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Fluvastatin
Clinical and Safety Profile

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Contents

Abstract

Therapy with HMG-CoA reductase inhibitors (statins) has been shown to significantly reduce major coronary events and death in a wide range of individuals at risk for these events. In addition, recent observations suggest that some of the clinical benefits associated with statin therapy may be pleiotropic; that is, independent of their cholesterol-inhibiting action. It is clear that the clinical benefits associated with statin therapy far outweigh the risks; however, there may be important clinical differences among agents within the class, related to both benefits and drug safety. Evaluation of the benefit-to-risk profile for each available statin should include considering the results of randomised clinical outcome trials, the safety record of each agent, effect on lipoproteins and evidence of beneficial pleiotropic properties.

Recently, data from several clinical outcome trials have shown that substantial benefits are associated with treatment with fluvastatin in diverse populations. In particular, data from two large, randomised clinical trials have demonstrated that fluvastatin is effective for secondary prevention of cardiac events in patients

following coronary intervention procedures, and for primary prevention of cardiac events in renal transplant recipients. Pleiotropic benefits for fluvastatin have been shown in experimental and clinical studies as well. Fluvastatin was the first statin available as an extended-release product (fluvastatin XL 80mg); both formulations have demonstrated efficacy and safety in a wide range of patients. Taken together, these clinical outcomes and safety data suggest a strong benefit-to-risk profile for fluvastatin.

In the US, there are currently six available HMG-CoA reductase inhibitors, commonly referred to as statins: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin, all of which significantly lower low-density lipoprotein (LDL)-cholesterol. All of these statins, with the exception of rosuvastatin, have demonstrated the ability to reduce cardiovascular events, compared with placebo, in randomised controlled trials (RCTs).[1-10] As a class, the benefits of statins far outweigh the small risks associated with their use; yet there may be important differences among the agents within the class. Clinical differences among statins are best judged by their comparative benefit-to-risk profile, considering the following characteristics: (i) pharmacokinetic profile; (ii) effects on the entire lipid profile; (iii) the results of RCTs designed to determine clinical outcomes; (iv) the safety record of each agent; (v) the potential for drug interactions; and (vi) the evidence for beneficial pleiotropic properties. Fluvastatin sodium (Lescol®)[1] has been commercially available internationally since 1994 and, thus, could be considered a relative newcomer among statins. In this paper we review data on fluvastatin and the extended release formulation (fluvastatin XL) regarding clinical outcomes in RCTs, safety, effect on lipoproteins and evidence of beneficial pleiotropic properties.

1. Benefits and Risks of Statin Therapy

1.1 Clinical Outcome Trials

RCTs have established beyond doubt that treatment with statins prevents coronary heart disease (CHD), and reduces the incidence of cardiovascular events and death in a wide range of patients.[1-10] A meta-analysis of data from five of these trials,[11] including more than 30 000 patients, indicated that, compared with placebo, therapy with statins reduces LDL-cholesterol by 28%, major coronary events by 31%, coronary deaths by 29%, cardiovascular deaths by 21% and all-cause mortality by 21%.[11] More recently, a meta-analysis of nine large, long-term statin trials found a 14% reduction in all-cause mortality and a 27% reduction in CHD events.[12] Furthermore, patients at high risk for CHD appear to benefit clinically from statin therapy, regardless of their baseline LDL-cholesterol levels.[6-8,10]

The first five major statin clinical outcomes RCTs[1-5] established the benefits of statin therapy for primary or secondary prevention of CHD events. Each of these trials compared simvastatin, pravastatin or lovastatin with placebo in more than 4000 patients for periods of ≥5 years. More recently, data have been reported for six additional major clinical outcome RCTs: the Heart Protection Study (HPS),[6] Lescol Intervention Prevention Study (LIPS),[7] Prospective Study of Pravastatin in the Elderly at Risk (PROSPER),[8] Assessment of Lescol in Renal Transplantation (ALERT),[9] Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)[10] and Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT).[12] Data from HPS,[6] which followed more than 20 000 individuals for an average of 5 years, demonstrated benefits of therapy with simvastatin in a wide range of patients, including women, the elderly, patients with diabetes mellitus or occlusive noncoronary vascular disease, and in individuals

1 The use of trade names is for product identification purposes only and does not imply endorsement.

with low total cholesterol levels at baseline. In the lipid-lowering arm of ASCOT,[10] treatment was stopped early (at 3.3 years) because the benefits of treatment with atorvastatin in reducing major cardiovascular events were substantial at that point. Clinical outcomes data for fluvastatin in LIPS[7] – the first clinical outcomes RCT to compare a statin with placebo in patients who have recently had a coronary intervention procedure – and for ALERT[9] – the first clinical outcomes RCT to compare a statin with placebo in renal transplant recipients – are discussed in detail in section 2. Pravastatin did not reduce either all-cause mortality or CHD significantly when compared with usual care in older participants with well controlled hypertension and moderately elevated LDL-cholesterol levels in ALLHAT-LLT;[12] however, the usual care group had greater reductions in LDL-cholesterol (11%) than typical for placebo-controlled trials, because of a high treatment rate with lipid-lowering agents, and the resultant absolute difference in LDL-cholesterol levels between the two treatment groups was small.

1.2 Safety

As a class, the statins have proven to have extremely good safety profiles over nearly 2 decades of clinical use. The reported rates of serious adverse events with statins have been very low (<1%), and include a slight risk for elevation of liver enzymes and myopathy.[13] The risk for reversible elevation of liver transaminases (defined by ALT and/or AST levels >3 times the upper limit of normal [ULN]) is approximately 1% for all statins.

Myopathy is defined as elevations of creatine kinase (CK) levels that are 10 × ULN in a patient with symptoms (generalised muscle pain, fatigue or weakness).[13] Myopathy is not an uncommon clinical event and may be caused by a wide range of precipitants besides statin therapy; it is estimated to occur in approximately 0.1% of patients who receive statin monotherapy.[14] Because of the potential for progression to rhabdomyolysis and even death, the very small risk of myopathy is the greatest safety concern associated with statins. Importantly, early identification of myopathy and suspension of suspected drug therapies or other potential precipitants will prevent progression to rhabdomyolysis with renal failure in the vast majority of patients.[13] Relative to other statins, cerivastatin had a higher reporting rate for rhabdomyolysis and related fatalities.[15-17] Although the risk of statin-associated fatality was still very small, it was as much as ten times greater than with other available statins, and cerivastatin was voluntarily withdrawn from the global market by its manufacturer in 2001.[18]

In more than 50% of cases of statin-related rhabdomyolysis, a drug interaction has been suspected[19] (table I). Drug interactions are particularly relevant with statin therapy, as patients with cardiovascular disease are often managed with multiple medications. Thus, the issue of drug safety is related to the potential for drug reactions with statin therapy; furthermore, muscle toxicity is known to be more likely when the systemic concentration of a statin is increased.[20] Overall, statins are highly selective inhibitors of HMG-CoA and, therefore, show little pharmacodynamic interaction with other drugs. Once absorbed, statins are metabolised in the liver, which is the site of their primary mechanism of action, and exhibit a high degree of hepatic first-

Table I. Clinically reported drug interactions with statins associated with rhabdomyolysis[19]

Drug	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Fibric acid derivatives	+	+	+	+	+
Ciclosporin	+	−	+	+	+
Nicotinic acid	−	−	+	+	+
Macrolides	+	−	+	+	+
Digoxin	+	+	+	+	+
Imidazole antifungals	+	−	+	−	+
Warfarin	+	+	+	+	+

+ indicates a reported case; − indicates no reported case.

pass clearance. Thus, in general, statins have low systemic bioavailability.

