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Benefits and Risks of Simvastatin in Patients with Familial Hypercholesterolaemia

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Abstract

Familial hypercholesterolaemia is a frequent, inherited, monogenic disorder, associated with accelerated development of atherosclerotic disease leading to coronary artery disease. Life expectancy of patients with familial hypercholesterolaemia is reduced by 15–30 years unless they are adequately treated with lipid-lowering therapy. Given the chronic nature of this disease, the selection of a therapeutic approach should be strongly based on its long-term safety and tolerability. The introduction of HMG-CoA reductase inhibitors has revolutionised the treatment of familial hypercholesterolaemia.

Simvastatin 40–80 mg/day effectively reduces serum low density lipoprotein (LDL)-cholesterol levels. Furthermore, simvastatin reduces triglycerides and mildly raises high density lipoprotein-cholesterol levels. In addition to the hypolipidaemic effect, other potentially important effects, such as improvement of

endothelial function and reduction of LDL oxidation and vascular inflammation, have been associated with HMG-CoA reductase inhibitor therapy. Simvastatin has also been shown to abolish the progression, and even facilitate the regression, of existing human atherosclerotic lesions.

The good safety and tolerability profile of simvastatin is clearly highlighted by the low rate of therapy discontinuation observed in several population-based clinical trials. The most common adverse events leading to the discontinuation of therapy are gastrointestinal upset and headache. Asymptomatic elevations in liver transaminase levels and myopathy are uncommon.

The overwhelming clinical evidence regarding the long-term use of HMG-CoA reductase inhibitor therapy in patients with familial hypercholesterolaemia together with the long-term safety data (particularly relating to simvastatin) provide support for the use of this drug as a first-line agent when pharmacological treatment is indicated. Early intervention with simvastatin treatment can be successfully implemented with favourable economic benefits.

1. Current Management of Familial Hypercholesterolaemia

Familial hypercholesterolaemia is an autosomal dominant disorder of cholesterol metabolism caused by mutations in the low density lipoprotein (LDL) receptor gene.[1] To date, more than 650 unique mutations have been described.[2] These mutations lead to a reduced number of functional LDL receptors in the liver, resulting in insufficient removal of LDL particles from the bloodstream, and a 2- to 3-fold elevation in plasma LDL-cholesterol (LDL-C) levels. Familial hypercholesterolaemia affects approximately 1 in 500 persons in the general population, with a few ethnic groups being more frequently affected.[3]

Familial hypercholesterolaemia is clinically characterised by the presence of tendon xanthomas or arcus corneae. In most patients there is also an excessive deposition of cholesterol in arterial walls, leading to accelerated atherosclerosis and premature coronary artery disease.[1] If left untreated, 75% of male patients with familial hypercholesterolaemia will experience a cardiovascular event before 60 years of age.[4-6] The mean age of onset of coronary artery disease in familial hypercholesterolaemia patients is between 40 and 45 years in men and 10 years later in women.[7-9]

To date, four other monogenic disorders that resemble familial hypercholesterolaemia, which are characterised by high LDL-C levels and premature atherosclerotic heart disease, have been described, including: (i) familial defective apolipoprotein (apo) B100 (FDB);[10-12] (ii) sitosterolaemia;[13] (iii) autosomal recessive hypercholesterolaemia;[14,15] and (iv) hypercholesterolaemia due to mutations in 7α-hydroxylase.[16] FDB is caused by point mutations in the apo B gene resulting in a reduced ability of the protein to bind to LDL receptors.[10] FDB is common only in central European countries.[11,12] Although patients with FDB usually have lower LDL-C levels than those with familial hypercholesterolaemia, these disorders are difficult to differentiate based upon clinical presentation.

