 75 years
- low socio-economic status
- non-white
- multiple daily dosing
- multiple drug regimens
- primary prevention, asymptomatic, feeling in good health
- lack of knowledge about disease, need for treatment and side effects
- Some comorbidity e.g. dementia, depression, MI after statin started

Good Compliance

- Prior good compliance
- Feeling in bad health
- Good relationship with physician, understanding of need for treatment
- Some comorbidity e.g. diabetes, hypertension, stroke, CHF

There have been a number of reviews of interventions to improve patient compliance [77, 78]. In brief, most interventions have a positive effect in the short term, but to be successful in the long-term a sustained multi-factorial approach is required. A combination of patient-focused, physician-focused, and system-focused interventions works best (Table 18).

Comment

In order to achieve maximum benefit from statin therapy patients need to take the drug at an appropriate dose, probably for the rest of their lives. The majority of patients for whom statins are prescribed in clinical practice either stop taking the drug altogether or take less than the prescribed dose within a year. This is likely to reduce or remove any benefit, and may even cause harm.

Table 18: Interventions to improve compliance with coronary heart disease medication [modified from 78].

Patient-focused	simple drug regimens, tailored to individual patient
	education about disease, need for therapy, how to take drug
	support from family, friends or carers
Physician-focused	good communication and regular contact
	appointment reminders and follow-up of missed appointments
	supply of compliance aids
System-focused	provision of lipid clinics
	use pharmacists and specially trained nurses

Stopping statins

Is it dangerous to stop taking statins? Given that statins are among the safest of drugs, this seemed a rather curious question to which the answer was blisteringly obvious. If statins were given to prevent something bad happening, then stopping them might make the bad thing more likely to happen. A quick search turned up two pieces of evidence which imply that stopping or changing statins could increase vascular risk by about three times. There are some complexities in the biology that might make this an interesting area to keep an eye on.

Changing statins in primary care [81]

This report was an audit of all patients who had changed their statin in the Otago region of New Zealand in a response to a reference pricing scheme. There were 126 such patients, and their hospital records were examined for fasting lipids and hospital admission for unstable angina, myocardial infarction, thrombotic stroke or peripheral artery occlusion for the six months before and after substitution of fluvastatin for simvastatin.

The mean dose of simvastatin of 22 mg was changed to a mean dose of 37 mg of fluvastatin. The change was accompanied by a significant rise in total cholesterol of 18%, LDL cholesterol by 34% and triglyceride by 13%. Significant increases occurred in 94% of the patients.

There was also a three-fold increase in thrombotic events (Table 19), from nine in the last six months on simvastatin to 27 in the first six months on fluvastatin.

Withdrawing statins in patients with acute coronary disease [82]

A randomised trial set out to test the efficacy of platelet receptor inhibition in the first 40 hours after the onset of chest pain in 3232 patients. Those results are of no interest here, but a retrospective analysis examined the outcomes of death,

Table 19: Thrombotic events in six months before and after change of statin

	Simvastatin	Fluvastatin
Mean dose (mg)	22	37
Events over six months		
Myocardial infarction	2	6
Unstable angina	7	15
Non-haemorrhagic stroke	0	4
Acute limb ischaemia	0	2
Total vascular events	9	27

126 patients over six months before and after substitution of fluvastatin for simvastatin

myocardial infarction, ischaemia and revascularisation in the 30 days after onset of chest pain according to statin therapy. Where there were full records:

- 1151 patients had no statins at any time,
- 369 had a statin treatment before their chest pain and continued with the statin after the onset of chest pain, and
- 86 had statin treatment before the onset of chest pain but had the statin discontinued at or after admission with chest pain.

Patients in these three groups were similar (age about 67 years, mostly men). Those on statin treatment had more hypercholesterolaemia diagnoses, but a 10% lower median total cholesterol than those who did not receive statins. Total cholesterol did not change in the 72 hours after withdrawal.

The main difference was in the rates of death and myocardial infarction in the 30 days after onset of chest pain. Patients on statins before and after admission had lower event rates than those not on statins (Figure 13). Those who had statin withdrawn had higher rates, not just higher than those continuing on statins (relative risk 2.9; 1.6 to 6.3), but higher than those never treated with a statin, though not significantly so (1.7; 0.9 to 3.6).