On the other hand, pharmacokinetic interactions with other drugs can affect the processes by which statins are absorbed, distributed, metabolised and excreted; thus, other agents commonly affect the bioavailability of statins. Differences in pharmacokinetic properties among statins result in some important differences in their drug interaction potential. All of the statins, except pravastatin, are primarily metabolised through the cytochrome P450 (CYP) enzyme system and many drug interactions are the result of inhibition of CYP enzymes, which are responsible for the metabolism of the majority of drugs currently used in clinical practice.[21] Of note, drug interactions are encountered with atorvastatin, lovastatin and simvastatin, which are metabolised extensively via the CYP3A4 pathway.[13,19,22] Drug interactions with statins that may increase systemic statin concentrations and, consequently, the risk of muscle toxicity, are most relevant. Interactions with drugs frequently used concomitantly in patients requiring statin therapy have been reported with fibric acid derivatives (fibrates), nicotinic acid, immunosuppressive agents, macrolides, imidazole antifungals, warfarin and digoxin.[13,22,23]

In addition, drug interactions that may potentially increase systemic statin concentration may occur at the excretion level as a consequence of competition for carrier-mediated transport across the bile canalicular membrane or excretion may be limited by affinity for active drug transporters, such as P-glycoproteins.[13,22] Recent studies have provided evidence that glucuronidation is an important metabolic pathway for elimination of the hydroxyl acid forms of statins in both humans and animals.[24] Fibrates – in particular gemfibrozil – are also eliminated by glucuronidation and appear to have a pronounced inhibitory effect on the elimination of the acid forms of lovastatin, simvastatin, cerivastatin, atorvastatin and rosuvastatin.[25-27] Cerivastatin and gemfibrozil share common pathways for degradation by both oxidation and glucuronidation; this may explain the significantly higher risk of rhabdomyolysis that has been seem with this combination of drugs, compared with other combinations of statins and fibrates. As yet, there are no data on the mechanism of elimination for the acid form of fluvastatin; however, a recent report confirms the safety of fluvastatin when administered with various fibrates.[28]

1.3 Pleiotropic Effects

Statins modify circulating lipid levels by inhibiting the conversion of HMG-CoA to mevalonate, which is the rate-limiting step in cholesterol synthesis. The clinical benefits of statins are generally assumed to result from their ability to lower serum total- and LDL-cholesterol levels; however, mevalonate is also the precursor of many nonsteroidal isoprenoid compounds that are vital for diverse cellular functions (figure 1).[29] These isoprenoids include: (i) isopentenyl adenosine, present in some types of transfer RNA; (ii) dolichols, required for glycoprotein synthesis; and (iii) polyisoprenoid side chains of ubiquinone and heme A, involved in electron transport. Additionally, several proteins have been identified that are modified post-translationally by the attachment of mevalonate-derived isoprenoid groups; members of this family are involved in a number of cellular processes including cell signalling, differentiation and proliferation.[30,31] Because of their potential effects on these varied compounds, it appears that statins may have non-lipid-related – or pleiotropic – properties that exert direct effects on the arterial wall that can interfere with the formation and progression of atherosclerotic lesions.[32-34] Proposed non-lipid antiatherosclerotic and anti-inflammatory effects of statins include: (i) inhibition of smooth muscle cell growth, cell adhesion, platelet activation and C-reactive protein (CRP) secretion; (ii) inhibition of metalloproteinase secretion by macrophages; (iii) increased fibrinolytic activity; (iv) induction of myocyte apoptosis in proliferative lesions; (v) increased expression and activity of nitric oxide synthase; and (vi) modulation of angiogenesis.[30,34,35] These mechanisms may, in turn, modify endothelial function, inflammatory responses, plaque stability, smooth muscle cell proliferation and thrombus formation.[30,33,34,36-40]