The increased levels of LDL-C in familial hypercholesterolaemia are associated with endothelial dysfunction and functional alteration of blood and vascular cells, leading to accelerated atherosclerosis.[17,18] All of these phenomena contribute to the very high frequency of premature cardiovascular disease observed in these patients. Aggressive pharmacological lipid-lowering and LDL-apheresis approaches in these patients have been associated with a significant slowing of progression, and even promote regression, of coronary atherosclerotic lesions.[19,20] These interventions also resulted in significant normalisation of endothelial dysfunction

and reduction in the circulating levels of several inflammatory and adhesive proteins.[18,21,22] Evidence supporting the benefits of lower LDL-C levels in these patients has been provided by angiography-based studies in which LDL-C reduction was shown to be the best individual predictor for the angiographically detected changes in atherosclerotic lesions in familial hypercholesterolaemia patients.[19]

At present, four classes of drugs are available for the treatment of familial hypercholesterolaemia patients, which include HMG-CoA reductase inhibitors, bile acid-binding agents (resins), nicotinic acid derivatives and fibric acid derivatives. Therapy with HMG-CoA reductase inhibitors, nicotinic acid derivatives and bile acid-binding agents should always be initiated following a dose titration regimen.

Few patients with familial hypercholesterolaemia achieve satisfactory LDL-C reductions using nicotinic acid derivatives, bile acid-binding agents or fibric acid derivatives as monotherapy,[23] and a combination of two or more of these agents is usually required to achieve the therapeutic goal. The selection of the appropriate therapeutic intervention should take into account the patient's age, sex, family history of cardiovascular disease, and the presence of other cardiovascular risk factors. Lipid-lowering intervention should be initiated as soon as the disorder is detected. The earlier the initiation of preventive measures, the higher the likelihood of success. The International Make Early Diagnosis to Prevent Early Death (MedPed) Program recommended that the therapeutic goal of LDL-C levels should be <4.1 mmol/L in familial hypercholesterolaemia patients with fewer than two cardiovascular risk factors.[24] However, these patients have high LDL-C levels from an early age, and most of them have subclinical atherosclerosis, as well as more than two cardiovascular risk factors. Therefore, the objective of primary prevention must be to achieve an LDL-C level below 3.4 mmol/L, and below 2.5 mmol/L in secondary prevention.[25]

The most commonly used combination is an HMG-CoA reductase inhibitor and a bile acid-binding agent. This combination could reduce LDL-C levels by up to 54–64%.[23] Usually, high doses of HMG-CoA reductase inhibitors, or combined treatment, are required to significantly reduce LDL-C levels and to achieve the therapeutic goal in LDL-C levels.[26] Some patients even require triple drug therapy with a bile acid-binding agent, an HMG-CoA reductase inhibitor and one of either a nicotinic acid derivative or a fibric acid derivative; but this regimen is associated with a higher risk of adverse effects, therefore, the safety of such a combination should be closely monitored.[24,27]

The introduction of this class of drugs has seen a radical improvement in the management of familial hypercholesterolaemia patients. With the exception of cerivastatin, HMG-CoA reductase inhibitors generally have good safety profiles and are potent LDL-C-lowering agents. Several large clinical trials involving HMG-CoA reductase inhibitors (including both primary and secondary prevention trials in a wide range of patients with hypercholesterolaemia, and more recently in patients with normal lipid levels) have provided conclusive evidence of the beneficial effects of lowering LDL-C levels on cardiovascular morbidity and mortality.[28-33] Overall, HMG-CoA reductase inhibitor therapy is associated with a 24–32% reduction of cardiac events.[28-33] However, there are very few published studies assessing the efficacy of HMG-CoA reductase inhibitors in the treatment of patients with familial hypercholesterolaemia, because these patients have been routinely excluded from the major HMG-CoA reductase inhibitor trials. In this sense, the Broome Registry is one of the few studies that has shown an improvement in the prognosis of familial hypercholesterolaemia patients treated with HMG-CoA reductase inhibitors.[34]

In general, all HMG-CoA reductase inhibitors produce dose-dependent reductions in total cholesterol (TC), LDL-C and triglyceride levels, and thus they should definitely be considered as the first-line therapy in patients with familial hypercholesterolaemia. Also, there is a variable effect on high density lipoprotein-cholesterol (HDL-C) levels, depending on the specific HMG-CoA reductase inhibitor and the baseline levels of HDL-C. In addition to their LDL-C-lowering effects, HMG-CoA reductase

inhibitors have other pharmacological properties that may have contributed to the reduction in total mortality and cardiovascular disease seen in clinical trials.[35]

