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Atorvastatin

An Updated Review of its Pharmacological Properties and Use in Dyslipidaemia

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Data Selection

Sources: Medical literature published in any language since 1997 on atorvastatin, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were 'atorvastatin' or 'CI 981'. EMBASE search terms were 'atorvastatin' or 'CI 981' or 'YM548'. AdisBase search terms were 'atorvastatin' or 'CI-981' or 'YM 548'. Searches were last updated 11 Sep 2001.

Selection: Studies in patients with hyperlipidaemia who received atorvastatin. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: atorvastatin, HMG-CoA reductase inhibitors, hypercholesterolaemia, hyperlipidaemia, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Atorvastatin is a synthetic hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor. In dosages of 10 to 80 mg/day, atorvastatin reduces levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglyceride and very low-density lipoprotein (VLDL)-cholesterol and increases high-density lipoprotein (HDL)-cholesterol in patients with a wide variety of dyslipidaemias. In large long-term trials in patients with primary hypercholesterolaemia, atorvastatin produced greater reductions in total cholesterol, LDL-cholesterol and triglyceride levels than other HMG-CoA reductase inhibitors.

In patients with coronary heart disease (CHD), atorvastatin was more efficacious than lovastatin, pravastatin, fluvastatin and simvastatin in achieving target LDL-cholesterol levels and, in high doses, produced very low LDL-cholesterol levels. Aggressive reduction of serum LDL-cholesterol to 1.9 mmol/L with atorvastatin 80 mg/day for 16 weeks in patients with acute coronary syndromes significantly reduced the incidence of the combined primary end-point events and the secondary end-point of recurrent ischaemic events requiring rehospitalisation in the large, well-designed MIRACL trial.

In the AVERT trial, aggressive lipid-lowering therapy with atorvastatin 80 mg/ day for 18 months was at least as effective as coronary angioplasty and usual care in reducing the incidence of ischaemic events in low-risk patients with stable CHD. Long-term studies are currently investigating the effects of atorvastatin on serious cardiac events and mortality in patients with CHD.

Pharmacoeconomic studies have shown lipid-lowering with atorvastatin to be

cost effective in patients with CHD, men with at least one risk factor for CHD and women with multiple risk factors for CHD. In available studies atorvastatin was more cost effective than most other HMG-CoA reductase inhibitors in achieving target LDL-cholesterol levels.

Atorvastatin is well tolerated and adverse events are usually mild and transient. The tolerability profile of atorvastatin is similar to that of other available HMG-CoA reductase inhibitors and to placebo. Elevations of liver transaminases and creatine phosphokinase are infrequent. There have been rare case reports of rhabdomyolysis occurring with concomitant use of atorvastatin and other drugs.

Conclusion: Atorvastatin is an appropriate first-line lipid-lowering therapy in numerous groups of patients at low to high risk of CHD. Additionally it has a definite role in treating patients requiring greater decreases in LDL-cholesterol levels. Long-term studies are under way to determine whether achieving very low LDL-cholesterol levels with atorvastatin is likely to show additional benefits on morbidity and mortality in patients with CHD.

Pharmacodynamic Properties

Like other members of its class, atorvastatin inhibits hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase *in vivo* and *in vitro*, and impedes the formation of mevalonic acid, which is the rate-limiting step in the biosynthesis of cholesterol. The reduction in intracellular cholesterol increases the number of low-density lipoprotein (LDL) receptors, thus increasing the clearance of LDL-cholesterol from plasma.

Atorvastatin reduces plasma levels of total cholesterol, LDL-cholesterol, very low-density lipoprotein (VLDL)-cholesterol, triglycerides and apolipoprotein B, as demonstrated in a number of studies in human volunteers and patients (see Therapeutic Efficacy section). The greater efficacy of atorvastatin than other currently available HMG-CoA reductase inhibitors in reducing total cholesterol and LDL-cholesterol levels is believed to result from a prolonged duration of HMG-CoA reductase inhibition rather than the degree of inhibition.

The marked reductions in triglyceride levels with atorvastatin result mainly from decreases in VLDL production, caused in part by inhibition of cholesterol synthesis. In addition, the increase in number of LDL receptors, combined with the decrease in LDL particles available to bind to these receptors, may enhance the binding of VLDL particles, thus reducing triglyceride levels.

Atorvastatin reduces LDL-cholesterol levels in patients with homozygous familial hypercholesterolaemia despite the absence of any functional LDL receptors in these patients. This effect appears to result from marked inhibition of cholesterol synthesis, which in turn decreases the rate of LDL production. The reductions in overall levels of triglycerides and cholesterol by atorvastatin are accompanied by an improvement in the LDL subfraction profile, with a shift towards the larger subfractions.

There is some evidence that atorvastatin, like other drugs of its class, may have beneficial pharmacodynamic effects in addition to lipid-lowering in patients with atherosclerosis and CHD. Atorvastatin improved endothelial function in patients with hypercholesterolaemia or diabetes mellitus. The improvement did not correlate with the reduction in cholesterol levels and is likely to be due to enhanced endothelial production of nitric oxide (NO) and/or decreased formation of oxygen-derived free radicals.

As well, atorvastatin possibly plays a role in the stabilisation of atherosclerotic plaques by reducing the accumulation of inflammatory cells within them. The

drug reduced the activation *in vitro* of nuclear factor Kappa-B, an inducer of chemokines involved in the inflammation in the atheromatous plaque. In studies of other effects, atorvastatin abolished macrophage infiltration in the arterial neointimal lesions in addition to reducing atheromatous lesion size in a rabbit model of atherosclerosis, and inhibited smooth muscle cell migration and proliferation in both *in vitro* and *in vivo* studies.

Treatment with atorvastatin has been shown to reduce spontaneous and ADP- and epinephrine-induced platelet aggregation, probably because of its effect on intraplatelet NO metabolism through an increase in intraplatelet NO synthase activity. Atorvastatin also reduced the enhanced susceptibility of LDL to oxidation, decreased cholesterol accumulation in macrophages and improved red cell deformability.

Most data indicate the drug has positive or negligible effects on non-lipid risk factors for CHD. The drug generally had no appreciable effect on fibrinogen levels, and most data from randomised trials demonstrated a possibly dose-dependent reduction in C-reactive protein levels. The drug generally had no effect on lipoprotein (a) levels in dosages up to 40 mg/day, but the largest such clinical trial (the ASAP study) showed a significant reduction in this parameter after 2 years' therapy with atorvastatin 80 mg/day.

Pharmacokinetic Properties

About 30% of an oral dose of atorvastatin is absorbed and undergoes extensive first-pass metabolism. The drug has a bioavailability of about 14% and is >98% protein bound in the plasma. No significant changes in area under the plasma concentration-time curve or elimination half-life were observed with the administration of atorvastatin 30 minutes after food intake, although the rate of absorption was reduced.

The single-dose pharmacokinetic parameters of atorvastatin are linear. After single doses of atorvastatin 10, 20 or 40mg in healthy male volunteers, time to reach peak plasma concentration was 0.6 to 0.9 hours. The pharmacological response (lipid-lowering action) is more accurately predicted by the dose administered than the plasma drug concentrations.

Metabolism of atorvastatin by cytochrome P450 (CYP) 3A4 produces ortho- and para-hydroxylated derivatives and various β-oxidation products. 70% of the HMG-CoA reductase inhibitory activity associated with atorvastatin has been attributed to its active ortho- and para-hydroxylated metabolites, which are equipotent to the parent drug.

The peak plasma concentration of atorvastatin is significantly increased in patients with hepatic failure and dosage needs to be reduced in such patients. However, renal impairment has no significant effect on the pharmacokinetic parameters of atorvastatin.

Clinically significant interactions of atorvastatin are likely to occur with its concomitant use with other drugs metabolised by CYP 3A4 including erythromycin, itraconazole, ethinyl estradiol, fusidic acid and cyclosporin.

Therapeutic Efficacy

The lipid-lowering effects of atorvastatin have been investigated in patients with various types of dyslipidaemia. At present the only clinical outcomes data are from studies of aggressive atorvastatin therapy in patients with CHD, but many large trials of atorvastatin are under way to examine the effect of the drug on morbidity and mortality.

Primary hypercholesterolaemia. The lipid-lowering efficacy of atorvastatin in

patients with primary hypercholesterolaemia is well established. The drug consistently reduces total and LDL-cholesterol levels in a nonlinear dose-dependent manner, with atorvastatin 10 to 80 mg/day producing reductions in serum LDL-cholesterol levels of about 35 to 60% in various placebo-controlled and non-comparative trials. Atorvastatin 10 to 80 mg/day reduced triglyceride levels by 17 to 45% and apolipoprotein B levels by 17 to 50%.

Target US National Cholesterol Education Program (NCEP) LDL-cholesterol levels (<4.1 mmol/L) were achieved in 91 and 100% of patients with low CHD risk receiving 10 and 20 mg/day of atorvastatin, respectively, in a placebo-controlled study. In the high CHD risk group, 27, 40, 64 and 82% of patients receiving atorvastatin 10, 20, 40 and 80mg, respectively, reached their target serum LDL-cholesterol levels (≤2.6 mmol/L).

Atorvastatin was more efficacious in lowering serum levels of LDL-cholesterol, total cholesterol and triglycerides than milligram equivalent doses of other currently available HMG-CoA reductase inhibitors in patients with hypercholesterolaemia. In large double-blind 1-year trials, reductions in total cholesterol, LDL-cholesterol, apolipoprotein B and triglyceride levels were significantly greater with atorvastatin 10 to 20 mg/day than with lovastatin 20 to 40 mg/day, pravastatin 20 to 40 mg/day or simvastatin 10 to 20 mg/day.

As well, a greater number of patients tended to reach US NCEP LDL-cholesterol goals or European Atherosclerosis Society goals with atorvastatin than with lovastatin, pravastatin, fluvastatin and simvastatin. Fewer patients receiving atorvastatin than these other agents require upward dose titration.

Atorvastatin increased high-density lipoprotein (HDL)-cholesterol levels by about 5 to 9% in most studies comparing the drug with others of its class.

Mixed hyperlipidaemia. In patients with mixed hyperlipidaemia, atorvastatin 10 to 20 mg/day produced greater reductions in serum LDL-cholesterol and total cholesterol but lesser reductions in serum triglyceride levels than fenofibrate 200 or 300 mg/day, bezafibrate 400 mg/day and nicotinic acid 3 g/day. The increase in HDL-cholesterol was less than that with fenofibrate and nicotinic acid and similar to that with bezafibrate.

Atorvastatin 10 mg/day was more efficacious in reducing serum LDL-cholesterol and triglyceride levels than simvastatin 10 mg/day in a well-designed, 6-week study involving 1378 evaluable patients with mixed dyslipidaemia (the ASSET trial), and than other comparator HMG-CoA reductase inhibitors in a smaller trial.

Type 2 diabetes mellitus. The efficacy of atorvastatin in lowering serum LDL-cholesterol levels is similar in patients with type 2 diabetes mellitus and those without the condition. Atorvastatin 10 mg/day produced a greater reduction in serum LDL-cholesterol levels than simvastatin 10 mg/day, pravastatin 20 mg/day or lovastatin 20 mg/day in patients with type 2 diabetes mellitus after 6 months, and the drug was superior to simvastatin after 54 weeks in the ASSET trial. More patients given atorvastatin 80 mg/day than 10 mg/day achieved target NCEP LDL-cholesterol goals in the DALI study.

Familial hypercholesterolaemia. Atorvastatin reduced serum LDL-cholesterol levels further in patients with familial hypercholesterolaemia who had previously received simvastatin alone, or in combination with cholestyramine. Reductions were similar to those in patients previously treated with combinations of simvastatin and fenofibrate or nicotinic acid. In the ASAP trial, atorvastatin 80 mg/

day significantly reduced, and simvastatin 40 mg/day increased, carotid intimal media thickness in patients with familial hypercholesterolaemia after 2 years.

Atorvastatin 80 mg/day significantly reduced total cholesterol and LDL-cholesterol levels in small numbers of patients with homozygous familial hypercholesterolaemia treated for 2 months.

Aggressive therapy in patients with coronary heart disease.

Atorvastatin is generally more efficacious than the other HMG-CoA reductase inhibitors in achieving the stricter serum LDL-cholesterol target levels in patients with established CHD, in terms of the percentage of patients achieving the targets on monotherapy with these drugs as well as the proportion of patients requiring upward dose titration or a combination with other lipid-lowering agents. This has led to investigation of whether more aggressive therapy can provide clinical benefits.

Aggressive reduction of serum LDL-cholesterol to 1.9 mmol/L, well below the recommended target, with atorvastatin 80 mg/day for 16 weeks in patients with unstable angina or non-Q-wave myocardial infarction significantly reduced the incidence of the combined primary end-point ($p = 0.048$ *vs* placebo) and the secondary end-point of recurrent ischaemic events requiring rehospitalisation ($p = 0.02$) in the large ($n = 3086$) randomised, double-blind, placebo-controlled MIRACL trial. There were no significant differences in other secondary end-points (death, myocardial infarction and cardiac arrest).

As well, the results of the AVERT trial showed that aggressive lipid-lowering therapy with atorvastatin 80 mg/day for 18 months was at least as effective as coronary angioplasty and usual care in reducing the incidence of ischaemic events in low-risk patients with stable CHD.

Other special patient groups. Use of atorvastatin in place of the previous unsuccessful lipid-lowering therapy in patients with severe resistant hypercholesterolaemia resulted in a significant further reduction in serum LDL-cholesterol and triglyceride levels and achievement of target serum LDL-cholesterol in a significant proportion of these patients.

Although there are no large controlled studies comparing atorvastatin with other HMG-CoA reductase inhibitors in patients with organ transplants, small studies, some of them retrospective, have found atorvastatin to further reduce serum LDL-cholesterol and triglyceride levels in patients with renal or cardiac transplants switched to this drug after previous unsuccessful therapy with simvastatin, pravastatin and fluvastatin. Atorvastatin was superior to pravastatin in a small 4-month trial in patients with cardiac transplants.

Similarly, preliminary results from generally small studies suggest that atorvastatin is effective in patients with end-stage renal disease undergoing dialysis.

Tolerability

Atorvastatin has been well tolerated in long-term clinical trials. In placebo-controlled studies, the incidence of adverse events (18%) in 1122 patients receiving atorvastatin up to 80 mg/day was similar to that in patients receiving placebo (18%; $n = 270$). No dose-related increase in adverse events was observed in these studies. Overall, the most frequently reported adverse events were constipation, flatulence, dyspepsia, abdominal pain, headache and myalgia. Adverse events reported with atorvastatin have been mild and transient.

Fewer than 2% of the 2502 patients who received atorvastatin withdrew from the trials because of adverse effects related to treatment. The incidence of with-

drawal was not dose dependent. In general, the adverse event profile for atorvastatin was similar to that observed with other HMG-CoA reductase inhibitors.

Mild hepatic involvement in the form of asymptomatic elevations in serum transaminase levels has been reported during treatment with atorvastatin in 0.7% of patients and was responsible for discontinuation of atorvastatin in 0.3%. The incidence of persistent elevation of transaminase levels was higher in patients receiving atorvastatin in doses of 80 mg/day (2.3%) than those receiving lower doses (up to 0.6%).

The incidence of myalgia with the use of atorvastatin (1%) has been found similar to that with placebo (1%) and other HMG-Coa reductase inhibitors (2%). Although isolated asymptomatic elevation of creatine phosphokinase (CPK) has been observed in patients receiving atorvastatin, persistent elevation of CPK (>10 times elevation on 2 consecutive occasions) along with muscle pain, tenderness or weakness has not so far been reported. Case reports of rhabdomyolysis are rare with atorvastatin use, most occurring with concomitant use with other drugs such as cyclosporin, fusidic acid and gemfibrozil.

Pharmacoeconomic Studies

Pharmacoeconomic studies have shown lipid-lowering with atorvastatin to be cost effective in patients with CHD, men with at least one risk factor for CHD and women with multiple risk factors for CHD. Atorvastatin has been found to be more cost effective than most other HMG-CoA reductase inhibitors, in terms of cost per year of life saved and cost of achieving target LDL-cholesterol levels. Atorvastatin 10 mg/day had the lowest acquisition cost per percent reduction in LDL-cholesterol levels among various dosages of the HMG-CoA reductase inhibitors investigated.

Dosage and Administration

Atorvastatin 10 to 80 mg/day may be used to reduce the raised lipid levels in patients with primary hypercholesterolaemia (heterozygous familial, homozygous familial or nonfamilial) or combined dyslipidaemia and diabetic dyslipidaemia.

The dosage of atorvastatin should be adjusted according to response. Atorvastatin may be taken at any time of day with or without food. Dosage reduction may be required in patients with hepatic insufficiency. The drug is contraindicated in patients with active hepatic disease or unexplained persistent elevations in serum transaminase levels.

Concomitant use of atorvastatin with cyclosporin, nicotinic acid, fibrates, erythromycin or azole antifungals is likely to increase the risk of adverse events such as myopathy and rhabdomyolysis.

Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The pharmacology and use of atorvastatin in the management of dyslipidaemias has been reviewed previously in this journal.[1] This review expands previous knowledge, concentrating on recent, large clinical trials (see glossary for acronyms).