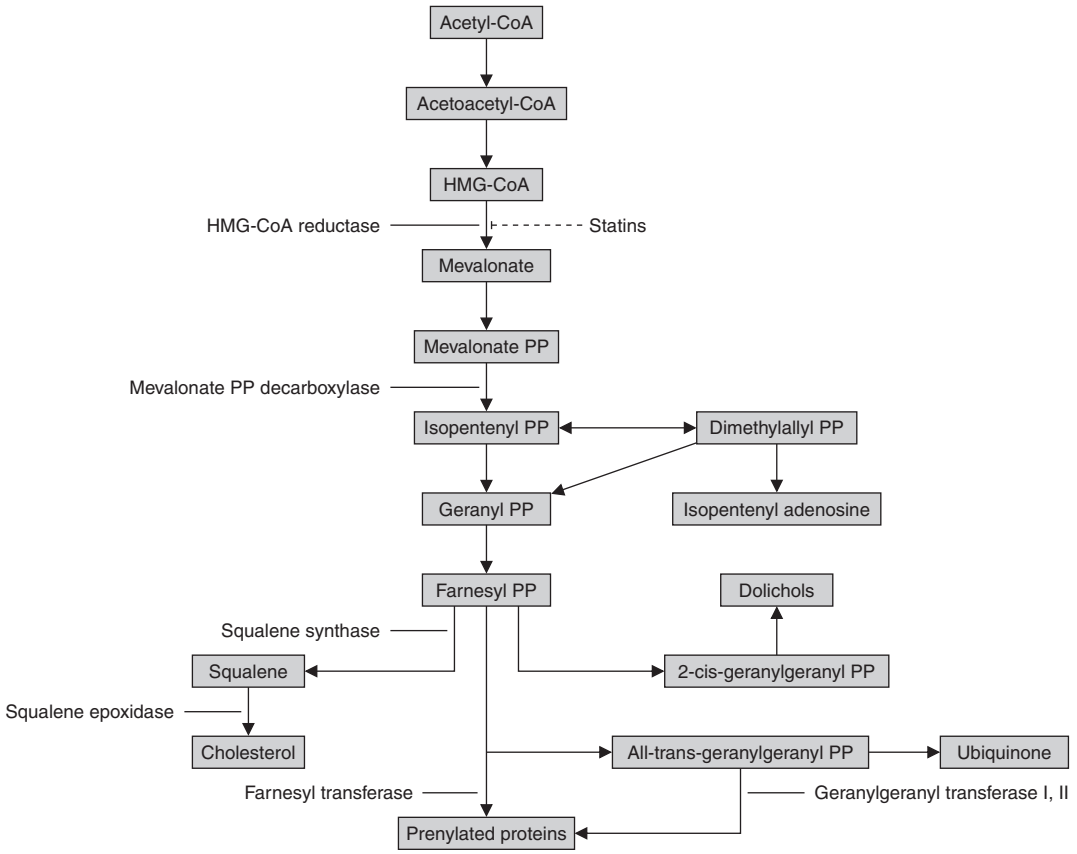


Fig. 1. Schematic of the mammalian cell mevalonate pathway (reproduced from Bellosta et al.,[29] with permission). **CoA** = coenzyme A; **PP** = pyrophosphate.

Experimental data have recently amassed demonstrating that statins exert a direct antiatherosclerotic effect on the arterial wall, although high dosages of statins are required to achieve some of these effects and corroboration is not yet available for many of these effects in human studies. A number of preclinical studies indicate that statins can be differentiated in terms of their pleiotropic properties.[33,41-48]

Clinical evidence of non-lipid-related effects of statins exist for anti-inflammatory effects, improvement of endothelial function and inhibition of smooth muscle cell proliferation.[30] Evidence for these non-lipid benefits have been supported by *post hoc* analyses of both the Cholesterol and Recurrent Events (CARE) trial[49] and West of Scotland Coronary Prevention Study (WOSCOPS).[50] Data from angiographic trials have also shown greater decreases in clinical events with statin therapy than may be expected based on the degree of lesion regression observed.[37]

2. Fluvastatin: Benefit-to-Risk Profile

2.1 Pharmacokinetic Properties

Fluvastatin is the first entirely synthetic statin. It is readily absorbed (98%), has no active metabolites, is highly protein bound (>99%) and is extensively cleared in the liver by first-pass effect. Excretion is primarily by the faecal route (>90%) with 6% by renal excretion.[22] Fluvastatin has several metabolic pathways which involve the CYP enzyme system,

but is primarily metabolised via the CYP2C9 pathway.[51] Thus, drug interactions with fluvastatin are reduced both because it is metabolised by multiple enzymes and because metabolism via the CYP3A4 pathway is limited. Drug interactions based on displacement of drugs highly bound to plasma proteins have not been demonstrated for fluvastatin, which shows the highest protein binding of all statins.[52]

Fluvastatin XL releases 80mg of fluvastatin over 8 hours. This formulation, compared with the immediate-release (IR) formulation, exhibits delayed absorption, lower bioavailability (6% vs 19–29% for fluvastatin IR), increased clearance and lower systemic exposure.[53] The slower delivery of fluvastatin increases its hepatic uptake and may serve to avoid hepatic saturation.[54]

2.2 Effects on Lipids

As reported in product literature, reductions in LDL-cholesterol with starting doses of statins are 39% with atorvastatin 10mg, 25% with fluvastatin 40mg, 33% with fluvastatin XL 80mg, 27% with lovastatin 20mg, 30% with lovastatin extended-release (ER) 20mg, 32% with pravastatin 20mg, 52% with rosuvastatin 10mg and 30% with simvastatin 10mg. Typically, doubling a statin dose increases the LDL-cholesterol reduction by about 6%; thus, the majority of LDL-lowering efficacy is achieved with the starting dose, which can then be increased by up to 6–18% by titrating the dose upward. The average placebo-subtracted reductions from baseline LDL-cholesterol among the major statin clinical trials ranged from 25% to 38%.

While treatment effects on LDL-cholesterol with fluvastatin 40 mg/day are modest compared with the starting dosages of other statins with the exception of lovastatin, treatment with fluvastatin XL 80 mg/day is similar to that with starting dosages of lovastatin, pravastatin and simvastatin. In a pooled analysis of clinical trial data, treatment with fluvastatin XL led to median reductions in LDL-cholesterol of 38% at 4 weeks; reductions of ≥40% were achieved by 40% of these patients.[55] Fluvastatin XL was effective in raising high-density lipoprotein (HDL)-cholesterol levels, with a mean overall increase of 8.7%, increasing to 21% in the subset of patients with baseline triglyceride levels ≥300 mg/dL (3.39 mmol/L). Median decreases in triglyceride levels were 19%, increasing to 31% in the subset of patients with baseline triglyceride levels ≥300 mg/dL. Other lipid parameters were also improved: the LDL : HDL cholesterol ratio was reduced by 38%, apolipoprotein (apo) B level was reduced by 25% and apoA-I level was increased by 8%.

A randomised, placebo-controlled trial[56] assessed the efficacy and safety of fluvastatin XL 80 mg/day in 1229 elderly (aged 70–85 years) men and women; the mean LDL reduction in this group was 31% after 6 months of treatment. Furthermore, in a small, placebo-controlled RCT conducted in 89 patients with type 2 diabetes,[57] fluvastatin XL 80 mg/day decreased LDL-cholesterol by 29% and triglycerides by 18% after 8 weeks of treatment. As is typical for this population, 79% of patients had an atherogenic lipid profile characterised by a preponderance of dense LDL particles (defined as apoB in LDL-5 and LDL-6 >25 mg/dL). In this group of patients, fluvastatin XL decreased dense LDL by 28%.