Comment

It may be pure coincidence that in both these reports there was a three-fold increased risk of an event after stopping a statin or changing to an ineffective dose, but it was the expected result. Neither study is definitive and merely serves to generate hypotheses, though ethics for the trial needed to prove the hypothesis may be difficult to come by, especially if the idea was to prove a larger than expected effect.

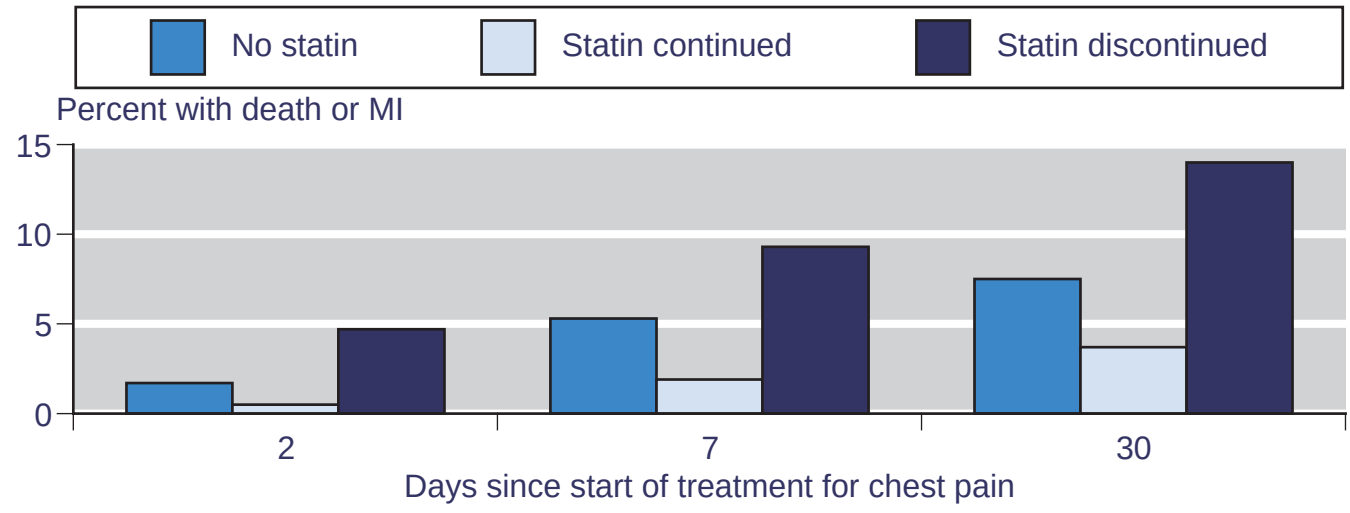
Statins are likely to do things other than just affect cholesterol levels. Endothelial nitric oxide production, leukocyte adhesion, platelet activation and LDL oxidation are all postulated mechanisms for which there is some experimental evidence. That is all very academic, but a better handle on the risk with stopping statins would be welcome.

There is an enormous experiment going on, in which millions of people are being prescribed statins and begin to take them. But most patients stop taking their statins after some time. If there is an increased risk with stopping, might an unintended consequence be that we actually cause more thrombotic events?

Unintended consequences also come from tinkering with therapy. The Otago "experiment" came from changes in reimbursement policy, so patients received insufficient doses of a less potent drug that probably altered their lipid control for the worse. When statin was changed from simvastatin to atorvastatin and lipid control changed for the better, the number of thrombotic events after the change was low, and no different from before the change [83].

Perhaps the take home message is not to mess about with statin therapy without a very good reason, and to make sure that lipid control is not impaired. Sure we need more data, but we know how to avoid the law of unintended consequences.

Figure 13: Outcome of death or MI for patients never treated with a statin, those in whom statin continues after onset of chest pain, and those in whom statin was discontinued after onset of chest pain



Other effects of statins

The following section looks at effects of statin on areas of the body other than vessels and cholesterol. This might be thought of as "adverse effects", though some adverse effects might be beneficial for some people. Anyway, what follows is a round up of the best evidence we could find. Especially important this, because some people will be taking statins for many years, or even decades.