Of the HMG-CoA reductase inhibitors available, simvastatin is the most widely used in the treatment of primary hypercholesterolaemia, including familial hypercholesterolaemia,[28,33,36-39] and is clearly an effective agent for lowering LDL-C levels in patients with familial hypercholesterolaemia. Simvastatin is derived synthetically from a fermentation product of *Aspergillus terreus*. It is given as an inactive lactone, and after oral ingestion is rapidly hydrolysed to the corresponding 3β-hydroxyacid form, the active inhibitor. The pharmacodynamic and pharmacokinetic properties of simvastatin have been reviewed in detail previously.[40,41]

Extensive clinical use and evaluation in controlled studies in patients with primary hypercholesterolaemia and familial hypercholesterolaemia, including long-term trials, have confirmed that simvastatin is well tolerated and the frequency of adverse events such as increases in transaminase and creatine phosphokinase levels is very low.[28,32,33,36-38] In the past 9 years, there have been about 24 million prescriptions for simvastatin in the UK, and the frequency of musculoskeletal adverse events and the rate of rhabdomyolysis were very low (0.004% and 0.0002% of total prescriptions, respectively), similar to those with atorvastatin.[39]

To date, there is no published review of the beneficial effects of simvastatin therapy in familial hypercholesterolaemia patients. The aim of this review is to describe the usefulness of simvastatin according to the available evidence of its safety, tolerability and efficacy in the treatment of familial hypercholesterolaemia.

2. Pharmacological Properties of Simvastatin

After an oral dose, approximately 60–85% of simvastatin is absorbed and undergoes extensive first-pass extraction in the liver, its primary site of action.[41,42] Age and sex do not affect the time required to achieve the peak plasma concentration of simvastatin, but the mean steady-state plasma concentration is higher in older than in younger individuals, and in women than in men (table I).[43] However, the effects of age and sex on the pharmacokinetic profile of simvastatin are not enough to necessitate dosage modifications.

Simvastatin is metabolised by cytochrome P450 (CYP) 3A4, but it is not an inhibitor of this isoform. Therefore, it is not expected to affect the plasma levels of other drugs metabolised by CYP3A4.[48] However, other drugs can affect the metabolism of simvastatin and increase the risk of adverse effects such as myopathy (table II). Because of the high hepatic extraction ratio of simvastatin and the low plasma levels, inhibition of CYP3A4 can produce a substantial increase in plasma concentration of the parent lactone and its active metabolite.

3. General Cardiovascular Benefits of Simvastatin

Two studies, the Scandinavian Simvastatin Survival Study (4S) and the Heart Protection Study

Table I. Pharmacological properties of simvastatin

Pharmacokinetic parameters in the general population[40-42]	
Elimination half-life (h)	1.9
Renal excretion (% oral dose)	13
Hepatic metabolism (cytochrome P450 3A4)	Yes
Bioavailability (after oral dose, relative to that after intravenous dose) [%]	<5
Effect of age on steady-state plasma concentrations[a]	40–60% higher in elderly
Effect of sex on steady-state plasma concentrations[a]	20–50% higher in women
Effect of food on absorption	None
Effect on serum lipid levels in patients with familial hypercholesterolaemia[36,38,44-47][b]	
Total cholesterol (%)	↓33–40
LDL-C (%)	↓41–50
HDL-C (%)	↑11–25
Triglycerides (%)	↓18–31

a Not enough to necessitate dose modifications. Simvastatin has a broad therapeutic window.

b In general, high doses of simvastatin were used (40–80 mg/day).

HDL-C = high density lipoprotein-cholesterol; **LDL-C** = low density lipoprotein-cholesterol; ↓ indicates a reduction; ↑ indicates an increase.

Table II. Drugs that are metabolised by or inhibit cytochrome P450 3A4 and may possibly interact with HMG-CoA inhibitors[a]

Antibacterial/antifungal agents	Clarithromycin, clotrimazole, erythromycin, fluconazole, ketoconazole, miconazole, norfloxacin
Cardiovascular agents	Amiodarone, amlodipine, felodipine, diltiazem, isradipine, nifedipine, quinidine, verapamil
CNS agents	Alprazolam, carbamazepine, fluoxetine, nefazodone, phenytoin, sertraline, triazolam
Others	Astemizole, cimetidine, cisapride, cyclosporin, grapefruit juice, HIV protease inhibitors, omeprazole, paracetamol (acetaminophen), terfenadine, tacrolimus

a Not an exhaustive list; not all have been documented to have clinically significant relevance.