2.3 Clinical Events Data from Randomised Controlled Trials

Recently, data from five clinical outcomes RCTs have been published that have established the clinical benefits of fluvastatin (table II). There are two large RCTs, LIPS[7] and ALERT,[9] that have extended the clinical benefits of statin therapy into two new populations: patients following percutaneous coronary intervention (PCI) and renal transplant recipients. Three other fluvastatin trials have also been reported that have shown clinical benefits with fluvastatin: the Lipoprotein and Coronary Atherosclerosis Study (LCAS),[58,59] Lescol in Severe Atherosclerosis (LiSA)[60] and Fluvastatin Angioplasty Restenosis (FLARE).[61] In addition, the Fluvastatin on Risk Diminishment after Acute Myocardial Infarction (FLORIDA) study[62] investigated the effect of fluvastatin 80 mg/day versus placebo on residual cardiac ischaemia (measured by 48-hour ambulatory ECG monitoring) and major cardiac

Table II. Randomised, placebo-controlled trials of fluvastatin with primary or secondary clinical endpoints

Trial	Population (n)	Study duration	Fluvastatin dose (mg/day)	Mean LDL reduction (%)	Clinical endpoint	Clinical outcome for treatment with fluvastatin
LCAS[58,59]	Patients with angiographic CHD (429)	2.5y	40	24	Primary: progression of angiographically proven atherosclerotic lesions	Significantly less progression of lesions ($p < 0.01$)
					Secondary: MACE and all-cause mortality	Significantly reduced incidence of clinical events in the subgroup of patients with low baseline HDL ($p = 0.002$)
LiSA[60]	Patients with clinical CHD (365)	12mo	40–80	27	Primary: cardiac death, nonfatal MI, and unstable angina	Significantly reduced incidence of cardiac events ($p < 0.05$)
FLORIDA[62]	Patients following acute MI (540)	12mo	80	21	Residual ischaemia or MACE	No significant difference between fluvastatin and placebo overall; trend towards reduction in MACE in patients with profound ischaemia at baseline
FLARE[61]	Post-PTCA[a] patients (1054)	40 wks	80	33	Primary: incidence of restenosis	No significant reduction in the incidence of restenosis
					Secondary: MACE and all-cause death	Significantly reduced the incidence of combined MI and total deaths ($p = 0.025$)
LIPS[7]	Post-PCI patients (1677)	3.9y (mean)	80	27 (median)	Primary: incidence of MACE	Significantly reduced the incidence of MACE by 22% ($p = 0.01$).
						Significantly greater benefits for patients with diabetes mellitus or multivessel disease
ALERT[9]	Renal transplant patients (2102)	5–6y	40–80	32	Primary: incidence of MACE	No significant reduction ($p = 0.139$)
					Secondary: combined cardiac death and nonfatal MI	Significantly reduced risk by 35% ($p = 0.005$)

a PTCA by balloon angioplasty.

ALERT = Assessment of Lescol in Renal Transplantation; **CHD** = coronary heart disease; **FLARE** = Fluvastatin Angioplasty Restenosis; **FLORIDA** = Fluvastatin On Risk Diminishment after Acute Myocardial Infarction; **HDL** = high-density lipoprotein; **LCAS** = Lipoprotein and Coronary Atherosclerosis Study; **LDL** = low-density lipoprotein; **LIPS** = Lescol Intervention Prevention Study; **LiSA** = Lescol in Severe Atherosclerosis; **MACE** = major adverse cardiac events; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **PTCA** = percutaneous transluminal coronary angioplasty.

events in patients during 12 months following an acute myocardial infarction (MI).

2.3.1 Lipoprotein and Coronary Atherosclerosis Study (LCAS)

Patients (n = 429) enrolled in LCAS[58] had CHD with documented angiographic lesions and mild-to-moderate elevations of LDL-cholesterol (mean, 146 mg/dL [3.78 mmol/L]); evaluable angiographic data were available for 340 patients. Over 2.5 years of follow up, fluvastatin-treated patients had mean LDL-cholesterol reductions of 24% and showed significantly less progression of qualifying lesions assessed by quantitative coronary angiography compared with placebo (p = 0.005). LCAS was an angiographic trial and, therefore, was not designed to detect statistically significant differences in clinical event rates; however, there was a 24% reduction in the fluvastatin group, compared with the placebo group, in the occurrence of clinical events (MI, revascularisation, unstable angina requiring hospitalisation or death), which was not statistically significant.

About 20% of the patients in LCAS (n = 68) had low baseline HDL-cholesterol levels (<35 mg/dL [0.91 mmol/L]) and a *post hoc* analysis of this cohort was conducted.[59] Among placebo-treated patients, those with low baseline HDL-cholesterol levels had significantly more angiographic progression than those with higher baseline HDL-cholesterol levels. Treatment with fluvastatin significantly reduced lesion progression among patients with low HDL-cholesterol (p = 0.0004); furthermore, fluvastatin treatment significantly lowered clinical events, compared with placebo, in these patients (p = 0.002). Achieved LDL-cholesterol reductions were similar in both high and low HDL-cholesterol patients; thus, the greater angiographic and clinical benefits of treatment with fluvastatin in patients with low baseline HDL-cholesterol cannot be entirely explained by LDL-cholesterol reductions. This was an important subgroup finding, as many patients with CHD seen in clinical practice do not have substantially elevated LDL-cholesterol; however, many have low HDL-cholesterol.

2.3.2 Lescol in Severe Atherosclerosis (LiSA)

In LiSA,[60] 365 patients with elevated LDL-cholesterol (>160 mg/dL [4.14 mmol/L]) and symptomatic, ischaemic CHD (based on exercise ECG testing) who were treated with fluvastatin 40–80 mg/day had a significantly lower incidence of cardiac events over 12 months of follow-up than placebo recipients (p < 0.05), a very early demonstration of clinical outcome benefits.

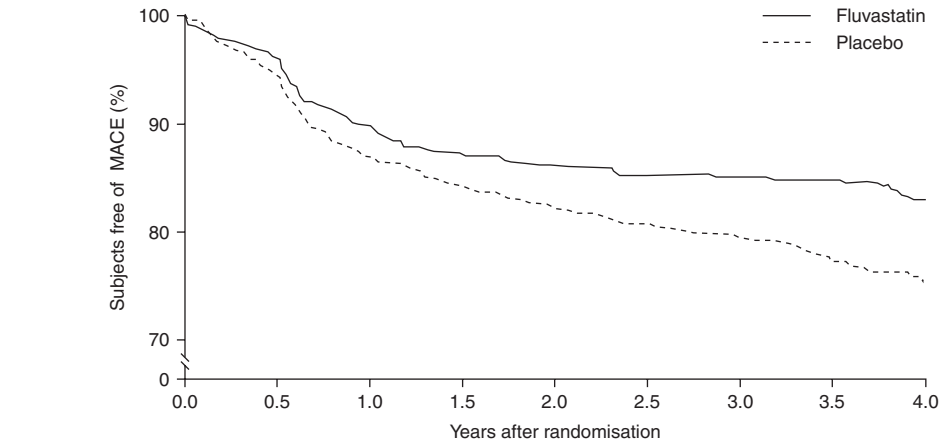
2.3.3 Fluvastatin Angioplasty Restenosis (FLARE)

In FLARE,[61] patients were randomised to either placebo or fluvastatin 40mg twice daily beginning 2–4 weeks before a planned PCI by balloon angioplasty, and were then followed for 40 weeks. Treatment with fluvastatin did not influence the rate of restenosis, just as trials with other statins have failed to show benefit on preventing restenosis.[63-66] Treatment with fluvastatin resulted in a statistically significant reduction in the combined outcomes of overall death and MI at 40 weeks (p = 0.025).