Statins and bone

An observational study in 69 type 2 diabetic patients has shown increases in bone mineral density (BMD) over 14 months in those treated with statins, compared to a reduction in BMD for untreated patients [84]. Fracture rates were not reported.

Re-examination of the UK General Practice Research Database (UK GPRD) [85] found no significant effect of statins on risk of fracture at any site, any dose, or any duration of treatment, compared with non-use of statins, after adjusting for confounding variables. This contrasts with other findings [86] from the same database, but using a smaller population.

Data from the Women's Health Initiative Observational Study [87] of postmenopausal women aged 50-79 years again found no significant reduction in risk of fracture with statin use. However, treatment for more than three years with the more potent statins (atorvastatin or simvastatin) gave modest protection to hip and lumbar vertebral BMD [88].

The BHF Heart Protection Study [15], a randomised controlled trial involving over 20,000 patients aged 40 to 80 years, treated with simvastatin for five years, prespecified hospitalisation for fracture as a tertiary outcome. It found no differences between placebo and treated groups for any fracture, or fracture at sites related to osteoporosis.

A cross-sectional study of 140 postmenopausal women treated with a statin (65% simvastatin) for at least two (median four) years, looked at markers of bone turnover, plasma levels of parathyroid hormone and BMD, compared to sex and age-matched population controls [89]. There was reduced bone turnover in statin-treated women compared to controls but there was no effect on BMD.

A cumulative meta-analysis of observational studies [90] has confirmed that the risk for hip and non-spine fractures is lower for older women taking statins. Prospective studies have not confirmed this, but we can be pretty sure that there is no increased risk of fracture from statins.

Statins and cancer

A number of epidemiological studies have reported an association between low cholesterol levels and increased incidence of cancer of the gastrointestinal tract. Most of the studies predate the introduction of statins in 1987, and when the lipid-lowering potential of these drugs was realised there were fears that they could increase the incidence of gastrointestinal cancers. However, causality remains controversial, and the association could be explained by confounding factors.

Two recent case control studies, involving over 10,000 individuals, have looked for changes in the rates of cancer at specific sites, but failed to demonstrate a clear association with statin use [91, 92].

The strongest evidence, in terms of methodological rigor, number of patients and duration of follow-up, comes from large, randomised, double-blind, placebo-controlled trials. A meta-analysis of five trials studied 30,817 patients treated for 5 years, and found no association between the use of statins and either fatal or non-fatal cancers [93].

Bandolier has added to the meta-analysis the results of another very large trial published subsequently [15]. No trial reported all of the outcomes, and most reported cancer in different ways (Table 20).

Looking at all cancers together might obscure a change in the rate of a specific type or site of cancer. Reporting of site-specific cancers in the trials was incomplete, but the available data showed little evidence that statins influence cancer rates at specific sites.

So far the data from large randomized trials is mostly reassuring, although incomplete. The average duration of the trials was five years, but most patients taking stains would

Table 20: Risk of fatal and non-fatal cancer with statin therapy

Event	Trials	Patients	Statin events/total	Placebo events/total	Relative risk (95% CI)
Non-fatal cancer					
excluding nonmelanoma skin cancer	3 (1)	31575	583/15792	576/15783	1.01 (0.90-1.13)
including nonmelanoma skin cancer	2 (2)	13173	374/6593	374/6580	1.00 (0.87-1.15)
Fatal cancer					
excluding nonmelanoma skin cancer	3 (1)	31575	436/15792	429/15783	1.02 (0.89-1.16)
including nonmelanoma skin cancer	2 (2)	13173	177/6593	186/6580	0.95 (0.78-1.16)
All cancers					
excluding nonmelanoma skin cancer	4 (3)	38198	1271/19114	1264/19084	1.00 (0.93-1.08)
including nonmelanoma skin cancer	4 (4)	40314	2110/20166	2067/20148	1.02 (0.96-1.08)

Trials included were: 1SSSS, WOSCOPS, HPS; 2 CARE, LIPID; 3 SSSS, WOSCOPS, AFCAPS, HPS; 4CARE, LIPID, AFCAPS, HPS

expect to do so for life. Cancers can occur after long latency periods following exposure to the carcinogen, and we do not yet have the length of follow-up necessary to exclude a carcinogenic effect of statins. The answer will come from epidemiological surveillance and studies with long-term follow-up.