1. Cholesterol Synthesis and HMG-CoA Reductase Inhibition

Cholesterol is an essential component of the cell membrane and is required for a number of important physiological functions. Most of the cholesterol present in the circulation is endogenous and is synthesised in the liver. It circulates in the

plasma bound to lipoproteins, which include the chylomicrons, very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high-density lipoproteins (HDL). About 60 to 75% of the plasma cholesterol is transported as LDL,[2] the levels of which are directly related to increased risk for atherosclerosis and coronary heart disease (CHD).[3]

LDL is formed from VLDL by the action of hepatic and endothelial lipase. Most LDL is removed from the circulation by the liver through binding with LDL receptors. The expression of these receptors is inversely proportional to the levels of cholesterol in the hepatocytes. The conversion of HMG-CoA to mevalonic acid by HMG-CoA reductase is a rate-limiting step in the formation of endogenous cholesterol. The inhibition of cholesterol formation by HMG-CoA reductase inhibitors, such as atorvastatin, reduces intracellular stores of cholesterol. This results in up-regulation of LDL receptors, which in turn increases the clearance of LDL-cholesterol from the plasma.[4,5]

Atorvastatin, like other HMG-CoA reductase inhibitors, has been used successfully in clinical practice for the reduction of plasma cholesterol in patients with hypercholesterolaemia (section 4).

Glossary: Acronyms for some major published clinical trials of atorvastatin[a]

AAA	Australian Atorvastatin Assessment study
ACCESS	The Atorvastatin Comparative Cholesterol Efficacy and Safety Study
ASAP	The effects of Atorvastatin versus Simvastatin on Atherosclerosis Progression study
ASSET	Atorvastatin/Simvastatin Safety and Efficacy Trial
AVERT	The Atorvastatin Versus Revascularization Treatments Study
DALI	Diabetes Atorvastatin Lipid Intervention study
GAIN	German Atorvastatin Intravascular Ultrasound study
MIRACL	Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering study
WATCH	Women's Atorvastatin Trial on Cholesterol study

a Other trials of atorvastatin (e.g. ATOMIX, CURVES, TARGET TANGIBLE) are not acronyms and cannot be defined.

2. Pharmacodynamic Properties

The pharmacodynamic properties of atorvastatin have been reviewed in detail in a previous issue of *Drugs*.[1] This section provides a brief overview of these data with emphasis on more recently published pharmacodynamic studies.

2.1 Effects on Lipid Metabolism

Inhibition of HMG-CoA reductase by atorvastatin has been demonstrated by several *in vitro* and *in vivo* studies.[6-13] The reduction in the rate of cholesterol biosynthesis has been shown by reduction in plasma mevalonic acid levels after atorvastatin administration in patients with familial hypercholesterolaemia.[14,15]

Reductions in plasma levels of total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides and apolipoprotein B (apoB) have been demonstrated with the use of atorvastatin in a number of studies in human volunteers and patients[16,17] (see also section 4).

Reduction in levels of apoB, which is a component of atherogenic lipoproteins such as LDL and VLDL, mainly results from the up-regulation of LDL receptors in the liver. However, other mechanisms, too, are involved, such as reduction of the secretion of apoB by enhancing its degradation, and lowering the stability of apoB associated with lipoprotein particles. This has been shown *in vitro* in a study investigating the effects of atorvastatin on the biogenesis of apoB in intact and permeabilised human hepatoblastoma-G2 cells.[18]

The greater efficacy of atorvastatin than currently available HMG-CoA reductase inhibitors in reducing total cholesterol and LDL-cholesterol levels (section 4) is believed to be due to a prolonged duration of HMG-CoA reductase inhibition rather than degree of inhibition. Using plasma and urinary levels of mevalonic acid as semiquantitative markers of HMG-CoA reductase activity, administration of atorvastatin 40 mg/day or simvastatin 40 mg/day in patients with familial hypercholesterolaemia suppressed cholesterol synthesis to a similar extent over the first 8 hours after administration. However, the duration of this inhibition

was significantly longer with atorvastatin ($p = 0.01$).[19] The prolonged binding of microsomal HMG-CoA reductase receptors by atorvastatin has been demonstrated by evaluation of hepatic HMG-CoA reductase and LDL-receptor genes in atorvastatin-treated rats.[20]

Atorvastatin produces a marked reduction in triglyceride levels. As HMG-CoA does not play a direct role in the regulation of triglyceride levels, other mechanisms have been suggested to explain this effect. In 27 patients with hypertriglyceridaemia who received atorvastatin 20 or 80 mg/day, the pattern of reduction in triglyceride levels was consistent with reduction in triglyceride-rich lipoproteins such as VLDL.[17] This is partly because of a reduction in synthesis secondary to the inhibition of cholesterol synthesis by atorvastatin, as cholesterol is required for the production of VLDL particles.[21] In addition, the increase in number of LDL receptors with atorvastatin combined with the decreased availability of LDL to bind them, may result in an increased binding of VLDL particles, thus reducing triglyceride levels.[21-23] Increased clearance of chylomicron remnants in the postprandial state has been shown in human[24] as well as animal studies.[25]

Atorvastatin reduces LDL-cholesterol levels in patients with homozygous familial hypercholesterolaemia despite the absence of any functional LDL receptors in these patients.[15,26,27] This effect appears to result from marked inhibition of cholesterol synthesis, which in turn reduces the rate of LDL production.[15] A correlation between reduction in LDL-cholesterol levels and suppressed cholesterol synthesis, as measured by 24-hour excretion[26] or plasma levels[15] of mevalonic acid, was found in 35 such patients who received atorvastatin 40 and then 80 mg/day for 4 weeks each ($r = 0.38$; $p = 0.02$)[26] and in 7 patients who received atorvastatin 80 mg/day ($r = 0.89$; $p = 0.007$).[15] In the larger study, reduction in LDL-cholesterol levels was greater with atorvastatin 80 mg/day than with 40 mg/day (28 and 17%, respectively; $p < 0.01$). However, there was no further decrease in LDL-cholesterol levels or urinary mevalonic acid excretion with higher atorvastatin doses (120 and 160 mg/day), suggesting a plateau effect on cholesterol synthesis.[26]

The reductions in overall levels of triglycerides and cholesterol by atorvastatin are accompanied by an improvement in the LDL subfraction profile with a shift towards the larger subfractions, as shown by a study in 9 patients with hypercholesterolaemia who received atorvastatin up to 80 mg/day for about 3 months.[28] In these patients, there was a 37% increase in the large LDL subfraction and a 50 and 100% reduction in medium and small LDL subfractions, respectively. Similarly, a reduction in small LDL subfraction was demonstrated in an 8-week study in 48 patients receiving atorvastatin 40 mg/day.[29]

Atorvastatin reduces the enhanced susceptibility of LDL to oxidation, an effect that has been shown to be caused by the hydroxy metabolites of atorvastatin (see section 3.2) rather than the parent drug.[30]

2.2 Non-Lipid Effects

The understanding of the pharmacological effects of atorvastatin and other HMG-CoA reductase inhibitors has led to the realisation that the benefits of these agents extend beyond simply lowering cholesterol levels. These properties include beneficial effects on vessel endothelial tissue, ability to stabilise atheromatous plaques by decreasing inflammation, effects on proliferation of smooth muscle, antithrombotic effect by inhibiting platelet aggregation and stimulation of fibrinolytic mechanisms, improvement of blood viscosity and flow, and decreased LDL oxidation (table I).

2.2.1 Effects on Endothelial Function

Endothelial dysfunction is considered an important early stage of atherosclerotic disease[62,63] and is a predictor of future cardiovascular events in patients with CHD.[64] Endothelial function measured non-invasively by flow-mediated vasodilation of the brachial artery (FMD) or response of forearm blood flow to acetylcholine infusion is usually impaired in patients with hypercholesterolaemia.

Table I. Non-lipid-lowering effects of atorvastatin

Improves endothelial function (see table II) by enhancing production of endothelial NO and/or decreasing formation of oxygen-derived free radicals[31-35]
Stabilises atheromatous plaques by reducing inflammation[36,37]
Suppresses proliferation of vascular smooth muscle cells[38,39]
Reduces platelet aggregation by increasing NO synthase activity[40-42]
Reduces factor VII coagulant activity[43]
Improves global fibrinolytic activity[44]
Inhibits low-density lipoprotein oxidation[30]
Reduces cholesterol accumulation in macrophages[38,45]
Effects on non-lipid CHD risk factors
• reduces C-reactive protein levels[46-49] (see table III)
• generally no change in fibrinogen levels[50-59]
• generally no change[57,58,60] or a decrease[61] in lipoprotein (a) levels

CHD = coronary heart disease; **NO** = nitric oxide.

Atorvastatin improved endothelial function in patients with hypercholesterolaemia,[31-33] renal transplant recipients,[65] and patients with type 1 diabetes mellitus without hypercholesterolaemia but with endothelial dysfunction[66] (table II). Atorvastatin and simvastatin had similar effects on FMD.[31] The improvement in FMD did not correlate with the reduction in cholesterol levels ($r = -0.18$; $p > 0.4$)[31] and was shown to occur as early as 2 weeks after starting atorvastatin therapy.[33]

Endothelial dysfunction in patients with hypercholesterolaemia is related to either decreased local release of nitric oxide (NO) by the endothelium and/or excess production of superoxide anions with consequent degradation of NO before it reaches the underlying smooth muscle.[67]

In vitro, atorvastatin 10 μmol/L enhanced endothelial NO synthase activity 2-fold, significantly increased endothelial-dependent NO-mediated relaxation of the rat aorta, and inhibited superoxide anion formation in endothelium-intact segments of rat aorta, porcine cultured endothelial cells and murine macrophage cells.[34] Atorvastatin 10 nmol/L to 1 μmol/L also reduced the cholesterol-induced abundance of caveolin-1 in endothelial cells, thus increasing NO synthase activity and NO production in another *in vitro* study.[35]

Adding *l*-arginine, which may also improve endothelial function,[66] or vitamin C, an agent known to improve endothelial function by scavenging oxygen free radicals,[32] did not increase the effect of atorvastatin. These findings suggest that the atorvastatin-related improvement in endothelial function is likely to be due to enhanced endothelial production of NO and/or decreased formation of oxygen-derived free radicals.

2.2.2 Effects on Plaque Stabilisation

Acute events in patients with CHD are usually precipitated by the rupture of unstable atherosclerotic plaques. Inflammatory cells, attracted to the vascular lesion by chemokines, have been implicated in the process of plaque rupture.

In cultured smooth muscle cells and mononuclear cells *in vitro*, atorvastatin 10^{-7} mol/L diminished the activation of nuclear factor kappa-B (NF-κB), an inducer of chemokines involved in the inflammation in the atheromatous plaque. It also reduced the angiotensin II- and tumour necrosis factor-α-induced overexpression of monocyte chemoattractant protein-1 (MCP-1) and interferon-inducible protein-10.[36]

In a rabbit model of atherosclerosis, atorvastatin 5 mg/kg/day for 4 weeks reduced the activity of NF-κB in macrophages and vascular smooth muscle cells, and significantly diminished MCP-1 in the neointima and media.[37] The drug also abolished macrophage infiltration in the arterial neointimal lesions in addition to reducing atheromatous lesion size measured as percentage of luminal area occupied by the lesion (10 *vs* 21% in controls; $p = 0.04$).[37] Atorvastatin 20 mg/day for 2 months resulted in a 38% reduction ($p < 0.05$) in levels of vascular endothelial growth factor, a factor that is involved in neovascularisation of the atheromatous plaque, in patients with CHD and hypercholesterolaemia.[68]

An inhibitory effect of atorvastatin on smooth muscle cell migration and proliferation, independent of its ability to reduce plasma cholesterol levels, has been shown in different models of proliferating cells, such as cultured arterial myo-

Table II. Summary of studies evaluating the effect of atorvastatin (ATO) in patients with endothelial dysfunction

Reference (study design)	Type of patients	No. of patients	Dosage (mg/day) and duration	Method of measuring endothelial function	Baseline[a] (%)	End-point (%)	p-value
Åsberg et al.[65] [b] (nc)	Renal Tx	22	10; 4wk	AUC_{Ach}	538[c]	682[c]	0.042
Marchesi et al.[33] (r, nb, pg)[d]	PM women with HCH	20	10; 2wk	FMD	3.8	9.2	<0.05
			10; 8wk		3.8	11.7	<0.05
Mullen et al.[66] (r, db, pc, pg)[d]	DM with normal C	21	40; 6wk	FMD	3.65	5.4	0.018
Perticone et al.[32] (r, co, db, pg)[d]	HCH	18	10; 1mo	FBF Ach	11.5[e]	14.9[e]	<0.0001
Simons et al.[31] (r, nb, pg)	HCH	20	ATO 10-80; 30wk	FMD	2.2	5.5	<0.01
		10	SIM 10-40		1.8	4.5	<0.01

a Normal value for FMD is 8 to 9%.

b Abstract.

c Expressed in 'AU' (not defined).

d Studies included control groups treated with diet only,[33] *l*-arginine 7g twice daily orally or placebo[66] or included a group of healthy controls.[32] There were no significant changes in these control groups.

e Expressed as ml/100ml tissue/min.

AUC_{Ach} = area under the plasma acetylcholine-time curve; **C** = cholesterol; **co** = crossover; **db** = double-blind; **DM** = type 1 diabetes mellitus; **FBF Ach** = forearm blood flow after acetycholine 30 μg/min; **FMD** = flow-mediated dilation; **HCH** = hypercholesterolaemia; **nb** = nonblind; **nc** = noncomparative; **pc** = placebo-controlled; **pg** = parallel group; **PM** = postmenopausal; **r** = randomised; **SIM** = simvastatin; **Tx** = transplant.

cytes[39] and rapidly proliferating carotid and femoral intimal lesions in rabbits.[38]

Atorvastatin reduced cholesterol accumulation in macrophages *in vitro* by blocking cholesterol esterification and endocytosis of modified lipoproteins, an effect prevented by mevalonic acid.[38] Inhibitors of acyl coenzyme A-cholesterol acyltransferase (ACAT), which can reduce cholesterol storage in macrophages and thereby in arterial lesions, are currently being evaluated. Atorvastatin was shown to act synergistically with CI-976, an ACAT inhibitor, to lower plasma LDL-cholesterol levels and to limit the development of atherosclerotic lesions in cholesterol-fed rabbits, as assessed by measurement of cross-sectional lesions and macrophage area in major arteries.[45]

2.2.3 Effects on Platelet Activity and Red Blood Cell Deformability

Atorvastatin 10 mg/day for 4 weeks increased intraplatelet NO synthase activity by ≈1.7-fold in 19 patients with hyperlipidaemia.[40] The likely effect of this may be an increase in NO production which would promote platelet deaggregation and vasodilation. Treatment with atorvastatin has been shown to reduce spontaneous platelet aggregation, ADP-induced aggregation and epinephrine (adrenaline)-induced aggregation in patients with CHD and combined hyperlipidaemia.[41] The antiaggregatory effect on platelets persists longer than the lipid-lowering effect on withdrawal of atorvastatin in patients with hypercholesterolaemia.[42]

Atorvastatin 10 mg/day for 6 months improved the red blood cell deformability index by 6% ($p < 0.01$) in 15 patients with hypercholesterolaemia.[69]

2.2.4 Effects on the Coagulation Process

A 3-month randomised double-blind study comparing the influence of equi-effective cholesterol-lowering doses of atorvastatin (10 mg/day), simvastatin and pravastatin (both 40 mg/day) on antithrombogenic and anti-inflammatory markers in 75 patients with hypercholesterolaemia showed that none of these HMG-CoA reductase inhibitors reduced prothrombin fragment 1+2 (F1.2) and d-dimer levels.[48] Pravastatin decreased levels of von Willebrand factor antigen. Pooled data from the 3 groups showed a significant reduction in von

Table III. Effects of atorvastatin (ATO) on C-reactive protein (CRP) levels in randomised, double-blind parallel group trials

Reference (study design)	Type of patients	No. of patients	Dosage (mg/day)	Duration	Effect on CRP levels at end-point (mg/L)	
					baseline	change
Van de Ree et al.[49] a (DALI)	Type 2 DM, no CHD	67	ATO 10	30wk	Median 2.84	–0.22
		64	ATO 80			–1.50**
		55	PL			+0.22
Aristegui et al.[47] a (ATOMIX)	CHD with mixed dyslipidaemia	34 in total	ATO 10-40	6mo	ND	–1.56**
			BEZ 400			–0.10
Jialal et al.[46] a,b	Mixed dyslipidaemia	19	ATO 10	6wk	Median 2.9	–1.1***
			SIM 20			–0.9***
			PRA 40			–0.7*
Joukhadar et al.[48]	HCH	24	ATO 10	3mo	1.9	0
		27	SIM 40		2.4	–0.5
		24	PRA 40		2.3	0
Kent et al.[73] a	HCH (33% CHD)	38	ATO 80	3mo	4	–0.4
		40	PRA 40		4.2	–0.5**

a Abstract.

b Crossover study.

BEZ = bezafibrate; **CHD** = coronary heart disease; **DALI =** Diabetes Atorvastatin Lipid Intervention study; **DM** = diabetes mellitus; **HCH** = hypercholesterolaemia; **ND** = no data; **PL** = placebo; **PRA** = pravastatin; **SIM** = simvastatin; * $p < 0.05$, ** $p < 0.005$, *** $p = 0.0008$ *vs* baseline.