2.3.4 Lescol Intervention Prevention Study (LIPS)

The reduction in cardiac events seen in the post-PCI population in FLARE was confirmed in LIPS, the first large, prospective, international RCT to investigate the effect of statin therapy on clinical outcomes following a successful PCI.[7] The results of this trial are important because, while PCI is associated with excellent short-term improvement in symptoms such as angina pectoris, patients continue to have high rates of cardiac events following these procedures. The study's primary clinical outcome was the incidence of major adverse cardiac events (MACE), defined as cardiac death, nonfatal MI or a reintervention procedure. Enrolment in LIPS comprised 1677 patients (aged 18–80 years, inclusive) in 57 centres in Europe, Brazil and Canada. Patients were randomised to fluvastatin 40mg twice daily or placebo within days of successful completion of their first PCI.

By 6 weeks, fluvastatin significantly reduced LDL-cholesterol by a median of 27% and these reductions were maintained throughout the follow-up period. Over a median follow-up time of 3.9 years, fluvastatin therapy resulted in a significant risk reduction of 22% in the incidence of MACE



Subjects at risk

Fluvastatin	844	757	713	692	268
Placebo	833	725	679	645	241

Fig. 2. Major adverse cardiac event (MACE)-free survival time, excluding reinterventions, in Lescol Intervention Prevention Study (LIPS). Data were calculated excluding surgical or percutaneous coronary reinterventions occurring in the first 6 months of follow-up for lesions treated at the index procedure. $p < 0.001$ by log-rank test (reproduced from Serruys et al.,[7] with permission).

compared with placebo ($p = 0.01$), a result that was independent of baseline total cholesterol levels. Analysis of the prespecified secondary endpoint of MACE, excluding revascularisation (surgical or PCI) during the first 6 months for lesions treated at the index procedure, indicated a significant 33% risk reduction with fluvastatin ($p < 0.001$) and significantly extended MACE-free survival time (figure 2). As in LCAS, higher-risk patients appeared to reap the greatest benefits. In patients with diabetes (12% of the total population), the risk reduction for MACE with fluvastatin was 47% ($p = 0.04$ compared with placebo), and in those with multivessel disease (37% of the total population) the risk reduction with fluvastatin was 34% ($p = 0.01$) [figure 3]. In a *post hoc* analysis, the fluvastatin group showed lower rates of cardiac death or nonfatal MI starting as early as 6 months. Thus, in LIPS, therapy with fluvastatin reduced LDL-cholesterol significantly and reduced the incidence of cardiac events, with benefits in the highest-risk patients. Fluvastatin was well tolerated, with no elevations in CK levels of ≥10 × ULN in the fluvastatin group. The clinical benefits were independent of baseline cholesterol levels and occurred in patients who had normal LDL-cholesterol levels at baseline. These results suggest that treating 19 patients for 4 years with fluvastatin would prevent one fatal or nonfatal major cardiac event.

2.3.5 Assessment of Lescol in Renal Transplantation (ALERT)

ALERT[9] was the first large RCT to study cardiac outcomes in renal transplant recipients, who are at extremely high risk for major coronary events and also at high risk for drug interactions, because of the need for chronic immunosuppressive therapy. Renal transplant recipients taking ciclosporin (cyclosporin) and with total cholesterol levels between 155 and 348 mg/dL (4 and 9 mmol/L) were randomly assigned to fluvastatin (n = 1050) or placebo (n = 1052) and followed for 5–6 years. As in LIPS, the primary endpoint was the incidence of MACE (defined as cardiac death, nonfatal MI or PCI).

After a mean follow-up of 5.1 years, fluvastatin lowered mean LDL-cholesterol levels by 32%. The absolute net reduction in LDL-cholesterol (1 mmol/L) and the percentage reduction in cardiac events with fluvastatin were similar to those observed in other major statin outcome trials (table III). Fluvastatin significantly reduced the risk of cardiac

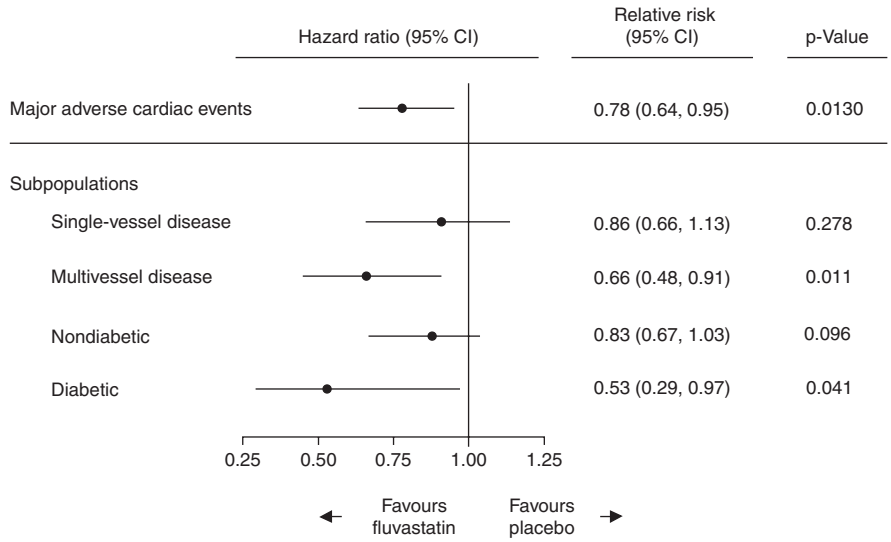


Fig. 3. Relative risk of major adverse cardiac events in the total population and subpopulations in Lescol Intervention Prevention Study (LIPS), showing greater clinical benefits in higher-risk populations. $p < 0.001$ for fluvastatin, compared with placebo (reproduced from Serruys et al.,[7] with permission).

death by 38% ($p = 0.031$) and of combined cardiac death or first definite nonfatal MI by 35% ($p = 0.005$), compared with placebo (figure 4). No significant difference was seen for the incidence of PCI compared with placebo; thus, the composite primary endpoint of first MACE showed a 17% risk reduction with fluvastatin that was not statistically significant ($p = 0.139$) [figure 4]. Adverse event rates were similar in both treatment groups, as were rates of discontinuation because of adverse events. The incidence of ALT elevations (≥3 × ULN) or CK elevations (≥5 × ULN) in ALERT was similar in fluvastatin- and placebo-treated patients, and no elevations were accompanied by musculoskeletal symptoms. The safety profile is perhaps the most remarkable aspect of this trial, as all the renal transplant patients enrolled in ALERT were receiving ciclosporin, 80% were receiving prednisone and 95% received concomitant cardiovascular medications (table IV). Along with LIPS, ALERT extends the evidence of clinical benefits with statin therapy for important high-risk populations who have not previously been studied in a major statin clinical outcome trial. These data indicate that the number needed to treat in order to prevent one cardiac death or nonfatal MI over 5 years would be 31 patients, representing a relatively small cost in overall care for this population.