(HPS), have evaluated the effect of simvastatin in the reduction of mortality and cardiovascular morbidity in different populations. In the 4S trial,[28] the effect of the reduction of LDL-C levels with simvastatin (20–40 mg/day) on total mortality was assessed in 4444 patients with coronary heart disease (CHD). Patients had baseline TC levels of 5.5-8.0 mmol/L (212–309 mg/dL). Patients were followed on average for 5.4 years. In this multicentre, randomised, double-blind, placebo-controlled study, simvastatin significantly reduced the risk of total mortality by 30%, CHD mortality by 42%, and major CHD events by 34%; the risk for undergoing myocardial revascularisation procedures (coronary artery bypass grafting or percutaneous transluminal coronary angioplasty) was reduced by 37%. These risk reductions were independent of baseline TC and LDL-C levels. An 8-year follow-up of the 4S study has confirmed that the reduction in the relative risk of total mortality in patients treated with simvastatin remained at 30%.[49]

The cardiovascular benefits of long-term therapy with simvastatin were also well established in the HPS.[33] In this trial, 20 536 adults (aged 40–80 years) with a high risk for developing cardiovascular disease (e.g. presence of coronary artery disease, other occlusive arterial disease or diabetes) were randomly allocated to receive simvastatin 40 mg/day or placebo for 5 years. The results demonstrated that lowering LDL-C levels with simvastatin in these very high-risk patients produced a substantial 24% reduction in the incidence of major cardiovascular events (coronary events, stroke and coronary revascularisation). These effects were independent of baseline cholesterol levels. The adverse event rates were similar in placebo and simvastatin groups, including that of myotoxicity (<0.1%) and elevation of liver enzymes (0.8%).

4. Efficacy of Simvastatin in Familial Hypercholesterolaemia

4.1 Homozygous Familial Hypercholesterolaemia

Patients with homozygous familial hypercholesterolaemia, with both LDL receptor alleles being abnormal, respond poorly to conventional doses of HMG-CoA reductase inhibitor therapy, because they produce only a small quantity of functional receptors, or no receptors at all. In a placebo-controlled, randomised, double-blind clinical study lasting 18 weeks,[50] 12 patients (aged 15–39 years) with homozygous familial hypercholesterolaemia received simvastatin 80–160 mg/day. Almost all patients (11 of 12) had reductions in LDL-C levels (25% with 80mg), and the magnitude of response was not predicted by the LDL receptor gene defect. Although LDL-C levels were not reduced to therapeutic goals (they remained approximately 10.1 mmol/L with the highest dose), the reduction obtained, if maintained, could reduce the risk for atherosclerosis. No serious clinical or biochemical adverse events occurred during the study. Treatment with high doses of HMG-CoA reductase inhibitors in homozygous familial hypercholesterolaemia patients is complementary to apheresis treatment. However, simvastatin 160 mg/day is not an approved dose of this drug.

Another study[51] compared the efficacy of tocopherol (vitamin E) with high doses of HMG-CoA reductase inhibitors (simvastatin 80–160 mg/day and atorvastatin 80 mg/day) in 15 patients with homozygous familial hypercholesterolaemia. Patients received 1000 mg/day of tocopherol acetate for 2 years. The rate of progression of carotid intima-media thickness was substantially faster in these

patients than in normal controls (0.19 vs 0.005 mm/year). After treatment with tocopherol, patients received high doses of simvastatin or atorvastatin for a further 2 years. The reduction in LDL-C (mean of 28%) with HMG-CoA reductase inhibitors was accompanied by regression and no further progression in carotid intima-media thickness in nearly all patients.

4.2 Heterozygous Familial Hypercholesterolaemia

The effects of a broad range of simvastatin doses have been evaluated in several short- and long-term studies in familial hypercholesterolaemia patients. These studies have shown that simvastatin was highly effective in reducing TC and LDL-C levels. A marked hypolipidaemic effect is seen within 2 weeks of starting treatment, and the maximum therapeutic response takes place within 4–6 weeks after the initiation of HMG-CoA reductase inhibitor therapy. The response is maintained during long-term therapy.