Willebrand factor antigen and F1.2 levels, with no significant difference between groups in all the parameters studied.

Atorvastatin 20 mg/day administered to 36 patients with hyperlipidaemia for 4 to 6 weeks reduced Factor VII coagulant activity by 16% ($p < 0.05$) and antigen levels by 11% ($p < 0.01$);[43] this factor plays a pivotal role in fibrin degradation and thrombus formation. Atorvastatin 40 mg/day, administered to 22 patients with hypercholesterolaemia for 6 months, significantly lowered the levels of plasminogen activator inhibitor-1 (by 32%; $p = 0.037$) which had been elevated at baseline.[70] Global fibrinolytic capacity, a measure of the efficacy of the entire fibrinolytic system, was significantly increased (by 60%; $p = 0.0001$) in 41 patients with CHD and hyperlipidaemia who received atorvastatin 10 to 20 mg/day for 12 weeks.[44]

2.2.5 Effects on Non-Lipid Risk Factors for Coronary Heart Disease (CHD)

Elevated levels of C-reactive protein (CRP), a prototype marker of inflammation, are associated with increased risk for cardiovascular disease.[71,72] Atorvastatin reduced CRP levels in most randomised comparative investigations of 6 to 30 weeks' duration (table III). Most data are available as abstracts.

Atorvastatin 80 mg/day, but not 10 mg/day, for 30 weeks significantly and dose-dependently reduced CRP levels in patients with type 2 diabetes mellitus and no CHD in the DALI study.[49] The higher dosage tended to reduce these levels in patients with hypercholesterolaemia with or without CHD after 3 months.[73] Atorvastatin 10 to 80 mg/day did not differ significantly from simvastatin 20 to 40 mg/day or pravastatin 40 mg/day in this effect (table III). There was a tendency for the decrease in CRP levels to correlate with decreases in LDL-cholesterol levels in 1 study[73] but not another.[46] Unlike atorvastatin 10 to 40 mg/day, bezafibrate (400 mg/day) did not alter CRP levels after 6 months in the ATOMIX study.[47]

Hyperfibrinogenaemia and lipoprotein (a) are considered independent risk factors for CHD.[74,75] A number of controlled studies found either no change[21,48,55-59] or, much less commonly, a de-

crease[76] in fibrinogen levels with the use of atorvastatin. Indeed, pooled data from controlled trials in about 900 patients did not reveal any significant changes in fibrinogen levels during atorvastatin therapy.[77] A few uncontrolled studies[50-53] have reported increases in fibrinogen levels of 19 to 44% with the use of atorvastatin, mainly in patients with severe hypercholesterolaemia. Fibrinogen levels also increased significantly in patients receiving atorvastatin (6 to 16% across all subgroups; $p < 0.01$) in a crossover study in 130 patients with hypercholesterolaemia, but there was a small insignificant fall in those receiving simvastatin 20 to 80 mg/day (5 to 6%) after 3 months.[54] Nonetheless, the bulk of the data from controlled trials indicates that atorvastatin has no appreciable effect on this parameter.

Most controlled studies that have measured lipoprotein (a) levels in patients receiving atorvastatin 10 to 20 mg/day for up to 1 year demonstrated no significant changes in this parameter,[57,58,60] in contrast to 1 noncomparative study reporting a 21% increase in lipoprotein (a) levels after atorvastatin 10 mg/day for 2 months ($p = 0.01$).[52] Notably, the large (n = 325) ASAP trial demonstrated a significant 14% decrease ($p < 0.0001$) after 2 years' therapy with atorvastatin in the higher dosage of 80 mg/day in patients with familial hypercholesterolaemia.[61] Effects on lipoprotein (a) levels with atorvastatin were similar to those with lovastatin 20 to 40 mg/day[57] and simvastatin 40 mg/day.[61]

3. Pharmacokinetic Properties

The pharmacokinetic properties of atorvastatin have been previously reviewed in *Drugs*.[1] This section provides a brief overview of these data supplemented with more recently published information.

3.1 Absorption and Distribution

Atorvastatin is administered in an active hydroxy-acid form, in a manner similar to fluvastatin and pravastatin, whereas lovastatin and simvastatin are administered as prodrugs requiring *in vivo* conversion to their active forms. About 30% of an oral dose of atorvastatin is absorbed and undergoes extensive first-pass metabolism.[78] The drug has a bioavailability of about 14%[79] and is >98% protein bound in the plasma.[80]

Administration of atorvastatin 30 minutes after food intake decreases the rate but not the extent of absorption.[81] Maximum steady-state plasma concentration (C_{max}) was reduced by about 50% and time to C_{max} (t_{max}) was delayed to twice that under fasting conditions ($p < 0.05$ for both).[82] In contrast, no significant changes in area under the plasma concentration-time curve (AUC) or elimination half-life ($t_{½}$) were observed. The drug can therefore be given with or without food.[81]

The single-dose pharmacokinetic parameters of atorvastatin are linear. After single doses of atorvastatin 10, 20 or 40mg in healthy male volunteers, t_{max} was found to be between 0.6 and 0.9 hours.[83] Mean C_{max} and AUC increased proportionally with increasing dose. The pharmacological response (lipid-lowering action) is more accurately predicted by the dose administered than the plasma concentrations.[84]

3.2 Metabolism and Elimination

Metabolism of atorvastatin by cytochrome P450 (CYP) 3A4 produces ortho- and para-hydroxylated derivatives and various β-oxidation products.[85] 70% of the HMG-CoA reductase inhibitory activity associated with atorvastatin has been attributed to its active metabolites, the ortho- and para-hydroxylated derivatives, which are equipotent to the parent drug.[86] Measurement of their plasma concentrations after 10 and 40mg of atorvastatin showed that C_{max} and AUC of these metabolites increased more than proportionally with dose, probably because of saturable elimination.[83] A negligible amount of atorvastatin is excreted in the urine.[78]

Multiple doses of atorvastatin do not lead to its accumulation in the body. After once daily doses of atorvastatin 10 or 20mg for 7 days, although plasma atorvastatin concentrations on day 7 were generally higher than on day 1, there were no sig-

nificant differences in C_{max} and AUC between days 1 and 7 for either dose.[87] The ortho-hydroxylated metabolite was found to be the major metabolite and its C_{max} was similar on days 1 and 7 after a 10mg atorvastatin dose. However, its C_{max} with a 20mg dose of atorvastatin was 1.6-fold higher on day 7.[87] Steady-state trough plasma concentrations of both atorvastatin and the ortho-hydroxylated metabolite were achieved by day 4.

3.3 Pharmacokinetics in Special Patient Groups

C_{max} and AUC of atorvastatin and the ortho-hydroxylated metabolite in the elderly were approximately 2-fold higher than in the young.[88] $t_{1/2}$, however, was the same in the elderly as in the young. Although AUC and $t_{1/2}$ were lower in women recipients than in men, no significant between-gender differences have been found in the lipid-lowering efficacy of atorvastatin.[57,89] C_{max} of atorvastatin is significantly increased in patients with hepatic failure and the dosage may need to be reduced in such patients (see section 7).[90] Renal impairment has no significant effect on the pharmacokinetic parameters of atorvastatin.[79]

3.4 Drug Interactions

Clinically significant pharmacokinetic drug interactions have been reported in patients receiving HMG-CoA reductase inhibitors such as atorvastatin in combination with various drugs.

When atorvastatin was coadministered with an antacid suspension containing aluminium/magnesium hydroxide, its C_{max} decreased by approximately 35% and t_{max} was doubled. However LDL-cholesterol reduction was not altered.[91] The rate and extent of atorvastatin absorption and its effects on LDL-cholesterol responses were not altered by the H_2 histamine receptor antagonist cimetidine.[92]

Plasma concentrations of atorvastatin decreased by approximately 25% when it was coadministered with colestipol.[93] However, reductions in LDL-cholesterol levels were greater when atorvastatin and colestipol were coadministered than when either drug was given alone.

Atorvastatin, ethinyl estradiol, itraconazole and erythromycin are all CYP 3A4 substrates and therefore may be expected to interact. Coadministration of atorvastatin 40 mg/day with an oral contraceptive containing ethinyl estradiol and norethisterone (norethindrone) resulted in an increase in C_{max} and AUC of both hormones.[94] Administration with itraconazole increased AUC and $t_{1/2}$ of atorvastatin 3-fold, whereas C_{max} was not affected.[95] C_{max} and AUC of atorvastatin increased by 38 and 33%, respectively, when the drug was coadministered with erythromycin.[96]

Grapefruit juice significantly increased AUC of atorvastatin by 2.5-fold ($p < 0.01$), probably by decreasing the CYP 3A4-mediated first-pass metabolism of atorvastatin in the small intestine.[97] Hence, grapefruit juice should be avoided in patients on atorvastatin therapy.

Atorvastatin 80 mg/day had no clinically significant effect on prothrombin time (PT) when administered to 12 patients receiving long-term warfarin treatment.[92] There was, however, a transient decrease in PT by 1.6 seconds during the first 4 days.

Following administration of digoxin 0.25 mg/day with atorvastatin 80 mg/day for 10 days in healthy volunteers, C_{max} and AUC of digoxin increased by 20 and 15%, respectively. t_{max} and renal clearance of digoxin were not affected.[98] However, administration of atorvastatin 10 mg/day with digoxin did not affect mean steady-state plasma concentrations of digoxin.

Concomitant administration of atorvastatin with the protease inhibitor combination lopinavir/ritonavir resulted in a 5.9-fold increase in AUC of atorvastatin,[99] and it was suggested that patients receiving this combination should be monitored for possible adverse effects of atorvastatin.

Although no specific pharmacokinetic studies on the concomitant use of atorvastatin with cyclosporin are available, rhabdomyolysis has been reported rarely when atorvastatin has been used in patients receiving cyclosporin (section 5.3.2).[100,101] There are reports of both elevations in[102] and unchanged[103,104] concentrations of cyclosporin with concomitant use of atorvastatin.

4. Therapeutic Efficacy

Atorvastatin has undergone extensive clinical evaluation and is available for the treatment of patients with various lipid disorders. Most published clinical trials with atorvastatin were randomised, comparative and multicentre; several were double-blind but a number were nonblind. Some studies used a treat-to-target format where the patients initially received starting doses of the study drugs, and the doses were increased if target LDL-cholesterol levels were not achieved after 4 to 12 weeks of therapy. Dietary restrictions were continued throughout the study period, and in most instances patients were not allowed to take other medications that might affect serum lipid levels (e.g nicotinic acid).

The primary end-point in the majority was the percentage reduction in serum levels of LDL-cholesterol from baseline (usually after at least 4 weeks of dietary control, with or without placebo administration) to the end of treatment. Other parameters measured were effects on total cholesterol, triglyceride and HDL-cholesterol levels, and the percentage of patients achieving target LDL-cholesterol levels. In most studies target LDL-cholesterol levels (the primary goal) were set according to cardiovascular risk category as defined by the National Cholesterol Education Program (NCEP) guidelines:[105]

- CHD and CHD risk equivalents: <2.6 mmol/L (100 mg/dl)
- multiple (≥2) risk factors: <3.4 mmol/L (130 mg/dl)
- 0-1 risk factor: <4.1 mmol/L (160 mg/dl).

However, some studies used European Atherosclerosis Society (EAS) guidelines[71,106] identifying goals of therapy to be total cholesterol levels <5 mmol/L (190 mg/dl) and LDL-cholesterol levels <3 mmol/L (115 mg/dl).[71]

To date there have been no published studies for atorvastatin with clinical end-points investigating the effect of the drug on morbidity and mortality, except those involving aggressive lowering of LDL-cholesterol in specific groups of patients with CHD (section 4.5.3). However, many such studies are planned or under way (section 8).

4.1 Patients with Primary Hypercholesterolaemia

4.1.1 Noncomparative and Placebo-Controlled Studies

The lipid-lowering efficacy of atorvastatin in patients with primary hypercholesterolaemia is well established. The drug consistently reduces serum total and LDL-cholesterol levels in a nonlinear dose-dependent manner,[107-111] with atorvastatin 10, 20, 40 and 80 mg/day producing reductions in serum LDL-cholesterol levels of 35 to 42%, 42 to 44%, 50% and 59 to 61%, respectively, in various placebo-controlled and noncomparative studies. As well, in a placebo-controlled double-blind randomised dose-response study in 55 patients, target NCEP LDL-cholesterol levels (<4.1 mmol/L) were achieved after 6 weeks in 91 and 100% of patients receiving 10 and 20 mg/day of atorvastatin, respectively, in patients with low CHD risk. In the high CHD risk group, 27, 40, 64 and 82% of patients receiving atorvastatin 10, 20, 40 and 80 mg/day, respectively, reached their target serum LDL-cholesterol levels (≤2.6 mmol/L).[109]

The fall in serum LDL-cholesterol levels with atorvastatin occurs rapidly, with 90% of the maximum observed reduction in serum LDL-cholesterol levels produced by atorvastatin 80 mg/day observed by the end of 2 weeks.[110] Serum LDL-cholesterol levels declined by 28% as early as 1 week after starting atorvastatin 10 mg/day in a placebo-controlled study.[112]

Atorvastatin 10 to 80 mg/day reduced triglyceride levels by 17 to 45% and apo B levels by 17 to 50%, respectively.[107,108,110,111] The effect on serum HDL-cholesterol levels was variable in these trials[107,108,110,111] but a more consistent effect was seen in comparative trials (see section 4.1.2). The effect on HDL-cholesterol is not dose related; higher doses of atorvastatin (40 and 80 mg/day) do not produce a greater increase in serum HDL-cholesterol and apolipoprotein A-1 levels than those achieved with a dosage of 20 mg/day.[55,113,114] Combined data from 25 clinical trials showed increases in HDL-cholesterol levels of 6.7, 8.2, 8.6 and

7.0% with atorvastatin 10, 20, 40 and 80 mg/day, respectively.[115] Increases in HDL-cholesterol levels were greater in a subgroup of patients with low baseline levels. The type of clinical trials included in this analysis were not described in this abstract.

4.1.2 Comparisons with Other HMG-CoA Reductase Inhibitors

Atorvastatin is generally more efficacious in lowering serum LDL-cholesterol, total cholesterol and triglyceride levels than milligram equivalent doses of simvastatin, lovastatin, fluvastatin and pravastatin (table IV). In most studies, the efficacy of 10 and 20 mg/day dosages of atorvastatin was equivalent to or better than that of the 20 and 40 mg/day dosages of the above HMG-CoA reductase inhibitors.

Effects on LDL-Cholesterol Levels

The randomised 8-week CURVES study[55] exemplifies the greater LDL-cholesterol-lowering ability of atorvastatin than others of its class at milligram equivalent doses (fig. 1). A number of other randomised studies, mainly multicentre and double-blind, have corroborated the higher efficacy of atorvastatin than milligram equivalent doses of simvastatin.[60,76,116,124] As well, patients who were switched from simvastatin 20 and 40 mg/day to atorvastatin 20 and 40 mg/day, respectively, experienced an additional 11% reduction in serum LDL-cholesterol after 8 weeks compared with those who continued receiving simvastatin in one study.[124]

The efficacy of 10, 20 or 40 mg/day of atorvastatin in lowering serum LDL-cholesterol and total cholesterol levels was equivalent to or better than that of 20, 40 or 80 mg/day, respectively, of simvastatin in other short-term studies,[114,116,117,124,125] although a few nonblind trials showed similar effects for both drugs.[114,117]

Reduction in serum LDL-cholesterol levels with atorvastatin 20 and 40 mg/day (n = 60) was similar to that with fluvastatin 40 and 80 mg/day (n = 60) in a 16-week randomised double-blind trial.[126] In an abstract report, atorvastatin 10 mg/day yielded smaller decreases in LDL-cholesterol levels after 12 weeks than rosuvastatin 5 and 10 mg/day, an HMG-CoA reductase inhibitor currently being developed.[118]

The long-term efficacy of atorvastatin 10 to 20 mg/day has been compared with that of lovastatin 20 to 40 mg/day,[57] pravastatin 20 to 40 mg/day[119,121] and simvastatin 10 to 20 mg/day[60] in randomised double-blind multicentre controlled studies of 1 year's duration (table IV). Patients initially received the lower dose of each drug, which was titrated to the higher dose if serum LDL-cholesterol levels did not reach NCEP targets after 16 weeks.

After 52 weeks of treatment, reductions in serum LDL-cholesterol levels were significantly greater with atorvastatin than lovastatin (37 *vs* 29%),[57] pravastatin (35 and 39% *vs* 23 and 29%)[119,121] or simvastatin (38 *vs* 33%).[60] The reductions in total cholesterol and triglyceride levels were also greater in atorvastatin-treated groups than in lovastatin-, pravastatin- and simvastatin-treated groups (all $p < 0.05$) [table IV]. Fewer patients receiving atorvastatin required upward dosage titration after 16 weeks of treatment compared with those receiving lovastatin (48 *vs* 62%),[57] pravastatin (27 *vs* 49%)[121] and simvastatin (24 *vs* 64%).[60]

More patients reached NCEP LDL-cholesterol goals with atorvastatin than with other HMG-CoA reductase inhibitors in many studies (table IV). In a 54-week treat-to-target trial, the median time taken to reach the target LDL-cholesterol level by patients receiving atorvastatin (85 days) was significantly less ($p < 0.05$) than those receiving simvastatin, lovastatin and fluvastatin (173, 232 and 269 days respectively).[122] Similarly, in the 6-month treat-to-target AAA study involving 1028 patients with hypercholesterolaemia treated at the primary care level (general practices), atorvastatin was more efficacious than simvastatin with or without cholestyramine in achieving target plasma cholesterol levels (≤5.0 mmol/L)[120] (table IV).