Statins and cognitive function

Impairment of cognitive function, or dementia, is common in older people, with 10% of those aged 65 or more being affected. It is a heterogeneous condition with mixed causes, many of which involve vascular changes in the brain, and there is evidence for involvement of lipids in these changes. The mechanisms are poorly understood.

A review [94] found seven observational studies investigating the relationship between cognitive function and dementia. There were three case control, three cohort, and one observational study: five presented data on treatment with any lipid-lowering agent, and all seven on treatment with statins. Cognitive impairment was defined as "a diagnosis of Alzheimer's disease, dementia, or cognitive dysfunction, using each study's own definitions".

All but one study (the observational study) adjusted for potential confounders and risk factors for dementia. There was a significant association between the use of a statin and reduced risk of cognitive impairment, compared to no use of any lipid-lowering drug. The association with use of any lipid-lowering drug compared to no use was weaker and not significant. The summary outcomes are presented in Table 21.

The authors conclude that use of statins, and possibly other lipid lowering drugs, seems to reduce the risk of cognitive impairment, but stress the need for randomised controlled trials to confirm this and investigate questions about dosage, duration, and the effects in different types of dementia. They suggest that the benefit observed with statins compared to other lipid lowering drugs may indicate a mechanism that is independent of cholesterol lowering, such as an antioxidant or anti-inflammatory effect. This is supported by the finding in one study that there was no significant difference in risk for groups with hyperlipidemia and either no drug or non-statin lipid-lowering drug treatment.

We should remember that these observational studies do not establish a causal link, although most made adjustments for a variety of confounding variables, and one investigated indication bias by adjusting for other markers for health, without affecting the result.

Table 21: Association between use of lipid lowering drugs and cognitive impairment

Comparison	Odds ratio	95% CI
Any LLD: users vs non users	0.62	0.28-1.38
Statin users vs any LLD non users	0.43	0.31-0.62

LLD = lipid lowering drug

Different ways of diagnosing dementia can produce wildly differing results [95]. These observational studies use a range of diagnostic systems that could result in at least four-fold differences in estimates of prevalence. Knowing this we should be even more careful about these observational results.

Statins and the liver

Statins are contraindicated in patients with active liver disease, and should be used with caution in those with a history of liver disease or high alcohol intake. Routine monitoring of liver enzymes during treatment with statins is recommended, mainly because premarketing clinical trials and animal studies showed minor elevations in serum alanine aminotransferase (ALT) enzyme levels, suggestive of possible hepatoxicity.

Randomised controlled trials have shown no difference between placebo and statin groups in the incidence of raised ALT levels (about 1%) [5, 15, 56], or withdrawals due to raised ALT levels [15]. No cases of serious liver disease were reported in trials.

Tolman [96] has reviewed the literature for lovastatin, which has been in use since 1986 and has 24 million patient-years of clinical experience (Table 22).

Estimates of rates for hepatitis and acute liver failure rely on spontaneous reporting, which is subject to bias, and almost always an underestimate. However, the authors point out that even if the reporting rate is 10%, the corrected rate for hepatitis (1/100,000) would be much lower than that seen with many commonly used drugs. For acute liver failure the rate of 1/130,000 would be equivalent to the background rate in the general population. Minor elevations in ALT were poorly predictive of hepatotoxicity and hence ineffective in preventing serious liver disease.

In a retrospective review of patient records in a primary care setting to determine the value of routine monitoring of enzyme levels (ALT and CK) in patients taking statins [96] there were 1194 patients, of whom 1014 (85%) had at least one monitoring test performed over the study period of one year. Of these, 10 (1%) had significant elevation, and five (0.5%) had a moderate elevation of transaminase levels. None appeared to be related to statin use. Similar results were obtained for the analysis of CK levels (6 (0.9%) sig-

Table 22: Effects of lovastatin on the liver [96]

Symptom	Evidence
ALT 3 x upper limit of normal	Rate: 2.6% at 20 mg/day, 5% at 80 mg/day. Dose related. Reversible with continuing therapy
Hepatitis	Rate: 9.7 per million patient-treatment years, but many mild and causality not established in most cases
Acute Liver Failure	Rate: 1 per 1.14 million patient-treatment years. Equivalent to background rate of idiopathic acute liver failure

nificant elevation, 14 (2.1%) moderate elevation, of which 2 were potentially due to a statin). They question the usefulness of routine monitoring in all patients taking statins.