2.3.6 Fluvastatin on Risk Diminishment after Acute Myocardial Infarction (FLORIDA)

In FLORIDA,[62] 540 patients post-MI were randomised to fluvastatin 80 mg/day or placebo. The primary endpoint was the effects of fluvastatin on 48-hour ambulatory ECG monitoring and clinical events. Because residual ischaemia was observed less frequently in the study population in FLORIDA (present at baseline in 60/540 [11%] of patients) than had been reported in other studies, the study was markedly underpowered and did not show any effect of fluvastatin treatment benefit on the composite primary endpoint of residual ischaemia or major clinical events at 12 months for the total population. However, there was a trend toward reduction in major clinical events in a *post hoc* analysis of patients with the most pronounced ischaemia at baseline ($n = 30$; $p = 0.08$).

2.4 Safety Profile

In order to review clinical trials for risk of myopathy with fluvastatin monotherapy, safety data

Table III. Low-density lipoprotein (LDL)-cholesterol levels and coronary heart disease (CHD) event rates[a] in major statin trials

Study	Agent (dosage, mg/day)	Sample size (n)	Follow-up (y)	Baseline LDL (mmol/L)	LDL-cholesterol net change[b] (mmol/L)	LDL-cholesterol reduction[b] (%)	CHD event rate/year[c]	CHD risk reduction (%)
4S[1]	Simvastatin (40)	4444	5.4	4.9	1.7	36	5.2[d]	34
WOSCOPS[2]	Pravastatin (40)	6595	4.9	5.0	1.3	26	1.5	32
AFCAPS/ TexCAPS[5]	Lovastatin (20–40)	6605	5.2	3.9	1.0	27	1.0[e]	37
CARE[3]	Pravastatin (40)	4159	5.0	3.6	1.0	28	2.6	24
HPS[6]	Simvastatin (40)	20 536	5.0	3.4	1.0	31	2.3	27
PROSPER[8]	Pravastatin (40)	5804	3.2	3.8	1.0	27	3.8	19
ASCOT-LLA[10]	Atorvastatin (10)	10 305	3.3	3.4	1.0	29	0.9	36
ALERT[9]	Fluvastatin (40)	2102	5.1	4.1	1.0	32	2.0	35
LIPID[4]	Pravastatin (40)	9014	6.1	3.9	0.9	25	2.6	24
LIPS[7]	Fluvastatin (80)	1677	3.9	3.4	0.9	27	1.8	31

a CHD events refers to cardiac death or nonfatal myocardial infarction, unless otherwise indicated.

b For treated patients; placebo-subtracted change from baseline (net change) and percentage change from baseline (percentage reduction).

c For placebo-treated patients.

d Including silent myocardial infarction plus resuscitated cardiac arrest.

e Including unstable angina.

4S = Scandinavian Simvastatin Survival Study; **AFCAPS/TexCAPS** = Air Force/Texas Coronary Atherosclerosis Prevention Study; **ALERT** = Assessment of Lescol in Renal Transplantation; **ASCOT-LLA** = Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; **CARE** = Cholesterol and Recurrent Events; **HPS** = Heart Protection Study; **LIPID** = Long-Term Intervention with Pravastatin in Ischaemic Disease; **LIPS** = Lescol Intervention Prevention Study; **PROSPER** = Prospective Study of Pravastatin in the Elderly at Risk; **WOSCOPS** = West of Scotland Coronary Prevention Study.

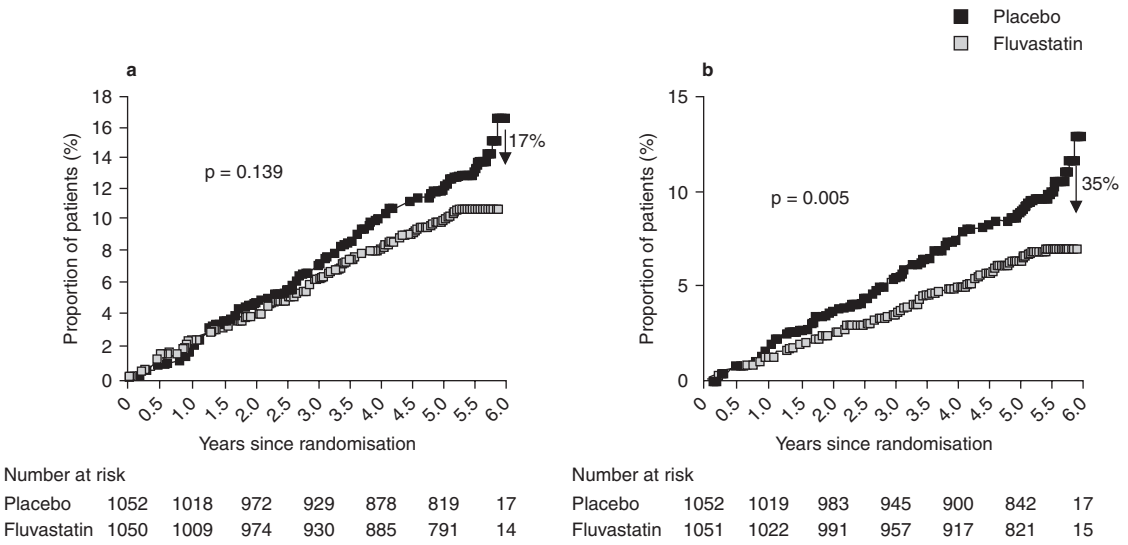


Fig. 4. Cumulative rates for primary composite endpoints of total major adverse cardiac events (**a**) and cardiac death or definite myocardial infarction (**b**) in Assessment of Lescol in Renal Transplantation (ALERT). Analyses by intent-to-treat (reproduced from Holdaas et al.,[9] with permission from Elsevier [The Lancet, 2003, Vol. 361, pages 2024-31]).

were pooled from all Novartis-sponsored RCTs between 1987 and 2001; in these studies, 8951 patients with hypercholesterolaemia received fluvastatin (20–80 mg/day) or placebo.[67] The percentages of patients with CK ≥5 × ULN and CK ≥10 × ULN were calculated and are shown in table V. In all of these studies, there were no cases of rhabdomyolysis or myopathy, and the frequency of elevated CK levels was similar to that of placebo.