4.2.1 Short-Term Effects on Lipid Levels

In 1986, Mol et al.[44] evaluated the effect of simvastatin 2.5–80 mg/day in patients with familial hypercholesterolaemia after 4 weeks' treatment. LDL-C levels were reduced by 18% with the lowest dose of simvastatin and by 42% with the highest dose. Two years later, the results after 24 weeks of therapy were reported.[45] In this extension study, 38 of 43 patients completed the trial. The simvastatin dose was titrated from 10mg twice daily up to 20mg twice daily. Ten patients were kept on this dose during the study, and 28 received a single dose of 40mg daily. A mean decrease in LDL-C of 45.3% was found with an oral dose of 40mg once daily. Overall, mean HDL-C levels had increased by 10–14%, LDL-C : HDL-C ratio had decreased by 50%, and triglycerides had decreased by 31%. Adverse events were infrequent and limited to a slight increase of alanine aminotransferase.

In another study, Hagemenas et al.[46] analysed the effects of different doses of simvastatin on parameters of cholesterol homeostasis in 24 familial hypercholesterolaemia patients. Plasma LDL-C levels were decreased by 36.6%, 45.6% and 47.1% with 20, 40 and 80mg, respectively. Compared with baseline, all doses significantly raised HDL-C (by approximately 14.5–25.4%) and reduced triglyceride (by approximately 28%) levels.

4.2.2 Long-Term Effects on Lipid Levels

Following the promising results obtained from short-term studies mentioned in section 4.2.1, the long-term safety and efficacy of HMG-CoA reductase inhibitor administration in familial hypercholesterolaemia patients were investigated. The first long-term study[36] assessed the use of simvastatin 20–80 mg/day for 6 years, either alone or in combination with other lipid-lowering agents. After 6 years, LDL-C levels were reduced by 44.6% with simvastatin monotherapy and 50.3% with simvastatin combined with another lipid-lowering agent. Furthermore, HDL-C levels were increased by up to 16% with both simvastatin alone and simvastatin combination therapy. The rate of discontinuation of therapy was low.

Recently, the efficacy and safety of simvastatin 80mg after 2 years was investigated in a Dutch cohort of patients with familial hypercholesterolaemia.[38] After 2 years of treatment, TC levels were reduced by 39.2%, LDL-C levels were reduced by 48% and triglyceride levels were reduced by 26.1%. HDL-C levels were increased by 12.7%. The reduction in LDL-C levels was sustained at different points and no tachyphylaxis to simvastatin was observed. A very interesting observation was that patients with the worst lipoprotein profile were the ones with the greatest benefit from high doses of simvastatin.[47]

4.2.3 Comparison of Simvastatin with Other HMG-CoA Reductase Inhibitors on Lipid Levels

Many patients do not reach an LDL-C level below 4.1 mmol/L with current therapies. It is well known that the majority of familial hypercholesterolaemia patients require high doses of HMG-CoA reductase inhibitor or combination therapy. Previous noncomparative studies in patients with familial hypercholesterolaemia treated with lovastatin, simvastatin and pravastatin have indicated that all three drugs reduce plasma LDL-C levels in a non-

Table III. Summary of comparative effects of simvastatin and other HMG-CoA reductase inhibitors on lipid profiles in patients with familial hypercholesterolaemia

Study	Study duration	No. of patients	Drug and dose	Mean change in lipid levels (%)			
			(mg/day)	TC	LDL-C	HDL-C	TG
Illingworth et al.[53]a	24 weeks each drug period	23	Simvastatin 20–80	↓22–34	↓29–43	↑12.8–17	↓14–23
			Lovastatin 20–80	↓17–27	↓23–35	↑12.8–15	↓9–22
Wierzbicki et al.[54]b	12 weeks	201 (111)c	Simvastatin 20	↓25	↓31	↑6	↓16.6
			Simvastatin 40	↓26	↓33	↑9	↓17
			Simvastatin + cholestyramine	↓30	↓36	0	↓22.8
			Simvastatin + cholestyramine + fibric acid derivative	↓31	↓39	↑16	↓24.8
			Atorvastatin 10	↓31	↓38	↑11	↓30
			Atorvastatin 20	↓31	↓38	↑8	↓29
			Atorvastatin 40	↓40	↓45	↑2	↓33.8
			Atorvastatin 80	↓40	↓45	↓11	↓37.3
Wierzbicki et al.[55]a	12 weeks	26	Simvastatin 80	↓40	↓47	↑8	↓22
			Atorvastatin 80	↓38	↓43	↓2	↓27
Smilde et al.[56]d	2 years	325	Simvastatin 40	↓33.6	↓41.2	↑13.8	↓17.7
			Atorvastatin 80	↓41.8	↓50.5	↑13.2	↓29.2

a Randomised, crossover study.