In patients without a history of liver disease elevations of serum ALT are uncommon during treatment with statins and are poorly predictive of hepatotoxicity. The value of routine monitoring of liver enzymes is questionable. Hepatitis and acute liver failure are rare, and probably no higher than those associated with other commonly used drugs, or the background rate in the general population.

Statins and macular degeneration

The association was investigated in a case control study in which all patients with at least one visit to a US veterans hospital and above age 50 were eligible for inclusion [97]. Only men were studied. All diagnoses were coded, together with information about medication prescribed, and date of prescription being filled. Cases of age related maculopathy diagnosed between 1997 and 2001 formed the cases, and for each case, 10 controls were selected, matched for age. For each case and each control use of statins before the diagnosis date or matching date was examined, together with use of other cholesterol lowering drugs. Other information about patient demographics and other diagnoses was also collected

There were 550 cases and 5,500 controls. The average age of men was 73 years, and there were higher rates of white race, diabetes, hypertension and cardiovascular and cerebrovascular disease in the cases than in the controls.

The proportion with a statin prescription filled was 7% among cases and 14% among controls, despite this higher rate of disease in cases. The odds ratio was 0.5 (95%CI 0.3 to 0.6), and this association was unchanged for present of past statin use, or with longer duration of use. The effect was present for statin users, or statin users and other lipid lowering drugs combined, but not for other lipid lowering drugs without statins.

The association was present and unchanged when the results were adjusted for confounding factors like diabetes, and was, if anything, stronger after adjustment.

What we have here is a very interesting association. There are other studies about statins and macular degeneration, but both were small, and the one suggesting a decreased progression of maculopathy with statins was published as a letter. But this is potentially important stuff, and clearly we need a proper randomised trial to answer the question.

Statins and muscle

Statins are known to be associated with muscle complaints, but the extent of the problem in terms of both severity and frequency is not well known, and the mechanism is unclear. A recent review in JAMA tries to address these points [98]. The review was thorough, including reports to the FDA and data from clinical trials, review articles, clinical guidelines, and case series, together with articles on the possible biochemical mechanisms involved.

The authors found a lack of clear definitions of reported muscle complaints, and chose to divide them into syndromes as follows:

Clinically important myositis and rhabdomyolysis : muscle pain with creatinine kinase (CK) levels more than ten times the upper limit of normal (ULN). Rhabdomyolysis occurs when the damage results in the release of cellular contents into the systemic circulation. Treatment is supportive and death can result from hyperkalaemia, cardiac arrythmia, renal failure and disseminated intravascular coagulation.
Mild CK elevations : raised CK levels that do not exceed ten times ULN. Patients may be asymptomatic.
Myalgia : muscle pain. It can affect patients' quality of life and compliance with medication.
Muscle weakness: This is frequently reported in association with clinically important myositis and rhabdomyolysis, but can also occur in patients without significant CK elevation.
Muscle cramps : These are not reported frequently.
Persistent myalgia/CK elevations after statin withdrawal : There are rare reports of these problems occurring during statin therapy and continuing after withdrawal. These patients may have other clinical conditions that have been unmasked by statin therapy.

Clinically important muscle complaints

There were 3,339 cases of statin-associated rhabdomyolysis identified in the Qscan FDA database from January 1990 and March 2002. Details are shown in Table 23. These data are compiled from voluntary physician reporting, which is well known to under report, but give some idea of the severity of the problem. Overall 7.8% of patients died.

Spontaneous reporting gives no indication of rate, since we do not know how many patients were treated but did not have an event. The rate of fatal rhabdomyolysis with statins has been estimated as 0.15 per million prescriptions in the USA. Rates for individual statins are shown in Table 24.

Once again, the data rely on voluntary reporting, so are likely to underestimate the problem. In addition the denominator is number of prescriptions not number of patients treated.