Table IV. Concomitant cardiovascular medications in Assessment of Lescol in Renal Transplantation (ALERT) [reproduced from Holdaas et al.,[9] with permission from Elsevier (The Lancet, 2003, Vol. 361, pages 2024-31)]

Medication	Fluvastatin (n = 1050)	Placebo (n = 1052)
Any cardiovascular drug	1001 (95.3%)	999 (95.0%)
Aspirin (acetylsalicylic acid)	371 (35.3%)	353 (33.6%)
Dipyridamole	21 (2.0%)	26 (2.5%)
Coumarin or warfarin	90 (8.6%)	94 (8.9%)
β-Adrenoceptor antagonists	649 (61.8%)	627 (59.6%)
Calcium antagonists	728 (69.3%)	738 (70.2%)
ACE inhibitor or ARB	520 (49.5%)	529 (50.3%)
Diuretics	590 (56.2%)	573 (54.5%)
α-Adrenoceptor antagonists	176 (16.8%)	170 (16.2%)
Other	316 (30.1%)	373 (35.5%)

ARB = angiotensin II receptor blocker.

As noted in section 1.2, myopathy is more likely to occur when statins are administered in combination with specific drugs, including fibrates.[68] In order to review clinical trials for risk of myopathy with fluvastatin-fibrate therapy, a pooled analysis of data from ten Novartis-sponsored studies conducted from 1987 to 2001, in which fluvastatin was administered in combination with a fibrate, was conducted.[28] Of 2592 patients included in the analysis, 1017 received fluvastatin 20–80 mg/day in combination with bezafibrate 200 or 400 mg/day, fenofibrate 200 mg/day or gemfibrozil 600 or 1200 mg/day; the other patients received either fluvastatin or fibrate monotherapy, or placebo. For the combination of fluvastatin with a fibrate, the frequency of CK elevations was not statistically different from that of placebo or of each drug used as monotherapy. Furthermore, no significant differences were found when the data were analysed by gender and age (men <65 years or ≥65 years; women <65 years or ≥65 years), and by duration of treatment (≤48 weeks or >48 weeks). Fluvastatin XL, with its low systemic availability and slight potential for drug interactions, may represent a first-choice statin for patients requiring combination lipid-lowering therapy.[69]

However, it should be noted that rhabdomyolysis has been reported with all statins, including fluvastatin, when combined with fibrates.[23]

The elderly are at greater than average risk for myopathy from any cause, and also at greater risk of progressing from myopathy to rhabdomyolysis because they are more likely to have less pronounced or atypical symptoms of myopathy. Thus, it is of particular importance to assess the safety of statin therapy in this population. In the RCT of 1229 elderly patients (mean age, 75.5 years; range, 69–92 years) discussed in section 2.2,[56] the overall safety profile of fluvastatin XL 80mg was similar to that of placebo and no patient had CK levels >5 × ULN.

As already discussed in section 2.3.5, fluvastatin has been found to be safely used in renal transplant recipients who were being concomitantly treated with ciclosporin.[9] No instances of drug-related rhabdomyolysis have been observed during clinical trials in which patients received fluvastatin and ciclosporin concomitantly.[9,70-76] There were two cases of rhabdomyolysis in the ALERT study,[9] one in a placebo-treated patient and one in a fluvastatin-treated patient; however, both cases were attributed by the investigators to trauma and not drug therapy. The safety of the combination of fluvastatin and ciclosporin in diabetic kidney transplant recipients has also been established.[71] In addition, fluvastatin has demonstrated safety and efficacy in patients with advanced chronic renal insufficiency,[77] and in patients with diabetic nephropathy who were being treated with dialysis.[78]

In all of the fluvastatin clinical outcome trials reviewed here, there were no cases of drug-related rhabdomyolysis, and critical CK levels were comparable with those of placebo-treated patients. In particular, fluvastatin XL (given at bedtime) has demonstrated excellent efficacy, tolerability and safety.[54,55,79,80] According to the US FDA MedWatch database reporting system,[17] rhabdomyolysis associated with fluvastatin represented only 1.6% (55 of 3339) of all reported cases.

2.5 Pleiotropic Properties

In numerous experimental studies, fluvastatin has shown potentially antiatherogenic pleiotropic effects by attenuating inflammatory cell dysfunction and responses to inflammatory molecules that are associated with thrombogenicity and instability in atheromatous plaque.[81] In many cases, these same effects were not seen with a comparator statin being investigated in the same study. Treatment with fluvastatin, but not pravastatin, significantly attenuated leucocyte-endothelial cell adhesion responses to platelet-activating factor and leukotriene B4 in postcapillary venules of hypercholesterolaemic rats.[82] This effect, which lowered the level of adherent leucocytes and improved leucocyte rolling velocity, occurred despite no changes seen in serum cholesterol after 10 days of treatment. Furthermore, fluvastatin, but not pravastatin, was found to induce apoptosis in rat cardiac myocytes,[83] reduce interleukin-6 *in vitro* in human vascular smooth muscle cells,[84] and inhibit proliferation of vascular smooth muscle cells.[85] Fluvastatin increased tissue plasminogen activator secretion and reduced the release of plasminogen activator inhibitor type 1 antigen in cultured human umbilical vein endothelial cells, while the addition of mevalonate suppressed this effect.[86] Fluvastatin also reduced macrophage accumulation in carotid lesions in rabbits.[42] Direct antioxidant effects on LDL, decreased atheromatous plaque formation, and inhibition of lipid peroxide levels and macrophage content in aortic atheroma-

Table V. Pooled data for elevated creatine kinase (CK) levels in 8951 patients receiving fluvastatin or placebo in randomised, controlled trials[67]

CK elevation	Placebo (%) [n = 2323]	Fluvastatin 20mg (%) [n = 2590]	Fluvastatin 40mg (%) [n = 4369]	Fluvastatin XL 80mg (%) [n = 1724]
≥5 × ULN	0.9	0.8	1.0	0.3[a]
≥10 × ULN	0.2	0.2	0.3	0.0

a p = 0.025 vs placebo; all other comparisons nonsignificant.

ULN = upper limit of normal.

tous plaque have been shown in several studies of cholesterol-fed rabbits treated with fluvastatin.[87,88]

LDL from ten hypercholesterolaemic patients was found to be less susceptible to lipid peroxidation after they had received fluvastatin therapy.[89] This inhibitory effect of fluvastatin therapy on LDL oxidation was found *in vivo* and *in vitro*, and probably involves both its propensity to bind to LDL and the subsequent stimulatory effect on LDL removal from the circulation.[90]

In several small clinical studies[91-98] (table VI), fluvastatin demonstrated significant therapeutic effects on a range of vascular outcomes that are closely linked to atherosclerosis and increased risk of cardiovascular events. In these studies, fluvastatin significantly improved vascular biological markers for microcirculation, myocardial perfusion and the rate of progression of carotid artery intima-media thickening in atherosclerotic lesions. Some of these effects may be directly related to the cholesterol-lowering effects of fluvastatin; however, other outcomes suggest the possibility of additional pleiotropic benefits from fluvastatin treatment. Furthermore, in LCAS[58] and LIPS,[7] the clinical benefits seen with fluvastatin were independent of baseline cholesterol levels, suggesting that non-lipid effects were involved.