b Prospective observational study. In this study, patients stopped prior medication with simvastatin, and after a washout period, they received atorvastatin on a theoretically matched LDL reduction protocol.

c 201 had severe hypercholesterolaemia, of whom 111 had familial hypercholesterolaemia.

d Prospective, randomised, double-blind study.

HDL-C = high density lipoprotein-cholesterol; **LDL-C** = low density lipoprotein-cholesterol; **TC** = total cholesterol; **TG** = triglycerides; ↓ indicates a reduction; ↑ indicates an increase.

linear dose-dependent manner.[52] Few studies have compared different HMG-CoA reductase inhibitors in heterozygous familial hypercholesterolaemia patients. Table III presents a summary of the studies assessing the effects of simvastatin and other HMG-CoA reductase inhibitors on lipid profiles in patients with familial hypercholesterolaemia.

In a randomised, crossover study, 23 familial hypercholesterolaemia patients were to receive either lovastatin or simvastatin, each at doses of 10, 20 and 40mg twice daily.[53] Each dosage period lasted 8 weeks. This study confirmed that the effects of simvastatin 20 and 40 mg/day on LDL-C levels were comparable to lovastatin 40 and 80 mg/day.[53] The maximum hypolipidaemic effect, a 43% reduction in LDL-C levels, was achieved with simvastatin 80 mg/day. A significant increase in HDL-C (approximately 17% at 80 mg/day for both drugs) was also observed.

One of the few studies that has compared the effectiveness of simvastatin with atorvastatin in familial hypercholesterolaemia was a prospective observational study of 201 patients with severe hypercholesterolaemia, of whom 111 had familial hypercholesterolaemia.[54] Participants were recruited into four groups, including simvastatin (20–40 mg/day) monotherapy, atorvastatin (10–80 mg/day) monotherapy, simvastatin plus cholestyramine therapy, or simvastatin in combination with cholestyramine and a fibric acid derivative. The reduction in LDL-C levels ranged from 38% with atorvastatin 10mg to 45% with atorvastatin 80mg, compared with 31% with simvastatin 20 mg/day alone and 39% with simvastatin 40 mg/day plus cholestyramine and a fibric acid derivative.

The same group that conducted the observational study mentioned in the previous paragraph have also published a trial comparing the effect of atorvastatin 80 mg/day with that of simvastatin 40 mg/day plus fenofibrate 200mg or simvastatin 40mg plus cholestyramine in 54 patients.[57] The effect of the simvastatin and fenofibrate combination on LDL-C levels was similar to that obtained with atorvastatin 80mg monotherapy. The combination of simvastatin and cholestyramine reduced LDL-C levels by approximately 36%. The combination of simvastatin and fenofibrate increased HDL-C levels by 25% and was more effective at increasing HDL-C levels than atorvastatin (2.3%).

In another prospective, open-label, crossover study, 26 patients with familial hypercholesterolaemia were randomised to receive simvastatin 80mg or atorvastatin 80mg for 12 weeks.[55] The two regimens were equally effective at reducing TC, LDL-C and triglyceride levels. In this study, a high dose of simvastatin raised HDL-C levels more than atorvastatin (see table III), resulting in a more favourable LDL : HDL ratio.