Randomised placebo-controlled trials support a low incidence of muscle problems, and may provide us with background and on-treatment event rates. Of 30 such trials identified by this review, 20 reported on rhabdomyolysis, and 18 on myositis. In no trial was there a significant difference between statin and placebo groups for either outcome, with only 12 cases reported in total. The included trials had mean or median durations ranging from 0.2 and 6 years, but were heavily dominated by the larger trials lasting five years. Numbers of patients treated and numbers of events are shown in Table 25, and estimates of rates are shown in Table 26.

Table 23: Reports of rhabdomyolysis to the FDA, January 1st 1990 to March 31st 2002

Drug	Number of reports	Reports of rhabdomyolysis due to drug %	Age%*		Outcomes %*	
			up to 50 years	greater than 50 years	Death, disability or hospitalisation	Life threatening
Cerivastatin	1869	57	5.8	68	67	8.2
Simvastatin	612	18	9.9	78	67	14
Atorvastatin	383	12	13	63	57	9.7
Pravastatin	243	7.3	8.6	63	72	10
Lovastatin	147	4.4	7.5	67	68	14
Fluvastatin	55	1.6	1.8	75	61	14
Total	3339	100	7.9	68	66	10

*percentages do not sum to 100 because of missing data

Table 24: Incidence of fatal rhabdomyolysis with different statins, using prescription data

Drug	Incidence (per million prescriptions)
Cerivastatin	3.16
Lovastatin	0.19
Simvastatin	0.12
Pravastatin	0.04
Atorvastatin	0.04
Fluvastatin	0.00

As a rough guide we can say that for every 100,000 patients treated for one year, four will suffer from rhabdomyolysis, and 33 will suffer from myositis, but these rates do not differ significantly from those observed in the placebo group.

Reporting of other less severe muscle problems in the trials was very incomplete, but showed no differences between statin and placebo groups.

Can the results of carefully controlled clinical trials of statin monotherapy be generalised to unselected patients in normal clinical practice? Muscle problems increase with serum concentration of statin, and many factors can potentially affect this concentration. These include body size and sex (volume of distribution), renal and hepatic function, age, hypothyroidism, debilitation, diabetes, concomitant medications and genetic factors (drug metabolism and catabolism).

Table 26: Incidence of rhabdomyolysis and myositis reported in randomised controlled trials

Event	Rate per 100,000 patients treated		NNH
	Statin	Placebo	
Rhabdomyolysis	20	14	17583
Myositis	170	150	5672

Concomitant medication

Many of the patients for whom statins are prescribed will suffer from other medical problems requiring medication. More than half of the reports of statin-induced rhabdomyolysis identified in the Qscan FDA database in this study were associated with concomitant medications affecting statin metabolism, and of these more than one third were associated with fibrates, and gemfibrozil in particular. Other concomitant medicines that might increase risk of statin-associated myopathy include amiodarone, azole antifungals, macrolide antibiotics or even grapefruit juice.

The mechanisms by which statins produce their effects on muscle are not well understood and are likely to be complex. A number of theories have been proposed and are discussed in the review. Briefly they include:

- destabilisation of cell membranes;
- reduction in production of small regulatory proteins important for myocyte maintenance, resulting in increased cytotoxicity;
- a shift towards anaerobic metabolism causing mitochondrial dysfunction.

Table 25: Rhabdomyolysis and myositis reported in randomised controlled trials

Event	Number of trials reporting	Number of patients		Number with event		Relative risk (95% CI)
		Statin	Placebo	Statin	Placebo	
Rhabdomyolysis	20	35406	35503	7	5	1.4 (0.45 - 4.42)
Myositis	18	29440	29568	49	44	1.12 (0.74 - 1.68)

Comment

Statins are associated with a range of muscle problems, but they are not common, and are nearly always reversible on withdrawal. In randomised controlled trials the frequency and severity of these problems did not differ between treated and placebo groups. A number of factors that are commonly present in patients who need to take statins can increase the likelihood of muscle effects.

Polyneuropathy and statins

Myopathy is a recognised risk associated with the use of lipid lowering drugs. In general practice in the UK one estimate is that the incidence of myopathy in users of lipid lowering drugs is 2.3 per 10,000 person years, with a relative risk compared with nonusers of 42 for fibrates and 8 for statins [99]. A new study [100] tells us that polyneuropathy is also likely to be a problem, and that it needs looking at.