In addition to these trials, preliminary results are available from the large (n = 3916) 54-week ACCESS trial comparing atorvastatin 10 to 80 mg/day

Table IV. Summary of randomised clinical trials comparing the efficacy of atorvastatin (ATO) with other HMG-CoA reductase inhibitors in patients with primary hypercholesterolaemia

Reference	Study design and duration	No. of patients	Dosage regimen (mg/day)	Mean change (%) in serum lipid levels from baseline to treatment end-point				Patients reaching NCEP target LDL-C levels
				total-C	LDL-C	TG	HDL-C	
Short-term studies								
Crouse III et al.[114]	nb, pg, mc 12wk	210	ATO 20		–45	–23	4	
		215	ATO 40		–51	–29.6	3	
		202	SIM 40		–43*	–23	6.7**	
		215	SIM 80		–49	–25**	6.6**	
Farnier et al.[116]	nb, pg, mc	109	ATO 10	–30	–37	–19	5.7	
	16wk	54	SIM 10	–23***	–29**	–5**	2.2	
		109	SIM 20	–27	–33*	–16*	3.0	
Recto et al.[117]	nb, co, mc	125	ATO 10	–27	–37	–22	8.1	
	6wk	125	SIM 20	–26	–35	–22	8.7	
		126	ATO 20	–31	–42	–25	8.5	
		126	SIM 40	–30	–41	–21	9.3	
Davidson et al.[118] a	db, pc, pg, mc	127	ATO 10	–25	–35	–19	8	
	12wk	128	ROS 5[b]	–28*	–40**	–17	13**	
		129	ROS 10[b]	–30***	–43***	–19	12*	
		132	PL	0	0	–1	4	
Long-term studies[c]								
Assmann et al.[119]	db, mc	210	ATO 10-20	–28	–39	–13	7	91
	52wk	69	PRA 20-40	–20*	–29†	–8*	9	48†
Barter & O'Brien[120]	nb, tt, pg, mc	691	ATO 10-80	–32	–43	–20	8.4	83[e]
(AAA)	6mo	337	SIM 20-40 + CHY 4g[d]	–27**	–38**	–9**	10.2	66**
Bertolini et al.[121]	db, mc	214	ATO 10-20	–25	–35	–14	7	71
	52wk	74	PRA 20-40	–16*	–23*	–3*	10	26**
Dart et al.[60]	db, mc	132	ATO 10-20	–30	–38	–21	7	
	52wk	45	SIM 10-20	–25*	–33*	–12*	7	
Davidson et al.[57]	db, mc	789[f]	ATO 10-20	–27	–37	–16	7	78
	52wk	260[f]	LOV 20-40	–21*	–29*	–8*	7	63*
Hunninghake et al.[122]	nb, pg, tt, mc 54wk	85	ATO 10-80 + COL 10g[d]	–28	–36	–20	9	95
		82	FLU 20-40 + COL 20g[d]	–15*	–22*	–2*	6	60*
		83	LOV 20-80 + COL 20g[d]	–21*	–28*	–16	10	77*
		87	SIM 10-40 + COL 20g[d]	–24*	–33	–11	11	83*
Illingworth et al.[123] g	db, pg, mc 36wk[g]	394	ATO 80		–53.6	–31.3	3	
		385	SIM 80		–48.1***	–23.6*	7.5***	

a Abstract.

b Rosuvastatin is currently under development and optimal dosages are not known.

c Patients received the lower dose initially, then dose was increased if LDL-C target level not achieved.

d Colestipol or cholestyramine was added if target LDL-C was not achieved with highest dose of first drug.

e Target total cholesterol ≤5.0 mmol/L.

f 70 atorvastatin and 67 lovastatin recipients received placebo for the first 16wk.

g Extension of Crouse et al.[114] Data are for weeks 18 to 36 of the study.

AAA = Australian Atorvastatin Assessment study; **C** = cholesterol; **CHY** = cholestyramine; **co** = crossover; **COL** = colestipol; **db** = double-blind; **FLU** = fluvastatin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LOV** = lovastatin; **mc** = multicentre; **nb** = nonblind; **NCEP** = National Cholesterol Education Programme; **pc** = placebo-controlled; **pg** = parallel group; **PL** = placebo; **PRA** = pravastatin; **ROS** = rosuvastatin; **SIM** = simvastatin; **TG** = triglycerides; **tt** = treat-to-target; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, † $p \leq 0.0001$, all *vs* ATO.

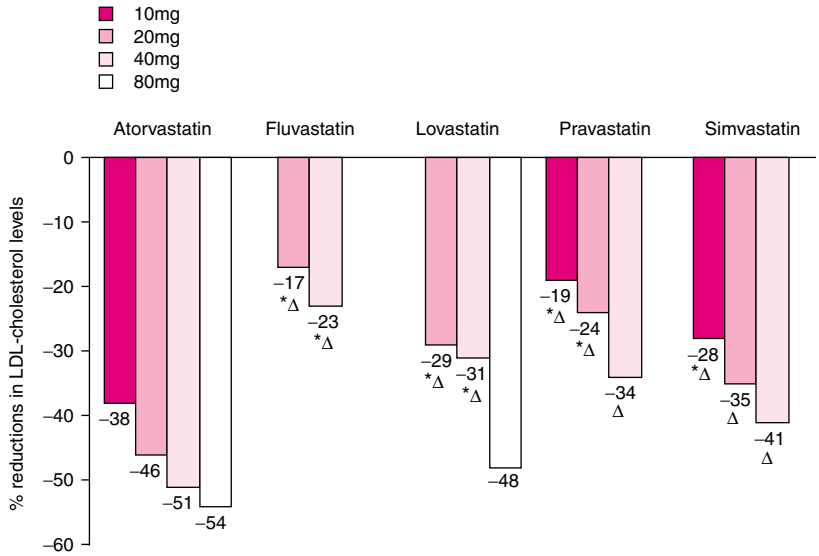

Fig. 1. Lipid-lowering efficacy of atorvastatin. Comparison of reductions in low-density lipoprotein (LDL)-cholesterol with various dosages of atorvastatin and other HMG-CoA reductase inhibitors in an 8-week randomised multicentre study (the CURVES study) in 534 patients.[55] * $p < 0.02$ *vs* atorvastatin 10 mg/day; Δ $p < 0.02$ *vs* atorvastatin 20 mg/day.

with simvastatin, pravastatin (both 10 to 40 mg/day), fluvastatin and lovastatin (both 20 to 80 mg/day).[127] At 6 weeks LDL-cholesterol levels decreased by 36% with atorvastatin and by 30, 20, 19 and 27%, respectively, with the other drugs ($p < 0.0001$ for all comparisons).

Effects on HDL-Cholesterol Levels

Atorvastatin increased HDL-cholesterol levels by about 5 to 9% in most studies (table IV). The size of the increase relative to that with other HMG-CoA reductase inhibitors tended to be smaller than with simvastatin in short-term studies (<16 weeks) [table IV]. In the 8-week CURVES study, simvastatin 40 mg/day caused a greater increase in HDL-cholesterol (9.6%) than atorvastatin 40 mg/day (4.8%; $p < 0.05$).[55] The elevation in apolipoprotein A-1 was also greater with simvastatin than with atorvastatin in a 12-week study measuring this parameter.[114]

Importantly, most long-term, mainly double-blind studies found no difference in the changes in HDL-cholesterol produced by atorvastatin and other HMG-CoA reductase inhibitors, including simvastatin, over 6 to 12 months (table IV).[57,60,119,121] An exception is the Illingworth et al. study[123] in which atorvastatin 80 mg/day produced significantly smaller increases in HDL-cholesterol levels than simvastatin 80 mg/day over the last 18 weeks of a 36-week trial (table IV).

4.2 Patients with Mixed Hyperlipidaemia and Hypertriglyceridaemia

Patients with mixed hyperlipidaemia have elevated serum levels of triglycerides as well as LDL-cholesterol. These patients require drug therapy to reduce levels of serum VLDL and VLDL remnants (triglycerides being their main component), as well as levels of LDL-cholesterol, to decrease the risk of premature atherosclerosis.[128,129] Monotherapy with HMG-CoA reductase inhibitors or with fibrates is often inadequate and combination therapy is required. In patients with isolated hypertriglyceridaemia, treatment with fibrates is efficacious but often produces significant adverse effects. A number of randomised, nonblind trials

have evaluated the efficacy of monotherapy with atorvastatin in patients with mixed hyperlipidaemia as well as those with isolated hypertriglyceridaemia (table V).

Atorvastatin 10 to 20 mg/day reduced serum LDL-cholesterol as well as triglyceride levels and increased HDL-cholesterol levels in patients with mixed hyperlipidaemia (table V). The efficacy of atorvastatin, as well as other HMG-CoA reductase inhibitors, in reducing triglycerides has been found to be dose-related in patients with hypertriglyceridaemia but not in those with normal triglyceride levels, as shown by an evaluation of a pooled database of 2689 patients with triglyceride levels <4.5 mmol/L (400 mg/dl) who participated in 7 separate studies with similar designs.[136] There was a greater reduction in triglyceride levels in patients with baseline levels >2.8 mmol/L (250 mg/dl) than in those with levels <1.7 mmol/L (150 mg/dl). Similarly, the decrease in serum triglyceride levels was significantly related to baseline levels ($r = 0.63$; $p < 0.001$) in 49 patients who received atorvastatin 10 mg/day for 2 months.[134]

Although there are few data comparing atorvastatin with HMG-CoA reductase inhibitors other than simvastatin, available nonblind comparisons of reductions in triglyceride levels by various HMG-CoA reductase inhibitors have shown the superiority of atorvastatin over simvastatin and, in a smaller study, pravastatin and fluvastatin (table V).

Monotherapy with atorvastatin 10 mg/day was more efficacious than that with simvastatin 10 mg/day over a 6-week period in the large, randomised treat-to-target ASSET trial.[135] Table V shows that

Table V. Summary of randomised clinical trials comparing the efficacy of atorvastatin (ATO) with that of other lipid-lowering drugs in patients with mixed hyperlipidaemia

Reference	Study design and duration	No. of patients	Dosage regimen (mg/day)	Mean change (%) in serum lipid levels from baseline to treatment end-point			
				total-C	LDL-C	TG	HDL-C
Comparisons with fibrates							
Bairaktari et al.[130]	nb, pg 16wk	45	ATO 10	–29*	–35*	–13	5.0
		46	FEN 200	–16	–18	–26**	16.6*
Bottazzo et al.[131] a	nb, pg	30	ATO 10	–25*		–28	8.5
	6wk	29	BEZ 400	–14		–37	9.8
		27	PL	–1		–2*	2.4***
Ooi et al.[132]	nb, pg, mc	39	ATO 10-20	–33*	–38*	–28	10
	24wk	35	FEN 300	–14	–6	–40*	23*
Comparison with nicotinic acid							
McKenney et al.[133]	nb, pg, mc	55	ATO 10	–26*	–30*	–17	4
	12wk	53	NIC 3g	–7	–2	–29*	25*
Comparisons with other HMG-CoA reductase inhibitors							
Branchi et al.[134]	nb, pg	49	ATO 10	–30*	–38*	–20*	3
	2mo	48	FLU 40	–21	–30	–7	11*
		50	PRA 20	–24	–32	–12	3
		50	SIM 10	–27	–36	–18	4
Insull et al.[135]	nb, pg, mc	712	ATO 10	–28***	–37***	–22***	7.4
(ASSET)	6wk	666	SIM 10	–22	–30	–16	6.9

a Abstract.

ASSET = Atorvastatin/Simvastatin Safety and Efficacy Trial; **BEZ** = bezafibrate; **C** = cholesterol; **FEN** = fenofibrate; **FLU** = fluvastatin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **mc** = multicentre; **nb** = nonblind; **NIC** = nicotinic acid; **pc** = placebo controlled; **pg** = parallel group; **PL** = placebo; **PRA** = pravastatin; **SIM** = simvastatin; **TG** = triglycerides; * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0001$, all *vs* comparator/s.

reductions in levels of triglycerides, total cholesterol and LDL-cholesterol were significantly greater with atorvastatin, while HDL-cholesterol levels increased by similar amounts in both groups. More patients achieved LDL-cholesterol goals with atorvastatin (56%) than with simvastatin (38%; p < 0.0001).

The greater efficacy of atorvastatin in reducing triglyceride levels is considered to be related to its superior efficacy in reducing serum LDL-cholesterol levels.[134,136] In a randomised 2-month study involving 191 patients with hypercholesterolaemia and triglyceride levels <4.5 mmol/L (400 mg/dl), patients receiving atorvastatin 10 mg/day had a greater reduction in serum triglyceride as well as LDL-cholesterol levels than those receiving simvastatin 10mg, fluvastatin 40mg and pravastatin 20mg daily.[134] The ratio of the percentage triglyceride reduction to the percentage LDL-cholesterol reduction was not significantly different in the 4 treatment groups, supporting the concept that greater efficacy in reducing serum triglyceride levels is related to that in reducing serum LDL-cholesterol.[134]

In patients with mixed hyperlipidaemia, atorvastatin, usually 10 mg/day for 6 to 24 weeks, produced greater reductions in serum LDL-cholesterol and total cholesterol but smaller reductions in serum triglyceride levels than fenofibrate 200[130] or 300[132] mg/day, bezafibrate 400 mg/day[131] and nicotinic acid 3 g/day.[133] The increase in HDL-cholesterol levels with atorvasatin was significantly less than that with fenofibrate and nicotinic acid and similar to that with bezafibrate (table V).

4.3 Patients with Type 2 Diabetes Mellitus and Dyslipidaemia

The principal features of dyslipidaemia in patients with type 2 diabetes mellitus are elevated levels of triglycerides and reduced levels of HDL-cholesterol, and an increased number of smaller, denser LDL particles. Superimposed on these abnormalities is a prevalence of hypercholesterolaemia similar to that found in the general population.[137]

Hypertriglyceridaemia has been implicated as a risk factor in several prospective clinical studies,[138] and available data suggest that LDL-cholesterol is more atherogenic in patients with type 2 diabetes mellitus than in other individuals.[139] Aggressive lowering of serum LDL-cholesterol and maintenance of triglycerides at the lowest possible level are recommended in patients with type 2 diabetes mellitus.[140]

4.3.1 Noncomparative Studies

About two-thirds or more of patients achieved target LDL-cholesterol levels in this type of trial. In two 16-week trials of atorvastatin 10 to 80 mg/day, all 88 patients with diabetes mellitus and hyperlipidaemia achieved target LDL-cholesterol levels in one study;[141] LDL-cholesterol levels were reduced by 50 to 66% and total cholesterol levels by 37 to 53% in another study of 100 such patients.[142] Approximately 59%[141] and 66%[142] of patients achieved LDL-cholesterol levels <2.6 mmol/L with the lowest dose.

The efficacy of atorvastatin in lowering serum LDL-cholesterol levels is similar in patients with type 2 diabetes mellitus and those without the condition (table VI).[135,143,144] Although reductions in triglyceride levels, in most studies, were also similar to those in patients without diabetes mellitus, a multicentre treat-to-target trial involving 200 patients with CHD (93 with type 2 diabetes mellitus and 107 without) reported a greater reduction in triglyceride levels in patients with type 2 diabetes mellitus than in nondiabetic patients (29 *vs* 19%; p = 0.04).[144]

In 155 patients with type 2 diabetes mellitus, including some patients with established CHD and those with familial hypercholesterolaemia, treatment with atorvastatin up to 40 mg/day (the majority receiving 10 mg/day) over a 9-month period resulted in a significant reduction in serum LDL-cholesterol (p < 0.01) and elevation of HDL-cholesterol (p < 0.05). Triglyceride levels decreased by 38% (p < 0.01).[149]

4.3.2 Comparative Studies

The larger reductions in LDL-cholesterol levels with atorvastatin than with other available HMG-

Table VI. Summary of clinical trials evaluating the efficacy of atorvastatin (ATO) in the management of dyslipidaemia in patients with type 2 diabetes mellitus

Reference	Study design and duration	No. of patients	Dosage regimen (mg/day)	Mean change (%) in serum lipid levels from baseline to treatment end-point				Patients reaching NCEP target LDL-C levels (%)
				total-C	LDL-C	TG	HDL-C	
Comparisons in patients with and without type 2 diabetes mellitus								
Black et al.[143]	Analysis of 21 studies	DM 156	ATO 10	–27	–36	–21		
		NDM > 2400	ATO 10	–27	–36	–17		
Bogaty et al.[144] a	nb, tt, mc 1-4mo	DM 93	ATO 10-8 0		–46	–29	0.8	98
		NDM 107	ATO 10-80		–49	–19†	3.4	93
Insull Jr et al.[135] (ASSET)	r, nb, mc 6wk	DM 343	ATO 10		–37			
		NDM 369	ATO 10		–37			
Comparisons with placebo (PL) and other HMG-CoA reductase inhibitors								
Djordjevic et al.[145] a	nb, pg 3mo	20	ATO 10-20	–27	–37	–25	14.1	37[b]
		30	FLU 20-40	–20*	–25*	–4*	8.8**	6[b]*
		20	SIM 20-40	–28	–36	–27	14.5	39[b]
Gentile et al.[146]	r, nb, pg, mc, pc 24wk	84	ATO 10	–29	–37	–24	7.4	
		78	SIM 10	–21*	–26*	–14*	7.1	
		81	PRA 20	–16**	–23**	–12*	3.2*	
		80	LOV 20	–18*	–21**	–11*	7.2	
		86	PL	+1**	–1**	–1**	–0.5	
Insull Jr et al.[147] (ASSET) a	r, nb, mc 54wk	346	ATO 10-80		–44.4	–15.2 to –32.7		ATO>SIM
		328	SIM 10-40		–36.5***	–5.5 to –27.8		
The DALI Study Group[148] c	r, db, pg, mc, pc 30wk	73	ATO 10	–30	–41	–25	6	71 (79.5)[d]
		72	ATO 80	–39††	–52††	–35	5.2	85† (76.4)[d]
		72	PL	0.5	–2.7	+10	–0.9	11*** (ND)[d]

a Abstract.

b European Diabetes Policy Group targets.

c All values for ATO 10 and 80 mg/day were significantly different from baseline ($p < 0.05$); no p-values versus PL were given.

d Percent reaching target triglyceride levels.