4.2.4 Effects on Lipid Levels in Children and Adolescents

Some controversy exists regarding the use of HMG-CoA reductase inhibitors in children and adolescents with familial hypercholesterolaemia. The majority of studies using HMG-CoA reductase inhibitors in children and adolescents have not been randomised or controlled and have had inadequate size and short duration. In one randomised trial in which lovastatin was administered to adolescents, it was demonstrated that long-term HMG-CoA reductase inhibitor administration did not interfere with normal growth, pubertal development and hormonal status of the patients.[58] Recently, the US FDA has authorised treatment with lovastatin in males aged >10 years and females 1 year after the menarche, if with an adequate diet they can not achieve LDL-C below 190 mg/dL.[59]

The use of simvastatin has also been evaluated in children with familial hypercholesterolaemia. Stein[60] was the first to report the hypocholesterolaemic effect of simvastatin and lovastatin in children with familial hypercholesterolaemia. After that study, a long-term trial showed that LDL-C levels were reduced by a mean of 37% in children and adolescents using simvastatin for 24 months.[61] However, the sample size (n = 16) was small. The hypolipidaemic effect of simvastatin 10 mg/day compared with a low-cholesterol diet in 16 children aged 7–12 years who were followed for 1 year was reported by Stefanutti et al.[62] After 12 months of follow up, patients who received simvastatin showed a significant reduction in TC and LDL-C levels of 24% and 29%, respectively, and a nonsignificant increase in HDL-C levels of 7%. Recently, the largest randomised, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of simvastatin (40 mg/day) in 173 children and adolescents with familial hypercholesterolaemia aged between 10 and 17 years has been published.[63] After 48 weeks of simvastatin therapy, there was a significant reduction in LDL-C levels of 41%. Simvastatin therapy was well tolerated and there was no evidence of any effect on growth and pubertal development in girls or boys.[63]

4.2.5 Effects on Atherosclerosis

In adults with familial hypercholesterolaemia, lifelong treatment with lipid-lowering drugs is indicated, because these drugs reduce the progression of coronary atherosclerotic disease.[19,64] Simvastatin has been compared with LDL-apheresis[65] and with atorvastatin[56] in the progression and regression of atherosclerotic disease in familial hypercholesterolaemia patients. The LDL-Apheresis Atherosclerosis Regression Study (LAARS) was a prospective, open, randomised study in 42 men with severe primary hypercholesterolaemia (76% were familial hypercholesterolaemia patients) and extensive coronary artery disease.[65] The primary objective was to determine the anti-atherosclerotic effect of very aggressive lowering of LDL-C levels with LDL-apheresis plus simvastatin (40 mg/day) and more conventional treatment using simvastatin alone (40 mg/day) at 2 years' follow up.

In this report of the LAARS study,[65] apheresis plus simvastatin reduced TC and LDL-C levels by a mean of 53% and 63%, respectively, compared with

reductions observed with simvastatin monotherapy of 40% and 47%, respectively. Both treatment groups showed a similar reduction in triglycerides and increase in HDL-C levels. There were no differences in cardiovascular events between the two groups. After 2 years of treatment, a significant decrease of ST-segment depression after the exercise stress test was observed in those receiving apheresis plus simvastatin, whereas no changes were found in those treated with simvastatin alone. The LAARS study showed that aggressive lipid-lowering treatment improved the ischaemic threshold, but no improvements in the angiographic endpoints were observed by the addition of LDL-apheresis to the conventional simvastatin treatment.[65] The improvement in the exercise test and the angiographic findings suggests that mechanisms other than changes in atherosclerotic stenosis play a role in the outcome of the exercise test.

The angiographic results of the LAARS trial were in agreement with those described in the familial hypercholesterolaemia regression study.[20] The familial hypercholesterolaemia regression study was the first randomised study to compare LDL-apheresis and lipid-lowering treatment in familial hypercholesterolaemia. The main results were that LDL-apheresis plus simvastatin was slightly more effective than simvastatin plus colestipol in reducing LDL-C plasma levels, but the two treatments did not differ in their effect on plaque regression, as assessed by angiography.[20]

HMG-CoA reductase inhibitor therapy was associated with an improvement in endothelium-dependent relaxation in the coronary arteries of patients with coronary artery disease.[66] Similar improvements have been observed in the brachial arteries of familial hypercholesterolaemia patients with and without evidence of coronary artery disease.[21,67] The observed functional improvement of the vasomotor function of coronary arteries, suggesting normalisation of the dysfunctional endothelium, precedes the significant anatomic changes in severely stenotic coronary arteries. In a second report of the LAARS study[68] the effect of both therapies (LDL-apheresis plus simvastatin and simvastatin alone) on the progression of peripheral vascular disease was analysed. The results of this study showed that intensive reduction in LDL-C levels prevented an increased prevalence of haemodynamically significant stenosis in the aortotibial tract and reduced the intima-media thickness of the carotid artery.