Study

This was conducted in a county of Denmark with a population of 465,000. Residents have a civil registration number that is used in discharge prescription registries, so that it is possible to find all residents with a particular disorder, and find out what drugs they have been prescribed.

In a five-year period to the end of 1998, all patients with a discharge of polyneuropathy were examined. Some lived elsewhere, some were diagnosed before the study period, some had predisposing conditions (renal failure, diabetes, thyroid), and others had no proper diagnosis or were wrongly diagnosed. Clinical diagnostic features were distal symmetric sensory symptoms or symmetric motor symptoms and no upper motor neurone signs, or both. Neurophysiological criteria were abnormal conduction in two or more peripheral nerves, with at least one being a leg nerve.

A diagnosis of peripheral neuropathy was only accepted if both clinical and nerve conduction criteria were compatible with the diagnosis. Several levels of confidence were defined for idiopathic polyneuropathy (Table 27). For each case, all inhabitants of the same sex and age were used to randomly choose 25 control subjects per case.

Table 27: Definition of diagnosis of polyneuropathy

Description	Definition
Definite	Adequate work up and tested for exclusion diagnoses and conditions, and no apparent cause of neuropathy established
Probable	Only sufficient information to rule out alcohol overuse, diabetes and renal insufficiency
Possible	Information not sufficient to ascertain presence or absence of any exclusion diagnosis

Table 28: Statin exposure in all cases and definite cases of polyneuropathy

Statin exposure	Cases	Controls	Odds ratio (95%CI)
All cases			
Never use	157	4084	1
Current use	8	49	4.6 (2.1 to 10)
Definite cases			
Never use	27	854	1
Current use	7	17	16 (5.7 to 45)

Results

There were 166 cases (mean age 59 years) of first time diagnosis of polyneuropathy in the five years, of which 35 were definite, 54 probable, and 77 possible. Of these nine (5.4%) had a previous exposure to statins (eight current users), with a median duration of 2.8 years. There were 4,150 controls, of whom 66 (1.6%) had exposure to statins (49 current users).

The relative risk of polyneuropathy for current users was 4.6 (2.1 to 10) for all cases with current use, and 16 (5.7 to 45) for definite cases with current use (Table 28). Odds ratios were higher for more than two years of use compared with less than two years, and for larger numbers of doses than smaller numbers.

The number needed to harm (NNH) based on all patients was calculated as 5,500 (2,200 to 18,500). In those over 50 the incidence of polyneuropathy in the background population was 1.7 per 10,000 person years, with an excess rate of 4.5 per 10,000 person years among those exposed to statins. That is roughly one excess case of polyneuropathy for every 2,200 (880 to 7,300) person years of statin use.

Comment

In 1998 about 1% of the Danish population used a statin. It's probably more now, both in Denmark and elsewhere. If a primary care organisation with 100,000 inhabitants had 1% taking statins, a case of polyneuropathy might be expected every second year. That's twice as frequent as a case of myopathy.

In primary care in England in 2001 there were about 13 million prescriptions for statins, at a cost of about £420 million. It is not possible to extrapolate too much from that, other than to conclude that with so much statin use, these rare adverse events will occur and should be noticed. Awareness of that may be important in limiting their impact. This is a powerful and interesting paper, demonstrating how good government information systems can be used for the good of its population. It is important in understanding risk, though not of causation nor mechanism.

Statins: when should you take the tablet?

For simvastatin, the evidence is that marginally better lowering of total and LDL cholesterol comes from taking the tablets in the evening than in the morning.

Most manufacturers of statins recommend that they are taken at night because physiological studies show that most cholesterol is synthesised when dietary intake is low. Bandolier 88 (June 2001) looked for clinical evidence to support taking statins in the evening, and found one small trial that was not terribly convincing in terms of credibility or clinical relevance. We asked for "a large study demonstrating that normal doses of evening statin produced convincingly lower cholesterol levels than normal doses of morning statin", and now have two studies that make things a little clearer.

Study1

The first study [101] enrolled 25 patients with coronary artery disease (mean age 66 years) who were stable on 10-40 mg simvastatin daily. Patients were randomised to receive their usual dose either in the morning or in the evening for six weeks, followed by the alternate regimen. Blood samples were taken after an overnight fast at baseline and at six and 12 weeks, after each treatment period, for determination of total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides.