ASSET = Atorvastatin/Simvastatin Safety and Efficacy Trial; **C** = cholesterol; **DALI** = Diabetes Atorvastatin Lipid Intervention study; **DM** = patients with type 2 diabetes mellitus; **FLU** = fluvastatin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LOV** = lovastatin; **mc** = multicentre; **nb** = nonblind; **NCEP** = National Cholesterol Education Programme; **ND** = no data; **NDM** = patients without diabetes mellitus; **pc** = placebo controlled; **pg** = parallel-group; **PL** = placebo; **PRA** = pravastatin; **r** = randomised; **SIM** = simvastatin; **TG** = triglycerides; **tt** = treat-to-target; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.0001$ *vs* ATO; † $p < 0.05$, †† $p < 0.005$ *vs* DM group or ATO 10mg; > greater efficacy than ($p < 0.001$).

CoA reductase inhibitors (section 4.1.2) are also apparent in patients with type 2 diabetes mellitus (table VI). The 54-week ASSET[147] trial demonstrated that the larger decreases in LDL-cholesterol with atorvastatin than with simvastatin were maintained in the longer term, although differences in triglyceride levels were not significant (table VI). Increasing the atorvastatin dosage from 10 to 80 mg/day had no further effect on triglyceride levels but increased the percentage of patients achieving NCEP LDL-cholesterol goals in the DALI study.[148]

4.4 Patients with Familial Hypercholesterolaemia

Cholesterol levels are often difficult to control with HMG-CoA reductase inhibitor monotherapy in patients with familial hypercholesterolaemia,

most of whom require additional therapy with a bile-acid sequestrant. The efficacy of atorvastatin in lowering LDL-cholesterol levels in patients with primary hypercholesterolaemia has prompted a number of attempts to use the drug as a high-dose monotherapy in patients with familial hypercholesterolaemia.

4.4.1 Noncomparative Trials

In a noncomparative study in 40 patients, 6 weeks' therapy with atorvastatin 40 and 80 mg/day reduced serum LDL-cholesterol levels by 44 and 50%, respectively.[150] Atorvastatin reduced serum LDL-cholesterol levels further in patients with familial hypercholesterolaemia who had previously received simvastatin alone or in combination with cholestyramine in nonblind 12-week trials.[151-153] Reductions were similar to those in patients previously treated with combinations of simvastatin and fenofibrate or nicotinic acid.[152,154] These findings are supported by results of a prospective observational study in patients with severe familial hypercholesterolaemia who received daily doses of atorvastatin 10mg (n = 56), 20mg (n = 55), 40mg (n = 38) and 80mg (n = 51) substituted, respectively, for previous therapy with simvastatin 20 or 40 mg/day, simvastatin 40 mg/day with cholestyramine 32 g/day or simvastatin 40 mg/day with cholestyramine and fenofibrate 200 mg/day.[153]

4.4.2 Comparisons with Other HMG-CoA Reductase Inhibitors

Two randomised double-blind parallel group trials have directly compared atorvastatin with other HMG-CoA reductase inhibitors (table VII). The long-term effect of atorvastatin 80 mg/day on the progression of carotid atherosclerosis in patients with familial hypercholesterolaemia was compared with that of simvastatin 40 mg/day (maximum recommended dose at the time of the study) in the ASAP trial. This 2-year randomised double-blind study in 325 patients used carotid intima media thickness (IMT), measured by quantitative B-mode ultrasound, as the primary endpoint.[61]

There was a significant reduction in IMT (−0.031mm; $p < 0.0017$) in patients receiving atorvastatin but an increase in IMT (+0.036mm) in patients receiving simvastatin. The reduction in IMT was correlated to the decrease in LDL-cholesterol levels ($r = 0.41$; $p = 0.01$) which was significantly greater with atorvastatin than with simvastatin, as were decreases in levels of total cholesterol and triglycerides. HDL cholesterol levels increased by 13% in both groups (table VII).

Preliminary results of another randomised, double-blind, 18-week trial showed rosuvastatin up to 80 mg/day (n = 435) to be more efficacious than atorvastatin up to 80 mg/day (n = 187) in reducing LDL-cholesterol and increasing HDL-cholesterol levels (table VII).[155]

Homozygous familial hypercholesterolaemia is characterised by high LDL-cholesterol levels, tendon xanthomas and premature CHD and is refractory to many therapies.[26] Atorvastatin 80 mg/day for 2 months reduced LDL-cholesterol levels by about 25 to 30% in small numbers of patients ($n < 35$) with homozygous familial hypercholesterolaemia.[15,26,27]

4.5 Special Patient Groups

4.5.1 Patients with Resistant Hypercholesterolaemia

A significant number of patients with hypercholesterolaemia do not achieve target LDL-cholesterol levels with maximum tolerated doses of usual drugs such as HMG-CoA reductase inhibitors, with or without fibrates. Use of atorvastatin in place of the previous unsuccessful lipid-lowering therapy in patients with severe resistant hypercholesterolaemia resulted in a significant further reduction in serum LDL-cholesterol and triglyceride levels and achievement of target serum LDL-cholesterol in a significant proportion of these patients.

In a nonblind study in patients refractory to simvastatin monotherapy,[157] reductions in serum LDL-cholesterol and triglyceride levels were significantly greater with atorvastatin than with simvastatin plus cholestyramine after 30 weeks (table VII). Similarly, in a large (n = 770) randomised, nonblind study in patients with hypercholesterolaemia refractory to monotherapy with other lipid-lowering agents, target serum LDL-

Table VII. Summary of randomised clinical trials evaluating the comparative efficacy of atorvastatin (ATO) in various subgroups of patients

Reference	Study design and duration	No. of patients	Dosage regimen (mg/day)	Mean change (%) in serum lipid levels from baseline to treatment end-point				Patients reaching NCEP target LDL-C levels
				total-C	LDL-C	TG	HDL-C	
Patients with familial hypercholesterolaemia								
Smilde et al.[61]	db, mc, pg	160	ATO 40-80	–42	–51	–29	13	
(ASAP)	2y	165	SIM 20-40	–34***	–41***	–18**	13	
Stein et al.[155] a	db, mc, pg	187	ATO 20-80	–42***	–50***	–32	3***	46
	18wk[b]	435	ROS 20-80	–46	–58	–28	12	61
Patients with resistant hypercholesterolaemia								
Habib et al.[156]	nb, pg, mc	385	ATO 10-40[c]	–18	–26	–3	+4	37
	12wk[b]	385	Others[c,d]	–7***	–10**	+2	+2	11***
Simons[157]	nb, mc	92	ATO 10-80	–42***	–49***	–33**	7	19[e]
	30wk[b]	44	SIM 10-40 + CHY 4g	–32	–38	–25	10	6
Patients with established coronary heart disease (CHD)								
Brown et al.[158]	nb, pg, mc, tt[b]	78	ATO 10-80	–30	–41	–19	7	79*[f]
	54wk	76	FLU 20-40	–20*	–30*	–2*	7	11
		78	LOV 20-80	–29	–41	–14	12	56
		76	SIM 10-40 (all with COL up to 10g if required)	–26	–37	–15	11	59
Marz et al.[159]	nb, pg, mc	1897	ATO 10-40	–33***	–44***	–19***		67***
(TARGET TANGIBLE)	14wk[b]	959	SIM 10-40	–29	–40	–13		53

a Abstract.

b Patients initially received lowest dose of each drug, then dose was increased at 6-weekly intervals if target levels not achieved, to the maximum shown; additional drug was added if target LDL-C levels were not achieved with highest dose.

c Baseline taken as levels achieved with previous therapy.

d Adjusting dose of previous drug, switching drugs, combining drugs, more aggressive diet.

e Target LDL-C <3.5 mmol/L.

f Percentage of patients achieving targets on monotherapy.

ASAP = the effects of Atorvastatin versus Simvastatin on Atherosclerosis Progression study; **C** = cholesterol; **CHY** = cholestyramine; **COL** = colestipol; **db** = double-blind; **FLU** = fluvastatin; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **LOV** = lovastatin; **mc** = multicentre; **nb** = nonblind; **NCEP** = National Cholesterol Education Program; **pg** = parallel group; **ROS** = rosuvastatin; **SIM** = simvastatin; **TG** = triglycerides; **tt** = treat-to-target; * $p \leq 0.05$, ** $p < 0.01$, *** $p \leq 0.001$ *vs* other groups.

cholesterol levels were achieved in more than 3 times as many atorvastatin recipients than in those continuing usual care including intensive diet therapy, increasing dosages or combinations of other drugs for 12 weeks ($p = 0.001$) [table VII].[156]

Atorvastatin in doses of 10, 20 or 80 mg/day depending on baseline LDL-cholesterol and presence of risk factors for CHD, when administered to 531 patients with hypercholesterolaemia refractory to treatment with other lipid-lowering agents (78% having received other HMG-CoA reductase inhibitors), resulted in achievement of EAS target LDL-cholesterol levels in 86, 88 and 52% patients with mild, moderate and high risk for CHD, respectively.[160] LDL-cholesterol levels decreased by 33, 48 and 53% in patients receiving atorvastatin 10, 20 and 80 mg/day, respectively.

In 21 patients with severe hypercholesterolaemia who had uncontrolled LDL-cholesterol levels despite receiving apheresis therapy in addition to simvastatin 40 mg/day, replacement of simvastatin with atorvastatin up to 80 mg/day resulted in a significant reduction in serum LDL-cholesterol in twenty of them.[161] Target LDL-cholesterol levels were achieved in 4 patients and apheresis could be discontinued in three.

4.5.2 Patients with Established CHD

Atorvastatin has been found to be more efficacious than the other HMG-CoA reductase inhibitors in achieving the stricter serum LDL-cholesterol target levels in patients with established CHD. Terms of assessment were the percentage of patients achieving the targets on monotherapy with these drugs, as well as the proportion of patients requiring upward dose titration or a combination with other lipid-lowering agents.[57,158,159]

In the largest of these trials, the nonblind randomised TARGET TANGIBLE study, about two-thirds of patients receiving atorvastatin 10 to 40 mg/day for 14 weeks achieved the target serum LDL-cholesterol (≤2.6 mmol/L) compared with about half of those receiving simvastatin 10 to 40 mg/day ($p < 0.001$) [table VII].[159] Fewer patients in the atorvastatin group required titration to 40 mg/day than in the simvastatin group (38 *vs* 54%; $p < 0.05$). 58% of patients in this study had proven CHD.

In a similar nonblind 54-week treat-to-target study in 308 patients with documented atherosclerosis,[158] the percentage of atorvastatin-treated patients (32%) who achieved the target LDL-cholesterol level of ≤2.6 mmol/L (100 mg/dl) without the addition of colestipol was significantly greater than in the fluvastatin, lovastatin and simvastatin groups. Colestipol was added if target levels were not achieved at maximum dosages. At 54 weeks, 83% of patients in the atorvastatin group achieved target LDL-cholesterol levels; this percentage was significantly higher ($p < 0.05$) than that in the fluvastatin group (50%) and similar to that in the lovastatin and simvastatin groups (81 and 75%, respectively). Table VII gives response rates for monotherapy with the various drugs.

Furthermore, 37% of a subgroup of patients with CHD in a 52-week double-blind placebo-controlled randomised study reached LDL-cholesterol targets with atorvastatin up to 20 mg/day (n = 120), compared with 11% of those receiving lovastatin up to 40 mg/day (n = 41) [$p < 0.05$].[57]

The efficacy of atorvastatin in achieving target LDL-cholesterol levels in women with risk factors or CHD has been assessed in a 16-week treat-to-target study involving 318 female patients (the WATCH trial).[162] Of 198 women with established CHD, 34 and 60% achieved target LDL-cholesterol levels with atorvastatin 10 and 20 mg/day, respectively. With maximal titration up to 80 mg/day, 80% of these women were able to reach target LDL-cholesterol levels. In those with ≥2 risk factors for CHD (n = 120), atorvastatin 10 and 20 mg/day resulted in lowering of LDL-cholesterol levels to target values in 63 and 79%, respectively.

A significantly greater change towards coronary atherosclerotic plaque stabilisation, as measured by the increase in percentage of hyperechogenic volume (assessed by using 3-dimensional intracoronary ultrasound), was observed in patients receiving atorvastatin 20 to 80 mg/day (40%) than those receiving other usual care (other HMG-CoA reductase inhibitors, fibrates or cholestyramine: 11%; $p = 0.01$) in the 12-month randomised GAIN trial in 131 patients.[163]

4.5.3 Aggressive Therapy in Patients with CHD

The reduction in long-term cardiac morbidity and mortality in patients with CHD with lowering of serum LDL-cholesterol levels to below 2.6 mmol/L has been proven without doubt. Whether aggressive lowering of serum LDL-cholesterol levels to 1.9 mmol/L (75 mg/dl) or below will achieve greater reduction in CHD remains to be determined. A number of studies evaluating the benefits of achievement of very low LDL-cholesterol levels with high-dose atorvastatin in patients with CHD are in progress (see section 8) and the results of two of these are available (table VIII).[164,165]

The MIRACL Study

Aggressive reduction of serum LDL-cholesterol to 1.9 mmol/L, well below the recommended target, was investigated in patients with acute coronary syndromes (unstable angina or non-Q-wave myocardial infarction) in the randomised double-blind MIRACL trial. 3086 patients received atorvastatin 80 mg/day or placebo for 16 weeks, starting 24 to 96 hours after hospital admission.[164]

The combined primary end-point (death, nonfatal myocardial infarction, cardiac arrest with resusci-

Table VIII. Summary of trials evaluating aggressive lowering of low-density lipoprotein cholesterol (LDL-C) with atorvastatin (ATO) in patients with coronary heart disease (CHD)

	The MIRACL study[164]a			The AVERT trial[165]b		
Design	Randomised, double-blind, placebo (PL)-controlled, multicentre			Randomised, nonblind, multicentre		
No. of patients	3086 (ATO 1538, PL 1548)			341 (ATO 164, PTCA 177)		
Patients	Unstable angina or non-Q-wave MI			Stable CHD, asymptomatic or mild to moderate angina, candidates for PTCA for stenosis of at least 1 coronary artery		
Intervention	ATO 80 mg/day initiated at 24 to 96 hours after admission			ATO 80 mg/day with usual antianginals		
Control	Placebo			PTCA procedure with usual care		
Duration	16wk			18mo		
Primary combined end-point (PEP)	Death, nonfatal acute MI, cardiac arrest with resuscitation, recurrent symptomatic myocardial ischaemia requiring emergency hospitalisation (RSMIH)			Ischaemic events (death from cardiac causes, nonfatal MI, resuscitated cardiac arrest, stroke, CABG, PTCA, worsening angina requiring hospitalisation)		
Results	ATO	PL	Significance	ATO	PTCA	Significance
Serum LDL-C levels	1.87 mmol/L (72 mg/dl)	3.2 mmol/L (124 mg/dl)		2 mmol/L (77 mg/dl)	3 mmol/L (119 mg/dl)	$p < 0.05$
PEP	14.8%	17.4%	RR 0.84; CI 0.7-1.0; $p = 0.048$	13.4%	20.9%	NS; $p = 0.048$ (designated significance value 0.045)
Subgroup analysis	RSMIH lower in ATO group (6.2 *vs* 8.4%; $p = 0.02$) Other PEP : NS			Ischaemic events after 6 months lower in ATO group (7 *vs* 10%; $p = 0.045$) Time to a first ischaemic event shorter in ATO group ($p = 0.03$)		
Secondary end-points	No significant between-group differences in the individual components of death, nonfatal acute MI, cardiac arrest with resuscitation, coronary revascularisation, worsening heart failure, worsening angina Incidence of nonfatal stroke (0.6 *vs* 1.4%, $p = 0.02$) and fatal plus nonfatal stroke (0.8 *vs* 1.6%; $p = 0.045$) lower in atorvastatin group					

a The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering study.

b The Atorvastatin Versus Revascularisation Treatment trial.