CRP levels have been shown to be an even stronger predictor of cardiovascular events than LDL-cholesterol in some investigations.[35,99,100] Fluvastatin significantly reduced CRP levels by 16% in patients with hyperlipidaemia ($p < 0.001$),[101] a finding that has also been found with other statins. However, the relationship between statin-induced CRP lowering and CHD risk is still uncertain.

3. Summary and Conclusions

Clinicians in the US can currently choose from six statins approved for patients requiring lipid-lowering therapy. With its safety profile and evidence of clinical benefits, fluvastatin can play an important role in the treatment of patients with hypercholesterolaemia. Fluvastatin XL has been shown to reduce LDL-cholesterol significantly and to an extent similar to lovastatin ER, pravastatin and simvastatin at starting dosages, although to a lesser extent than atorvastatin and rosuvastatin. Because of its safety profile, fluvastatin and fluvastatin XL represent an excellent choice for:

- patients needing moderate LDL-cholesterol reductions to achieve LDL-cholesterol goals;
- patients requiring combination therapy with other lipid-lowering agents;
- patients taking multiple medications that place them at high risk for drug interactions during statin therapy; and
- high-risk patient populations, including patients with renal disease, renal transplantation patients and patients who have undergone coronary intervention procedures.

As reviewed, data from RCTs have shown that fluvastatin demonstrates clinical benefits in high-risk patients, including two very important populations that had not been previously studied: patients after PCI and renal transplant recipients. In LIPS,[7] fluvastatin significantly reduced the risk of MACE over 5 years when initiated immediately after a first PCI, even in patients with average cholesterol levels. Fluvastatin-treated patients were able to achieve on average LDL-cholesterol levels of <100 mg/dL (<2.6 mmol/L). In ALERT,[9] fluvastatin reduced mean LDL-cholesterol by 32% (1 mmol/L), with a reduction in cardiac death and nonfatal MI without any increase in myopathy or other adverse events compared with placebo. The remarkable safety observed in renal transplant recipients, who were receiving ciclosporin and multiple other drugs, provides important new evidence of the safety of fluvastatin in high-risk patient populations. As reviewed, fluvastatin has a number of pharmacokinetic factors that combine to limit the risk of muscle exposure and toxicity, and compared with the immediate-release formulation, the 80mg ER formulation has lower systemic exposure with greater hepatic uptake and improved efficacy for reduction of LDL-cholesterol.

Guidelines in both the US and Europe place greater emphasis on identification and treatment of high-risk patients with statin therapy. Factors that

Table VI. Clinical trials with fluvastatin showing renal and vascular benefits

Reference	Population (n)	Duration	Study drug	Clinical outcome
Gheith et al.[91]	Patients with idiopathic nephrotic syndrome (43)	1y	Fluvastatin vs control group	Proteinuria, serum albumin and creatinine clearance were significantly better and renal fat deposits were significantly less in fluvastatin-treated patients. There were no significant differences in glomerular sclerosis or interstitial fibrosis between the two groups
Inoue et al.[92]	Patients with hypercholesterolaemia (40)	16 wks	Fluvastatin vs pravastatin	Fluvastatin, but not pravastatin, significantly improved two measures of endothelial function: antibody levels for oxidised LDL ($p < 0.01$) and forearm blood flow measured by plethysmography ($p < 0.001$)
Hausberg et al.[93]	Renal transplant recipients (36)	24 wks	Fluvastatin 40 mg/day vs placebo	Fluvastatin improved brachial artery vasodilation and blood flow measured by Doppler analysis
Hedblad et al.[94]	Patients with carotid plaque but no symptoms of carotid artery disease (793)	36mo	4×4 factorial trial of placebo, fluvastatin 40 mg/day, and metoprolol CR/XL 25 mg/day	Fluvastatin independently reduced progression of common carotid $IMT_{(mean)}$ ($p = 0.002$) and metoprolol independently reduced progression of carotid bulb $IMT_{(max)}$ ($p = 0.014$). No additive or synergistic effect between the two treatments was noted
Haak et al.[95]	Patients with LDL-cholesterol >160 mg/dL (48)	12 wks	Fluvastatin 40 mg/day vs placebo	Fluvastatin significantly reduced post-occlusion time to peak capillary blood flow at the nail by approximately 50%, measured by capillary microscopy and laser Doppler fluximetry ($p < 0.001$)
Eichstädt et al.[96]	Patients with clinical CHD (22)	24 wks	Open-label fluvastatin	Fluvastatin improved myocardial perfusion during exercise testing in ischaemic segments by 29% as measured by ^{201}Tl (thallium) single photon-emission CT ($p < 0.001$)
Romano et al.[97]	Patients with type IIa hypercholesterolaemia (26)	12 wks	Fluvastatin 80 mg/day vs placebo	Fluvastatin reduced plasma levels of P-selectin ($p = 0.0015$) or ICAM-1 ($p = 0.0033$) and increased NO generation ($p = 0.0046$)
Guethlin et al.[98]	Patients with angiographic CHD (15)	24 wks	Open-label fluvastatin 60–80 mg/day	Fluvastatin improved coronary stress blood flow and flow reserve measured by dynamic ^{13}N-labeled ammonia PET imaging in conjunction with adenosine. Responders demonstrated improvement in symptoms of angina pectoris

CHD = coronary heart disease; **CR/XL** = controlled release-extended release; **CT** = computerised tomography; **ICAM** = intercellular adhesion molecule; **IMT** = intima-media thickness; **LDL** = low-density lipoprotein; **NO** = nitric oxide; **PET** = positron emission tomography.

increase global risk, such as age, diabetes, low HDL-cholesterol and hypertension, also commonly require multiple medications along with lifestyle modifications. Elderly patients receiving multiple drugs are at the highest risk for drug-drug interactions, including myopathy with statins. Fluvastatin has an excellent safety record in clinical studies in the elderly,[56] in combination with fibrates[28] and in renal transplant recipients on ciclosporin.[9] Regardless of the choice of statin, physicians should warn all high-risk patients of signs and symptoms of myopathy to further minimise the risk for rhabdomyolysis.

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