The study found a statistically significant increase in total and LDL-cholesterol when simvastatin was taken in the morning compared to the evening, but no changes in HDL-cholesterol or triglycerides. Levels at baseline did not differ from levels for the corresponding time of dosing during the study, and no period effects or treatment-period interactions were found. The investigators also measured high, sensitive C-reactive protein as a marker of effects on the immune system, and found that levels were not influenced by time of dosing.

Study 2

The second study [102] enrolled 60 patients (mean age 66 years) who were stable on 10 or 20 mg simvastatin daily, taken in the evening. Patients were randomised to receive their usual dose in the morning or the evening for eight weeks, and fasting blood samples were taken at baseline and at eight weeks to determine total, LDL-, and HDL-cholesterol and triglycerides.

Again, the study found a statistically significant increase in total and LDL-cholesterol, but not HDL-cholesterol or triglycerides, when simvastatin was taken in the morning compared to the evening. Levels of alanine transferase were also measured and were not affected by time of dosing.

Comment

These studies support the recommendation that simvastatin should be taken in the evening to maximise lipid-lowering effects. It is not clear whether time of dosing influences other effects of statins, such as endothelial function and plaque stability, but the first study suggests that it does not influence effects on the immune system mediated by C-reactive protein.

The size of the change is probably of clinical relevance, but only if evening dosing is reliable. There is an inverse relationship between patient compliance and both number of drugs and number of doses per day, and there can be fur-

Table 29: Lipid levels at baseline and after morning or evening dosing of simvastatin (n=25)

	mmol/L			
Lipid fraction	Evening (SD)	Morning (SD)	Change (95% CI)	p value
Total cholesterol	4.5 (0.9)	4.8 (1.1)	0.34 (0.14 to 0.52)	0.002
LDL-cholesterol	2.5 (0.7)	2.8 (0.9)	0.39 (0.24 to 0.54)	<0.001
HDL-cholesterol	1.4 (0.3)	1.4 (0.3)	-0.04 (-0.12 to 0.05)	NS
Triglycerides	1.4 (1.0)	1.4 (0.9)	0.01 (-0.16 to 0.18)	NS

Table 30: Levels of lipids at baseline and difference in change after morning versus evening dosing of simvastatin (n=60)

	mmol/L		
Lipid fraction	Baseline (SD)	Change (95% CI)	p value
Total cholesterol	4.4 (0.8)	0.38 (0.17 to 0.59)	0.001
LDL-cholesterol	2.4 (0.6)	0.25 (0.06 to 0.44)	0.012
HDL-cholesterol	1.3 (0.3)	0.02 (-0.03 to 0.08)	0.43
Triglycerides	1.6 (0.8)	0.09 (-0.31 to 0.48)	0.67

ther loss in compliance when medication regimens are changed. What is really important is that the patient takes the drug reliably, and if that is easier with morning dosing, the extra10 to 13% reduction in LDL-cholesterol potentially achieved with evening dosing is probably worth foregoing. An evening dose is more easily forgotten.

Finally, these studies have looked at simvastatin, and may not apply to other statins. One trial using atorvastatin found no differences with morning and evening dosing, which may be explained by its longer half life.

Summary

This overview has sought to bring together all the relevant information about statins available up to early 2004.

Statins are important for lots of reasons. Cholesterol-lowering drug prescriptions have increased seven-fold in the last five years in the UK, with statins accounting for 92% of prescriptions and 95% of cost (about £350 million a year in 2001). Simvastatin (43%) and atorvastatin (32%) were the most commonly prescribed, though it is likely that rosuvastatin will join them because of its potency. There are estimates that about 1% of adults take a statin, and that in future that could rise to 10% (though someone will have to pay). Not everyone prescribed a statin takes it, and this could dramatically reduce their benefit for a population.

Long-term benefits are reduced heart attacks and strokes, and the evidence for this is extremely robust, with a number of large studies, both industry sponsored and independently sponsored. They all give the same result. But when many people are taking tablets for many years, we have to think about rare but serious adverse effects.

As always, and with any review, new information could come out tomorrow that changes our, and your, view. But given that statins have now been available for over a decade, and been widely prescribed, the chance of new information overturning the old is extremely unlikely.

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