CABG = coronary artery bypass graft surgery; **CI** = 95% confidence interval; **MI** = myocardial infarction; **NS** = not significant; **PL** = placebo; **PTCA** = percutaneous transluminal coronary angiography; **RR** = relative risk.

tation, or recurrent ischaemia requiring rehospitalisation) occurred in 14.8% of patients in the atorvastatin group compared with 17.4% in the placebo group ($p = 0.048$, relative risk 0.84; 95% confidence interval 0.7 to 1.0). Although there was no significant between-group difference in risk of the individual components (secondary end-points) of death, nonfatal myocardial infarction or resuscitated cardiac arrest, atorvastatin treatment significantly reduced the incidence of recurrent ischaemic events requiring emergency rehospitalisation compared with placebo (6.2 *vs* 8.4%; $p = 0.02$).[164] The incidence of nonfatal or fatal stroke was also lower in patients receiving atorvastatin than in those receiving placebo (0.8 *vs* 1.6%; $p = 0.045$) [table VIII]; the number of patients with stroke was small in both groups. There was no significant relationship between the occurrence of a primary end-point event and the baseline LDL-cholesterol levels or the percentage reduction in LDL-cholesterol levels.

The AVERT Study

The results of the AVERT trial showed that aggressive lipid-lowering therapy with atorvastatin 80 mg/day for 18 months was at least as effective as coronary angioplasty and usual care in reducing the incidence of ischaemic events in low-risk patients with stable CHD.[165] In this nonblind multicentre study, 341 patients with stable CHD who were candidates for elective angioplasty for at least one significant coronary artery stenotic lesion were randomised to receive either the indicated angioplasty (n = 177), with the usual care, or atorvastatin 80 mg/day (n = 164) with the usual antianginal therapy.

As shown in table VIII, after 18 months serum LDL-cholesterol levels achieved were significantly ($p < 0.05$) lower in the atorvastatin-treated group [2 mmol/L (77 mg/dl)] compared with the angioplasty group [3 mmol/L (119 mg/dl)]. 22 patients in the atorvastatin-treated group (13.4%) had at least one primary end-point event (CHD death, nonfatal myocardial infarction, coronary bypass surgery, angioplasty and worsening angina pectoris requiring hospitalisation) compared with 37 patients (20.9%) in the angioplasty group ($p = 0.048$; designated significance level adjusted by interim analysis was $p = 0.045$). Subgroup analysis showed that patients who achieved LDL-cholesterol below 1.9 mmol/L (75 mg/dl) experienced fewer ischaemic events (10%) than those who achieved levels between 1.9 and 2.6 mmol/L (75 and 100 mg/dl), and above 2.6 mmol/L (13 and 22%, respectively; p-values not provided).[166] Time to a first ischaemic event was significantly lower in the atorvastatin group ($p = 0.03$).

4.5.4 Patients with Organ Transplants

Hyperlipidaemia with elevation of cholesterol and triglyceride levels occurs in a majority of patients with cardiac or renal transplants and contributes to the high morbidity and mortality due to cardiovascular disease among these patients. There have been concerns about a possible increase in incidence of rhabdomyolysis as well as elevation of cyclosporin levels because of interaction of cyclosporin with HMG-CoA reductase inhibitors (section 3.4). Lower doses of HMG-CoA reductase inhibitors have been used in most studies in these patients.

In noncomparative studies atorvastatin reduced total and LDL-cholesterol levels in small numbers of patients with renal transplants (table IX).[65,104] Although there are no large controlled studies comparing atorvastatin with other HMG-CoA reductase inhibitors in patients with organ transplants, small studies, some retrospective, have found atorvastatin to produce further reductions in LDL-cholesterol levels of up to 30% in patients previously treated with other HMG-CoA reductase inhibitors (simvastatin, pravastatin and fluvastatin) [table IX]. Triglyceride levels decreased significantly (by 26%) in patients with hypertriglyceridaemia but not in those with previously normal triglyceride levels (table IX).[169]

Atorvastatin produced significantly greater reductions in LDL-cholesterol and triglyceride levels compared with pravastatin (both $p \leq 0.001$) in the only directly comparative study, a 4-month randomised crossover trial in 39 patients with cardiac transplants (table IX).[103] More patients (74%) achieved total cholesterol levels of <5.2 mmol/L (200 mg/dl) with atorvastatin 10 mg/day than with pravastatin 20 mg/day (26%).

4.5.5 Patients with HIV Infection

Patients with HIV infection who are receiving drugs from the protease inhibitor group are prone to develop a syndrome of abnormal fat redistribution, hyperlipidaemia, insulin resistance and hyperglycaemia.[170]

Three small studies of about 4 to 6 months' duration have reported the effects of atorvastatin on protease inhibitor-related hyperlipidaemia. In ten patients receiving atorvastatin as the sole antihyperlipidaemic agent (starting daily dose of 10 mg/day), mean total cholesterol and triglyceride levels were reduced by 19% ($p = 0.004$) and 21% (not significant) respectively, after 5.3 months.[171] In another study, 14 patients experienced 21 and 39% reductions in serum cholesterol and triglyceride levels after 6 months of atorvastatin 10 to 20 mg/day.[172]

Table IX. Summary of clinical trials evaluating the efficacy of atorvastatin (ATO) in patients with organ transplants (TX)

Reference	Study design and duration	No. of evaluable patients	Dosage regimen (mg/day)	Mean change (%) in serum lipid levels from baseline to treatment end-point			
				total-C	LDL-C	TG	HDL-C
Noncomparative studies							
Alvarez et al.[104]	6mo (renal TX)	24	ATO 10-20	–31	–37	–22	–1
Åsberg et al.[65]a	4wk (renal TX)	22	ATO 10	–27	–42		
Comparison with pravastatin (PRA)							
Magnani et al.[103]	r, nb, co 4mo (cardiac TX)	39	ATO 10-20	–33***	–45**	–24***	+2
		39	PRA 20-40	–21	–30	–8	–1
Comparisons after switchover to atorvastatin[c]							
Kobashigawa et al.[167]a	3mo (cardiac TX)	28	ATO 10	–18*	–17	–8	–5
Patel et al.[168]a	3mo (cardiac TX)	30	ATO 20-40		–31***		+3
Romero et al.[169]	3mo (renal TX)	10	ATO 10	–19*	–26*	–9 –26[b]*	–2

a Abstract.

b In 5 patients with TG >1.7 mmol/L.

c After previously unsuccessful therapy with other HMG-CoA reductase inhibitors.

C = cholesterol; **co** = crossover; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **nb** = nonblind; **r** = randomised; **TG** = triglycerides; * $p < 0.05$, ** $p = 0.001$, *** $p < 0.001$ *vs* previous therapy or comparator.

Adding gemfibrozil produced greater reductions: in patients receiving a combination of atorvastatin with gemfibrozil (n = 19), there was a reduction of 30 ($p = 0.004$) and 60% ($p = 0.01$), respectively, in cholesterol and triglyceride levels at 6.5 months. However, this combination may increase the risk of myopathies (section 7).

These limited data suggest potential efficacy of atorvastatin in these patients, but no conclusions can be drawn at present.

4.5.6 Patients with Renal Failure

Patients with end-stage renal disease (ESRD) have a higher prevalence of dyslipidaemia,[173,174] which is not corrected by renal replacement therapy,[174] and a much greater risk of cardiovascular disease than the general population.[175] These patients are considered to be a 'highest-risk' group for cardiovascular events.[173]

At present, there are few studies of atorvastatin in such patients. With the exception of a placebo-controlled trial[176] most contain small patient numbers, and the majority are presented as abstracts (table X). However, a large prospective trial of atorvastatin in patients undergoing haemodialysis is under way (see section 8).

Among this high-risk population atorvastatin consistently reduced total cholesterol and LDL-cholesterol levels when given for 1 to 4 months. Triglyceride levels decreased significantly in most but not all studies (table X). In the large placebo-controlled trial 85 and 16% of patients given atorvastatin 10 mg/day and placebo, respectively, achieved EAS targets for LDL-cholesterol after 4 weeks ($p \leq 0.001$), and all changes in lipid levels in the atorvastatin group were significant versus placebo (table X).[176] Atorvastatin up to 40 mg/day administered for 4 months resulted in achievement of target LDL-cholesterol levels in 19 of 20 patients without CHD and 7 of 9 patients with a history of CHD undergoing peritoneal dialysis. 15 of 19 patients with hypertriglyceridaemia achieved target triglyceride levels.[177]

Combining atorvastatin with α-tocopherol was not more effective than atorvastatin plus placebo in patients undergoing haemodialysis or peritoneal

Table X. Efficacy of atorvastatin (ATO) in patients with dyslipidaemia and end-stage renal disease (ESRD) undergoing dialysis

Reference (study design)	Patient type	No. of evaluable patients	Dosage in mg/day	Duration	Mean change (%) in serum lipid levels from baseline to end-point			
					total-C	LDL-C	TG	HDL-C
Noncomparative trials								
Hufnagel et al.[177]	PD	20 no CHD	ATO 10-40	4mo	–33	–42**	–37**	
		9 CHD			–36	–46**	–26**	
Le Roux et al.[178]	HD	19	ATO 20	4mo	–29***			–27***[b]
Stegmayr et al.[179] [a]	ESRD	40	ATO 10	1mo	–26**	–47**	–16*	
Comparative trials								
Diepeveen et al.[180] [a] (r, db, pc, pg) [c]	ESRD	HD (6) PD (5)	ATO 20 + TOC 800IU	12wk	HD:–37*	–58*	–16	0
					PD:–38*	–52*	–20	+9
		HD (6) PD (4)	TOC 800IU + PL		HD:+4.5	+3.8	+10	0
					PD:–3.7	+3.4	–24	+10
		HD (6) PD (7)	ATO 20 + PL		HD:–35*	–48*	–27*	–10
					PD:–34*	–50	–39*	0
Wheeler et al.[176] [a] (r, db, mc, pc, pg)	PD	82	ATO 10-40	16wk	–29††	–40††	–14††	+7†
		95	PL		–6	–9	+11	–3

a Abstract.

b Change in total-C/HDL-C ratio.

c Results for the placebo group not shown. There were no significant differences from baseline for this group in any parameter except HDL-C ($p < 0.05$).

C = cholesterol; **CHD** = coronary heart disease; **db** = double-blind; **HD** = haemodialysis; **HDL** = high-density lipoprotein; **LDL** = low-density lipoprotein; **mc** = multicentre; **pc** = placebo controlled; **PD** = peritoneal dialysis; **pg** = parallel group; **PL** = placebo; **r** = randomised; **TG** = triglyceride; **TOC** = α-tocopherol. * $p < 0.05$, ** $p < 0.001$, *** $p < 0.0005$ *vs* baseline; † $p < 0.001$, †† $p < 0.0001$ *vs* PL.

dialysis, although this randomised double-blind study enrolled small numbers of patients.[180]

5. Tolerability

5.1 General Profile

Atorvastatin has been well tolerated in clinical trials as revealed by an analysis of pooled data from 21 clinical studies, 17 of which were multicentre, and 2502 patients given the drug.[181] Of these, 1253 patients (50%) received the drug for at least 1 year.

In placebo-controlled studies, the incidence of adverse events (18%) in 1122 patients receiving atorvastatin up to 80 mg/day was similar (18%) to the incidence in those receiving placebo (n = 270) (fig. 2a). No dose-related increase in adverse events was observed in these studies. Overall, the most frequently reported adverse events with atorvastatin in these trials were constipation, flatulence, dyspepsia and abdominal pain, headache and myalgia. Adverse events reported with atorvastatin have been mild and transient.

Fewer than 2% of the 2502 patients who received atorvastatin withdrew from the trials due to adverse effects related to treatment. The incidence of withdrawal was not dose dependent.[181] The adverse events responsible for withdrawal included nausea, depression, myalgia, abdominal pain and abnormalities in liver function tests, each of which occurred in fewer than 0.3% of atorvastatin-treated patients.

Serious adverse events were reported by approximately 30 of 2502 patients (5%) receiving atorvastatin.[181] In only two patients (<1%) were they considered to be related to treatment with atorvastatin. These included one patient with acute pancreatitis and another with cholestatic jaundice. Both recovered without sequelae. One patient with toxic epidermal necrolysis following atorvastatin

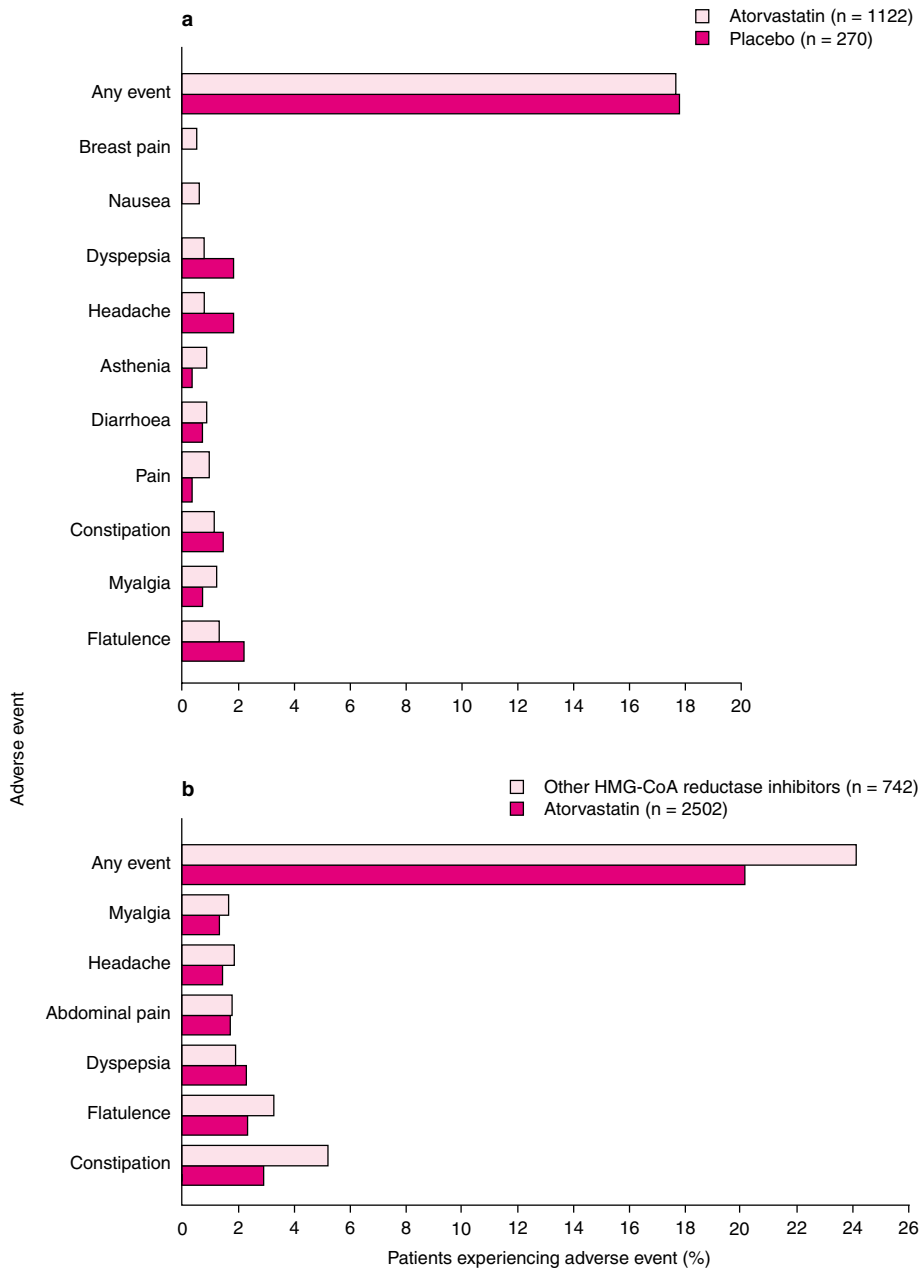

Fig. 2. Tolerability of atorvastatin. Pooled tolerability data from 21 clinical trials comparing the incidence of various adverse events in patients receiving atorvastatin (n = 2502) with those receiving (**a**) placebo (n = 270) and (**b**) other HMG-CoA reductase inhibitors (n = 742);[181] (statistical analysis not conducted).

use has been reported.[182] In another patient, severe thrombocytopenia was presumed to be caused by an idiosyncratic reaction to atorvastatin.[183]

5.2 Compared with Other Drugs

In general, the adverse event profile for atorvastatin was similar to that observed with other HMG-CoA reductase inhibitors (fig. 2b).[181] In a large study in 2856 patients with CHD, the incidence of drug-related adverse events in patients receiving atorvastatin (n = 1897) in doses of 10 to 40 mg/day for 14 weeks was similar to that in patients receiving simvastatin 10 to 40 mg/day.[159] Myalgia, nausea and abdominal pain occurred in <1% of patients in each group. Asthenia was experienced by 0.3 and 0.8% of patients in the atorvastatin and simvastatin group, respectively ($p < 0.05$).

A number of studies evaluating the benefits on prevention of CHD of aggressive lowering of LDL-cholesterol with atorvastatin are in progress and two have been completed (section 4.5.3). The safety profile of atorvastatin in patients in whom very low LDL-cholesterol levels were achieved has been examined in a subgroup of a pooled analysis of data from 21 clinical trials.[184] The incidence of adverse events in patients with at least one LDL-cholesterol value below 2.1 mmol/L (80 mg/dl) with atorvastatin therapy (n = 319) was 24%, which was similar to that with all atorvastatin-treated patients (20%) and patients receiving other HMG-CoA reductase inhibitors (24%).

The tolerability profile of atorvastatin has been found to be better than that of fenofibrate or nicotinic acid. Fewer patients had adverse events with atorvastatin 10 to 20 mg/day (29%) than with fenofibrate 300 mg/day (42%) over a 12-week study period (n = 84).[132] More patients receiving fenofibrate (14%) were withdrawn because of adverse events than those receiving atorvastatin (2%). The incidence of adverse events with nicotinic acid 3 g/day administered for 12 weeks (66%) was 6-fold greater than with atorvastatin 10 mg/day (11%) in 105 patients with hypertriglyceridaemia.[133]

Studies with a follow-up of 1 year or more have confirmed the safety profile of atorvastatin. Data over a 2-year period are available from the extension of a 1-year randomised double-blind study comparing the efficacy and safety of atorvastatin (10 to 80 mg/day) with lovastatin (20 to 80 mg/day). 655 and 212 patients receiving atorvastatin and lovastatin, respectively, completed a second year of follow-up for analysis of safety parameters.[185] In this abstract report, the overall safety profile of atorvastatin was similar for the first and second years and was similar to that of lovastatin. Drug-related adverse events occurred in 19 and 12% of patients receiving atorvastatin in the first and second year, respectively.[181]

5.3 Specific Events

5.3.1 Effects on Hepatic Function

Mild hepatic involvement in the form of asymptomatic elevations in serum transaminase levels has been reported during treatment with HMG-CoA reductase inhibitors. In the pooled analysis of clinical trials with atorvastatin, persistent elevation of greater than three times the upper limit of normal was reported in 0.7% of patients and was responsible for discontinuation of atorvastatin in 0.3%.[181] The incidence of persistent elevation of transaminases was higher in patients receiving atorvastatin in doses of 80 mg/day (2.3%) than in those receiving lower doses. In patients receiving doses of 10, 20 and 40 mg/day, the incidence (0.2, 0.6 and 0.6%, respectively) was similar to that with placebo (0.4%). At all doses, the majority of episodes of elevation in transaminase levels occurred in the first 16 weeks after initiation of treatment with atorvastatin.[181] There was no relationship to age, sex, alcohol intake or body mass index.[181]

There have been isolated reports of cholestatic hepatitis in two patients with familial hypercholesterolaemia[186] and one patient with systemic lupus erythematosus.[187] Acute hepatitis occurred in one patient who was also receiving phenobarbital.[188] In all these patients, liver function improved on stopping atorvastatin.

5.3.2 Effects on Muscle

The incidence of myalgia with the use of atorvastatin (1%) has been found to be similar to that with placebo (1%) and other HMG-CoA reductase inhibitors (2%).[181] Although isolated asymptomatic elevation of creatine phosphokinase (CPK) has been observed in patients receiving atorvastatin, persistent elevation of CPK (>10 times elevation on two consecutive occasions) along with muscle pain, tenderness or weakness has not so far been reported with the use of atorvastatin.[181]

Rhabdomyolysis[153] and dermatomyositis[189] have each been reported in one patient with familial hyperlipidaemia receiving atorvastatin monotherapy. In the few other published case reports of patients developing rhabdomyolysis while receiving atorvastatin, concomitant therapy included gemfibrozil,[190] fusidic acid[191] or cyclosporin.[100,101] The combined use of fibrates and HMG-CoA reductase inhibitors is generally not recommended because of the potential for increased risk of myopathy and rhabdomyolysis (section 7).[192]

In patients with organ transplants receiving cyclosporin, use of atorvastatin 10 mg/day resulted in myalgia and myositis in two of 48 patients in one study.[168] In two other studies using atorvastatin in doses up to 20 mg/day in patients receiving cyclosporin, serum CPK levels were elevated in two of 24[104] and two of 39 patients.[103]

6. Pharmacoeconomic Studies

The long-term benefits of lowering serum cholesterol and LDL-cholesterol in patients with hypercholesterolaemia are well established. However, to utilise health resources optimally it is essential that economic evaluation of costs and benefits of lowering lipids in various subsets of patients at risk for CHD is available to physicians and health policy-makers to guide them in deciding which patients to treat.

A number of studies used modelling analysis to compare the economic benefits of lowering serum lipids with various HMG-CoA reductase inhibitors in terms of cost per year of life saved (YLS).[193,194] Others used cost of achievement of target LDL-cholesterol or of per unit lowering of serum lipid as surrogate markers to compare the cost effectiveness of various lipid-lowering agents.[195-201]

6.1 Studies Using Analytical Models of Cost Effectiveness

A study utilising a decision analytical Markov model compared the cost and consequences of using five HMG-CoA reductase inhibitors at their usual starting daily doses (atorvastatin 10mg, simvastatin 10mg, lovastatin 20mg, fluvastatin 20mg and pravastatin 20mg) in various risk categories for primary as well as secondary prevention of CHD.[193] The reductions in serum lipid levels for each drug were derived from data approved by the US Food and Drug Administration (FDA) for product labelling. Annual risks of coronary event occurrence were estimated using the Framingham Heart Study coronary risk equations. The perspective of cost was for a third-party payer with current estimates of only the direct medical costs of CHD used to assign costs to health states and acute coronary events. Net cost was measured as total cost of therapy minus savings in CHD treatment discounted at an annual rate of 3%. Outcome measurements were net cost, maximum gain in life expectancy and cost per YLS.

Results showed that the maximum gain in life expectancy was achieved with the use of atorvastatin. Although the net cost was lower with fluvastatin than with atorvastatin because of the lower acquisition cost of the former, cost effectiveness was greater with atorvastatin than all the other HMG-CoA reductase inhibitors studied resulting in a greater gain in life expectancy for a given level of expenditure. The incremental cost per YLS among all the HMG-CoA reductase inhibitors was the lowest with atorvastatin. When the cost effectiveness of lipid-lowering was studied in various risk groups, the incremental cost per YLS with atorvastatin versus no therapy was below $US40 000 (currency year 1997) among males in all categories except those in the 45-year age group with moder-

ate elevation of LDL-cholesterol (4.9 mmol/ L) and no additional risk factors. Among women, similar cost effectiveness was achieved in only those with at least three risk factors or those with existing CHD.[193]

A similar model was used in another study that compared the cost effectiveness of use of HMG-CoA reductase inhibitors (atorvastatin, simvastatin, pravastatin, lovastatin and fluvastatin) in a cohort of patients between the ages of 60 and 85 years with established CHD.[194] Percent reductions in incidence of CHD secondary to reductions in LDL-cholesterol levels with HMG-CoA reductase inhibitors were derived from the results of the Scandinavian Simvastatin Survival Study (4S).[202] The patients were assumed to be taking doses of HMG-CoA reductase inhibitors necessary to provide a long-term reduction of 35.57% in LDL-cholesterol levels as seen in 4S. The maximum daily doses considered were atorvastatin 20mg, simvastatin 40mg, lovastatin 80mg, fluvastatin 80mg and pravastatin 40mg. Only direct costs of HMG-CoA reductase inhibitor therapy and cardiac events were considered. Cost effectiveness was measured as ratio of costs to YLS discounted at 3% per year. Using the baseline assumptions of this model, the cost per YLS saved was found to be the lowest with atorvastatin ($US5421; currency year 1999) and highest with lovastatin ($US15 073).

6.2 Studies Using Surrogate Markers

Although ideal measures of effectiveness of lipid-lowering therapy would include clinical outcomes such as incidence of fatal or non-fatal CHD, life expectancy, or quality-adjusted life-years, their use is often not feasible because of the expenditure of time and money required to conduct clinical trials. Hence, a number of surrogate markers such as the percent change in LDL-cholesterol levels, the ratio of LDL-cholesterol to HDL-cholesterol, and percentage of patients attaining goal LDL-cholesterol levels have been used to examine the cost effectiveness of lipid-lowering therapies.

Two cost-effectiveness analysis studies have compared atorvastatin with other HMG-CoA reductase inhibitors (fluvastatin, lovastatin, pravastatin and simvastatin) by calculating the annual acquisition cost of the drug per percent reduction in LDL-cholesterol achieved (table IX). While investigators in one performed a meta-analysis on patients in 56 trials evaluating HMG-CoA reductase inhibitor monotherapy,[195] the other investigators conducted a *post hoc* pharmacoeconomic analysis[196] of a multicentre, randomised 8-week efficacy study (CURVES).[55] Both studies found atorvastatin to be the most cost-effective regimen in terms of cost per percentage reduction in LDL-cholesterol levels achieved (table XI).

The total treatment costs of achieving the target LDL-cholesterol levels with various HMG-CoA reductase inhibitors have been compared in a number of studies (table XII). These included the cost

Table XI. Annual acquisition costs[a] of various HMG-CoA reductase inhibitors for each percentage reduction in LDL-C at various doses

Drug (mg/day)	US dollars spent per % reduction in LDL-C levels	
	Hilleman et al.[195] [b]	Hilleman et al.[196] [c]
ATO 10	18	18
20	22	23
40	24	25
80		47
FLU 20	21	27
40	20	20
80	34[d]	
LOV 20	34	30
40	49	51
80	76[d]	67
PRA 10	35	37
20	30	31
40	46	40
80	68[d]	
SIM 5	28	
10	26	28
20	39	39
40	34	34
80	57[d]	
160	101[d]	

a Figures rounded off.

b 1998 prices; results from a meta-analysis.

c 1999 prices; *post hoc* analysis of the CURVES study.[55]

d Based on 40mg preparations.

ATO = atorvastatin; **FLU** = fluvastatin; **LDL-C** = low-density lipoprotein-cholesterol; **LOV** = lovastatin; **PRA** = pravastatin; **SIM** = simvastatin.

Table XII. Comparison of cost per patient of achieving NCEP LDL-cholesterol targets with various HMG-CoA reductase inhibitors

Reference	Design	Level of CHD risk	Cost per patient to achieve target LDL-cholesterol level				
			atorvastatin	fluvastatin	lovastatin	pravastatin	simvastatin
Hilleman et al.[195]	Meta-analysis[a] US$ (1998)	High	954[b]	1308	2556	2173	3368
		Moderate	673	619[b]	1045	1112	824
		Low	664	457[b]	850	737	652
		Overall	842[b]	1014	1935	1703	2344
Koren et al.[198]	r, mc (54wk)[c,d] n = 662 US$ (1996)	High	1313[b]	1670	2235		1614
		Overall	1064[b]	1542	1972		1471
MacLaine & Patel[199]	Meta analysis[a] plus newer literature £ (not stated)	Moderate	3721 (383)[e]	3382 (820)[e]		4296 (1213)[e]	4086 (431)[e]
Smith et al.[197]	r, mc (54wk)[d] n = 336 £ (1997)	High	501[b]	1130		906	613
Smith[201] [f]	r, mc (54wk)[g] n = 3262 US$ (not stated)	Moderate-high	915	1393-2421[h]	1393-2421[h]	1393-2421[h]	1393-2421[h]

a Meta-analysis of 56 studies with 101 monotherapy cohorts.
b Included costs related to adverse events.
c Lowest cost among drugs evaluated.
d Modified European Atherosclerosis Society targets (2.63 mmol/L).
e Incremental cost-effectiveness ratio relative to no treatment.
f Abstract.
g Used clinical data from the ACCESS trial.[127]
h Specific costs per patient were not given for each comparator drug ($p < 0.01$ *vs* atorvastatin for each comparison).

ACCESS = Atorvastatin Comparative Cholesterol Efficacy and Safety Study; **CHD** = coronary heart disease; **LDL** = low-density lipoprotein; **mc** = multicentre; **NCEP** = US National Cholesterol Education Program Adult Treatment Panel II guidelines; **r** = randomised.

of acquisition of the study drug as well as any additional combination drug, if required to achieve the goal, general practitioner/specialist visits and laboratory tests. The cost of adverse events was included in several studies.[195,197,200]

Atorvastatin was found to be the most cost-effective single drug compared with simvastatin, fluvastatin, pravastatin and lovastatin for achieving target serum LDL-cholesterol in the overall patient population in a meta-analysis of 56 trials with 101 monotherapy cohorts.[195] Analysis of various subgroups showed that atorvastatin was the most cost-effective drug for high-risk patients (those with CHD) whereas fluvastatin was the most cost-effective agent for low-risk (<2 risk factors for CHD) and moderate-risk patients (≥2 risk factors for CHD).[195] However, another model using a meta-analysis of current literature found atorvastatin to have the lowest incremental cost-effectiveness ratio (relative to no treatment) in patients with moderate risk.[199]

Preliminary pharmacoeconomic analysis[201] of the results of the large ACCESS trial[127] showed that atorvastatin recipients had fewer physician visits than patients given comparator drugs in weeks 6 to 18 (2.81 *vs* 2.95 to 3.45; $p < 0.01$ for all comparisons) and a lower cost per outcome (table XII).

In a prospective randomised controlled multicentre study comparing the efficacy and cost effectiveness of atorvastatin, simvastatin, lovastatin and fluvastatin in 662 patients with mild to moderate hypercholesterolaemia, atorvastatin was the most cost-effective agent for achieving target LDL-cholesterol levels in the overall study population as well as in the subgroups of patients with and without CHD.[198] Another prospective randomised multicentre study comparing atorvastatin, simva-

statin, fluvastatin and pravastatin in patients with established CHD found the cost of achieving modified EAS target LDL-cholesterol levels (<3 mmol/L; 115 mg/dl) to be the lowest with atorvastatin.[197] However, in a cost-minimisation analysis based on the results of the study mentioned above[197] and comparing the total annual cost of drug acquisition for simvastatin and atorvastatin, the average daily maintenance cost of simvastatin was lower than that of atorvastatin in the majority of European countries.[203]

7. Dosage and Administration

Oral atorvastatin 10 to 80 mg/day may be used to lower lipid levels of patients with primary hypercholesterolaemia (heterozygous familial, homozygous familial or nonfamilial), mixed hyperlipidaemia and diabetic dyslipidaemia, who do not respond to lifestyle measures (including standard cholesterol-lowering diet). The usual starting dosage is 10mg once daily.[204]

Lipid levels should be analysed within 2 to 4 weeks of treatment onset or titration and the dosage of atorvastatin should be tailored according to response. Liver function tests should be performed before initiating treatment with atorvastatin and periodically thereafter.[86]

Atorvastatin may be taken with or without food at any time of day. No dosage adjustment is required in older patients and patients with renal failure. However, dosage reductions may be required in patients with hepatic insufficiency. Atorvastatin is contraindicated in patients with active hepatic disease or unexplained elevations in serum transaminase levels, and pregnant or breast-feeding women.[204]

As with other HMG-CoA reductase inhibitors, concomitant use of atorvastatin with cyclosporin, nicotinic acid, fibrates, erythromycin or azole antifungals is likely to increase the risk of adverse events such as myopathy and rhabdomyolysis (see also section 5.3.2).[204-207]

8. Place of Atorvastatin in the Management of Dyslipidaemias

CHD remains the leading cause of death and is a major cause of morbidity among men and women in the US and other developed countries.[3,208,209] The role of elevated levels of cholesterol and LDL-cholesterol in the pathogenesis of atherosclerosis has been well established.[3,210] Reduction of plasma cholesterol levels by pharmacological means in patients with hypercholesterolaemia has been shown to prevent atherosclerotic plaque progression[211] and reduce both fatal and nonfatal coronary events in patients with or without coronary artery disease.[202,212-215]

The considerable evidence showing reduction of CHD risk with the reduction of elevated cholesterol levels is reflected in the inclusion of cholesterol lowering as an essential part of the recommendations on CHD prevention. The treatment guidelines for primary and secondary prevention, both from the US and Europe, emphasise the need for assessment of overall CHD risk in an individual in order to determine when to start lipid-lowering treatment. The US NCEP guidelines recognise risk factors for CHD and classify patients into low, moderate and high risk for CHD depending on the number of risk factors present. Target LDL-cholesterol levels are allocated for each of the three risk groups. The updated clinical guidelines of the NCEP have included in the high-risk group patients with diabetes mellitus without CHD and persons with a more than 20% risk for CHD within 10 years, based on Framingham projections.[105] In the Joint European Guidelines for Coronary Prevention, the probability of experiencing a coronary event is calculated using a risk chart and the decision to start therapy made accordingly.[71]

It is generally recommended that initial cholesterol lowering should begin with lifestyle changes.[208] These include increased physical activity, weight reduction and change in dietary habits. The reductions in cholesterol levels achieved by these measures are modest and most patients require drug therapy to achieve cholesterol reduction goals.[208]

HMG-CoA reductase inhibitors are more effective than other classes of lipid-lowering drugs in reducing LDL-cholesterol to target levels and reducing CHD risk. As a result, HMG-CoA reductase inhibitors are recommended as first-line lipid-lowering drug therapy in patients who are at risk of CHD or who have established CHD.[71,209]

The efficacy and safety profile of HMG-CoA reductase inhibitors (statins) has prompted a number of large-scale placebo-controlled trials to evaluate the effect of long-term use of these drugs on mortality and morbidity due to atherosclerotic disease. Long-term reduction of cholesterol by use of these drugs has been shown to reduce the incidence of CHD when used for primary prevention in patients with moderate to severe hypercholesterolaemia (WOSCOPS; pravastatin)[214] as well as those with normal to mildly elevated cholesterol but low HDL-cholesterol (AFCAPS; lovastatin).[215] Several secondary prevention trials have also demonstrated survival benefit with the use of HMG-CoA reductase inhibitors in patients with moderate to severe hypercholesterolaemia (4S; simvastatin)[202] as well as normal cholesterol levels (CARE,[212] LIPID;[213] both pravastatin).

These benefits are generally believed to be related to LDL-cholesterol reduction.[216,217] Similar benefits are likely to be achieved by LDL reduction with other HMG-CoA reductase inhibitors such as atorvastatin, which have not been tested directly for reduction in CHD except in trials involving aggressive reduction of LDL-cholesterol with atorvastatin in specific groups of patients with CHD (section 4.5.3). A number of long-term clinical trials assessing the effect of atorvastatin on clinical end-points in various patient groups are now under way (table XIII).

The HMG-CoA reductase inhibitors currently available are atorvastatin, lovastatin, pravastatin, fluvastatin and simvastatin. Comparative efficacy studies involving lovastatin, pravastatin, fluvastatin, simvastatin and atorvastatin have established that atorvastatin produces the greatest reductions in LDL-cholesterol levels at milligram equivalent doses as well as at maximum recommended doses (section 4.1.2). Atorvastatin therapy is also more likely to achieve target LDL-cholesterol levels at the starting dose than treatment with the other HMG-CoA reductase inhibitors, thus requiring less frequent dose titration. Fewer patients with high risk for CHD require the addition of another lipid-lowering agent to atorvastatin than to other HMG-CoA reductase inhibitors to achieve the stricter LDL-cholesterol goals. Data reported in abstracts suggests that rosuvastatin, an HMG-CoA reductase inhibitor under development, may produce greater reductions in LDL-cholesterol levels than atorvastatin, but efficacy and safety data with this new agent are limited relative to others of this class, and the optimal dosage has not been determined.

The available long-term trials of HMG-CoA reductase inhibitors, apart from showing clinical benefits, have provided substantial evidence for the long-term safety profile of these drugs. However, the HMG-CoA reductase inhibitor cerivastatin, which had shown efficacy similar to[102,226,229] or lower than[230,231] that of atorvastatin in several trials, was recently voluntarily withdrawn from the market worldwide by the manufacturer following suggestions that 52 deaths may be linked to the drug. Cerivastatin has been reported to cause severe rhabdomyolysis, particularly when given in high doses and with gemfibrozil.[232,233]

Atorvastatin has shown a similar safety profile to currently available HMG-CoA reductase inhibitors and to placebo (section 5). Adverse events have been mild and transient and rarely necessitated drug withdrawal. Mild elevations in hepatic transaminase levels have occurred infrequently. As with other HMG-CoA reductase inhibitors currently on the market there have been rare instances of rhabdomyolysis during atorvastatin therapy. These, however, have mostly occurred during concomitant use of the drug with agents such as fibrates which increase the risk of rhabdomyolysis (section 5.3.2); such combinations should be avoided.

Table XIII. Ongoing randomised clinical trials of atorvastatin (ATO)

Acronym	Full title	No. and type of patients	Comparator	Duration (y)	Primary clinical end-point
Clinical end-point studies					
ALLIANCE[218]	Aggressive Lipid Lowering Initiation Abates New Cardiac Events study	2443 with history of CHD	Usual lipid-lowering care	4	Rate of major cardiovascular events (cardiac death, revascularisation, nonfatal MI, unstable angina requiring hospitalisation, resuscitated cardiac arrest)
ASCOT[219]	Anglo-Scandinavian Cardiac Outcomes Trial	9000 with hypertension	Placebo (+ AHT)	5	Rate of nonfatal MI and fatal CHD
ASPEN[220]	Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in NIDDM	2421 with type 2 DM with or without MI	Placebo	4-8	Time to occurrence of a cardiovascular event (cardiovascular-related death, nonfatal MI, recanalisation, CABG, nonfatal stroke)
CARDS[221]	Collaborative Atorvastatin Diabetes Study	2750 type 2 DM; no MI or CHD	Placebo	4	Time to occurrence of a cardiovascular event (cardiovascular-related death, nonfatal MI, recanalisation, CABG, nonfatal stroke)
DDDD; 4D[222]	Determination of Cardiovascular Endpoints in NIDDM Dialysis Patients study	1200 type 2 DM with dialysis for <2y	Placebo	2.5	Incidence of cardiovascular mortality (fatal MI, sudden death, death during coronary intervention, death from heart failure; death from other coronary causes)
IDEAL[223]	Incremental Decrease in Endpoints Through Aggressive Lipid Lowering trial	8600 with CHD	Simvastatin	5.5	Incidence of a major coronary event (CHD death or nonfatal MI)
SPARCL[224]	Stroke Prevention by Aggressive Reduction of Cholesterol Levels study	4200 with TIA or stroke	Placebo	5	Time to occurrence of fatal or nonfatal stroke
TNT[225]	Treating to New Targets study	10 000 with clinically evident CHD	ATO 10 *vs* 80 mg/day	5	Incidence of a major coronary event (CHD death or nonfatal MI)
Regression/surrogate end-point studies					
BELLES[226]	Beyond Endorsed Lipid Lowering with EBCT Scanning trial	600 PM women	Pravastatin	1	Percent change from baseline in total coronary calcium volume score
REVERSAL[227]	None	600 with CHD presenting for coronary angiography or intervention	Pravastatin	1.5	Change in total plaque volume for all slices of anatomically comparable segments of the target coronary artery, using intravascular ultrasound
SAGE[221]	Study Assessing Goals in the Elderly	1500 elderly with CHD	Pravastatin	1	Percent change in the total duration of myocardial ischaemic events
TREADMILL[a][228]	TREatment of peripheral Arterial Disease with Moderate or Intensive Lipid Lowering	351 with intermittent claudication	ATO 10 *vs* 80 mg/day *vs* placebo	1	Change from baseline in absolute claudication distance

a Formerly PVD (Peripheral Vascular Disease study).

AHT = antihypertensive; **CABG** = coronary artery bypass graft; **CHD** = coronary heart disease; **DM** = diabetes mellitus; **EBCT** = electron beam tomography scanning; **MI** = myocardial infarction; **NIDDM** = type 2 (non-insulin dependent) diabetes mellitus; **PM** = postmenopausal; **TIA** = transient ischaemic attacks.

Given the similarity in safety profiles, the choice of an HMG-CoA reductase inhibitor may thus depend upon such factors as the cost of therapy and the likelihood of achieving target LDL-cholesterol levels in each individual situation.

A number of pharmacoeconomic studies have evaluated lipid-lowering treatment interventions including HMG-CoA reductase inhibitors. In general, results showed a wide range of cost-effectiveness ratios (cost per YLS) depending on specific risk factors and treatment. For example, HMG-CoA reductase inhibitors appear to be very cost effective when used for secondary prevention in patients with established CHD, but their cost effectiveness in primary prevention of CHD has varied in different studies. Atorvastatin was cost effective (<$US40 000/YLS) for primary prevention in all categories of males except those in the 45-year age group with moderate elevations of LDL-cholesterol and no additional risk factors. Among women, a similar cost effectiveness was found only in those with at least three risk factors for CHD. Atorvastatin was the most cost-effective HMG-CoA reductase inhibitor in terms of cost per YLS in studies using a Markov model comparing the drug with simvastatin, fluvastatin, lovastatin and pravastatin[193] in all categories of patients and with all available HMG-CoA reductase inhibitors in elderly patients with CHD.[194] The cost of achieving LDL-cholesterol target levels was also lowest with atorvastatin compared with simvastatin, fluvastatin, lovastatin and pravastatin in the overall patient population and among those at high risk for CHD. Among patients at low or moderate risk for CHD, the cost of achieving the target levels was lowest with atorvastatin in one study and with fluvastatin in another (section 6.2). The ongoing ALLIANCE study (table XIII) includes a prospective economic analysis comparing resource utilisation with atorvastatin versus usual lipid-lowering treatment.[221]

In patients with mild hypercholesterolaemia without significant risk factors for CHD, the low percent reduction in LDL-cholesterol required to reach target levels is likely to be achieved by monotherapy with any of the HMG-CoA reductase inhibitors, including atorvastatin. Additionally, in patients at high risk for CHD, atorvastatin is also a good option as, apart from improved cost effectiveness, it is more likely to succeed as monotherapy than the other currently available HMG-CoA reductase inhibitors in achieving the lower target LDL-cholesterol levels recommended for these patients.

The higher efficacy of atorvastatin compared with most other HMG-CoA reductase inhibitors in reducing triglyceride levels makes it an effective drug for patients with mixed hyperlipidaemia (section 4.2). In patients with isolated hypertriglyceridaemia where reduction in LDL-cholesterol levels is not the primary concern, nicotinic acid or a fibrate are appropriate initial choices because of their greater efficacy in lowering triglyceride levels.[131-133] However, as the adverse effects of these agents often lead to poor compliance, atorvastatin may be considered a good alternative.

The safety and efficacy of atorvastatin in lowering lipid levels, and evidence from pharmacodynamic studies of favourable effects of the drug on atheromatous plaques and endothelial function (section 2.2), have prompted studies evaluating aggressive lowering of lipids with atorvastatin to well below the recommended targets in patients with CHD.

Results of the AVERT study (section 4.5.3) showed that aggressive lipid lowering with atorvastatin in patients with stable angina resulted in a 36% lower incidence of ischaemic events than in those receiving percutaneous transluminal coronary angioplasty (PTCA) and usual care. This difference did not reach the designated significance level of $p = 0.045$ adjusted from $p = 0.05$ by interim analyses. However, the study showed a significantly longer time to first ischaemic event ($p = 0.03$). There was a reduction in LDL-cholesterol levels to 2 mmol/L, well below the target levels advocated by the US and European guidelines, without any significant increase in the incidence of adverse events.

The authors concluded that aggressive lipid lowering with an HMG-CoA reductase inhibitor is

at least as effective as PTCA/usual care in decreasing the number of ischaemic events in stable patients with 1- or 2-vessel CHD. This has been contested in the literature by others who have pointed out certain shortcomings of the study.[234-236] Studies aimed at evaluating the additional benefit of aggressive lowering of LDL-cholesterol in patients receiving angioplasty or coronary bypass grafts for more severe CHD, and conversely, additional benefit of these invasive procedures in patients who have achieved very low LDL-cholesterol levels, are required to settle some of the issues raised in this debate.

Most studies evaluating the role of lipid-lowering therapy in patients with CHD excluded patients with recent cardiac events. These studies have established the role of lipid-lowering therapy in prevention of subsequent cardiac events and death. However, the incidence of serious complications including death, myocardial infarction and progressively recurrent unstable angina requiring intervention is highest in the first month after a cardiac event.

Early aggressive lipid-lowering therapy was evaluated in the MIRACL trial (section 4.5.3), where the use of high-dose atorvastatin (80mg daily) started within 96 hours of an episode of unstable angina or non-Q wave myocardial infarction resulted in a significant reduction in the incidence of events in the combined primary end-point and in the secondary end-point of recurrent symptomatic ischaemia requiring hospitalisation. However, there was no reduction in the incidence of other secondary end-point events including death, resuscitated cardiac arrest and myocardial infarction. Moreover, atorvastatin did not affect the incidence of early coronary events occurring in the first 5 weeks after the initial event, which constituted 70% of the total coronary events documented during the 16-week trial.

In most long-term trials evaluating the effect of lipid lowering on CHD, clinical benefits have been proportional to the decrement in LDL-cholesterol achieved, although the incremental benefit is less at lower levels. It has been possible to achieve very low levels of LDL-cholesterol with atorvastatin without any increase in adverse events. However, whether achieving lower levels than those recommended results in greater reductions in CHD remains an unanswered question. *Post hoc* analyses of major studies such as WOSCOPS, CARE and 4S have given conflicting results.[237-239]

Numerous long-term atorvastatin studies addressing these and other issues are in progress (table XIII). The TNT study is evaluating the effects of LDL-cholesterol lowering to ≤1.9 mmol/L (75 mg/dl) with atorvastatin in patients with history of myocardial infarction.[225] The ALLIANCE trial will compare the incidence of major cardiac events in patients with CHD receiving atorvastatin up to 80 mg/day to achieve target LDL-cholesterol levels of ≤2.0 mmol/L (80 mg/dl), or 'usual' therapy.[218] Another randomised study, the IDEAL trial, is designed to answer whether greater percentage reductions in LDL-cholesterol levels achieved by atorvastatin 80 mg/day than with 'usual therapy' with simvastatin 20 to 40 mg/day will demonstrate additional clinical benefit in patients with CHD.[223] As well, the BELLES trial will compare atorvastatin 80 mg/day with pravastatin 40 mg/day in 600 postmenopausal women to assess the presence of asymptomatic CHD; the primary end-point is the percent change from baseline in total calcium volume scores in the coronary artery tree, as measured by electron beam tomography (EBT).[226] Results of the above studies are likely to help decide whether the guidelines on target LDL-cholesterol levels need to be revised to lower values.

In patients with type 2 diabetes mellitus, lowering of lipid concentrations with HMG-CoA reductase inhibitors has been shown to reduce cardiovascular morbidity and mortality.[202,212] Patients with diabetes mellitus without CHD, too, have now been included in the high-risk group for CHD in the recent NCEP guidelines for lipid lowering.[105] The use of HMG-CoA reductase inhibitors may be considered first-line therapy in patients with diabetic dyslipidaemia, especially in those with ele-

vated levels of non-HDL-cholesterol and modestly elevated triglycerides.[240]

Atorvastatin is equally efficacious in patients with and without diabetes mellitus (section 4.3), and its triglyceride lowering ability makes it a good choice for lipid lowering in patients with type 2 diabetes mellitus. Patients with markedly elevated levels of triglycerides or chylomicronaemia, however, are not candidates for first-line treatment with HMG-CoA reductase inhibitors.[240]

Chronic renal disease, with or without diabetes mellitus, carries a greater risk of cardiovascular disease than is seen in the general population; among patients undergoing haemodialysis or chronic ambulatory peritoneal dialysis the prevalence of CHD is about 40%.[175] HMG-CoA reductase inhibitors are first-line treatment in these high-risk patients.[173] Available data are limited at present, but preliminary results demonstrate significant and consistent reductions in total and LDL-cholesterol levels in patients undergoing dialysis who receive atorvastatin (section 4.5.6). Several long-term studies – ASPEN,[220] CARDS[221] and 4D[222] – are investigating the effect of atorvastatin on coronary events, including death, in patients with type 2 diabetes mellitus; patients in the ASPEN trial are receiving dialysis.[220]

As well, several trials currently under way are to examine the efficacy of atorvastatin on clinical end-points in patients with hypertension (ASCOT[219]) and stroke (SPARCL[224]), and its effects on surrogate end-points in patients with intermittent claudication (TREADMILL[228]), the elderly (SAGE[221]) and patients undergoing coronary angiography or intervention (REVERSAL[227]) [table XIII].

In patients with organ transplants, hyperlipidaemia is an important factor contributing to increased morbidity and mortality from CHD. Early start of therapy within the first year of transplant has been shown to reduce the incidence of CHD in these patients.[241] There has been concern about increased incidence of muscle-related adverse events and altered cyclosporin concentrations because of interaction between cyclosporin and HMG-CoA reductase inhibitors. Although pravastatin, because of its different metabolic pathway, may be considered to be the first-line drug in these patients,[242] in a few small trials low dose atorvastatin has been found to be well tolerated and has been shown to improve lipid profiles in patients not responding to other lipid-lowering therapy (section 4.5.4).

Patients with familial hypercholesterolaemia are difficult to treat and cholesterol levels often remain uncontrolled despite the use of combinations of lipid-lowering agents in maximum tolerable doses. Monotherapy with atorvastatin in doses up to 80 mg/day has been found to be at least as efficacious as combinations of other HMG-CoA reductase inhibitors and fibrates or resin-uptake inhibitors and more effective than simvastatin 40 mg/day monotherapy in one trial (section 4.4). In patients with refractory hypercholesterolaemia, replacement of previous unsuccessful therapy with atorvastatin monotherapy produces further improvements in LDL-cholesterol levels (section 4.5.1).[156,157]

Patients receiving protease inhibitors for HIV disease are prone to hyperlipidaemia consisting of elevated levels of triglycerides and LDL-cholesterol and a reduction in HDL-cholesterol levels. The long-term clinical significance of these abnormalities and the benefit of achieving NCEP targets in these patients have not yet been defined. There has been only limited experience with the use of low dose atorvastatin or gemfibrozil, alone or in combination, in these patients (section 4.5.5).

In conclusion, atorvastatin is an HMG-CoA reductase inhibitor with a safety profile similar to, and lipid-lowering efficacy higher than, other members of its class, and thus is a first-line therapy in low- to high-risk patients requiring lipid-lowering drugs. In addition to this broad role, atorvastatin has a definite place in the management of hypercholesterolaemia in patients at high risk for CHD, in patients with familial hypercholesterolaemia, diabetes mellitus and in those with very high LDL-cholesterol levels where a large percentage reduction in LDL-cholesterol levels is required. As well,

the drug is a valuable option as monotherapy in patients who are refractory to, or who are intolerant of, combination therapy with other drugs. The ability of atorvastatin to achieve levels of LDL-cholesterol well below the currently recommended targets is likely to be utilised if the long-term trials currently under way show additional benefits of very low LDL-cholesterol levels on CHD morbidity and mortality.

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