Smilde et al.[69] recently evaluated the effect of simvastatin on carotid and femoral artery wall stiffness and thickness in familial hypercholesterolaemia patients. Patients received simvastatin or atorvastatin (40–80 mg/day) for 1 year, and the results suggested that a reduction of at least 45% in LDL-C levels was necessary in patients with familial hypercholesterolaemia to show an improvement in intima-media thickness of the common carotid artery and in the compliance and distensibility of common femoral artery. These effects were seen despite the fact that target goals in LDL-C levels were not achieved in the majority of patients.

Smilde et al.[56] have also recently conducted a randomised, double-blind trial, termed the Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) study, in 325 patients with familial hypercholesterolaemia. This study assessed the effects of atorvastatin 80 mg/day and simvastatin 40 mg/day on lipid profile and atherosclerosis progression, with the primary endpoint being changes in the carotid intima-media thickness. After 2 years of treatment, intima-media thickness had decreased in the atorvastatin group (−0.031mm) whereas it had increased in the simvastatin group (0.036mm). It is important to take into account that the selected dose of atorvastatin (80 mg/day) demonstrated a significantly higher hypolipidaemic effect than simvastatin 40 mg/day. The reduction in LDL-C levels was 50.5% with atorvastatin compared with 41.2% with simvastatin (see table III). Nevertheless, in the simvastatin group, regression of the carotid intima-media thickness was observed in 42% of patients. The suggested that a reduction of at least 45% in LDL-C levels is necessary to modify carotid intima-media thickness progression into regression.

4.2.6 Genetic Determinants of Simvastatin Response

Few studies have been designed to elucidate the genetic determinants that modulate the response to simvastatin in familial hypercholesterolaemia patients. Although controversial, most of the results suggest that the LDL receptor gene mutation is one of the most important determinants of responsiveness to simvastatin therapy. In a study by Sijbrands et al.,[70] familial hypercholesterolaemia patients with mRNA positive and negative for LDL receptor gene mutations were not different in their response to simvastatin.

In a retrospective study, Heath et al.[71] investigated the possible role of sex, presence or absence of xanthomata, apo E genotype and the type of LDL receptor gene mutations in the response to simvastatin treatment in 109 patients with definite or probable familial hypercholesterolaemia. All patients responded to simvastatin (10–40 mg/day) and 42% of patients achieved an LDL-C level under 4.1 mmol/L. With simvastatin 40 mg/day, LDL-C levels were reduced by 35% in patients with severe mutations, however, none of these patients achieved an LDL-C level of less than 4.1 mmol/L. On the other hand, simvastatin 40 mg/day reduced LDL-C levels by 49% in patients with mild mutations, and 45% of these patients achieved LDL-C levels of less than 4.1 mmol/L. No additional effect was observed in patients with severe mutations with simvastatin 20 or 40mg. In addition, sex or apo E genotype had no effect on the response to HMG-CoA reductase inhibitors. Despite the small number of patients with a detected mutation in this study, the results suggested that simvastatin had a greater effect on those with mild mutations, probably because of an upregulation of residual LDL receptor activity. Similar results have been found by Chaves et al.[72]

Recently, Vohl et al.[73] studied 47 adolescents with familial hypercholesterolaemia selected on the basis of the type of LDL receptor gene mutation. Among them, 33 were carriers of a receptor-negative mutation, whereas 14 were carriers of a receptor-defective mutation. Although most patients showed benefits with simvastatin (20 mg/day), the hypolipidaemic response was significantly lower in patients with the defective allele compared with those who were heterozygous for a receptor-negative mutation (31% vs 39%). The mean percentage decrease in LDL-C was significantly higher in patients carrying the E2 allele (50% for E3/E2) compared with those carrying E3 or E4 (38% for both E3/E3 and E3/E4) only in the receptor-negative group. These results were similar to those obtained in individuals without familial hypercholesterolaemia.[74]

The difference in LDL-C response between the various classes of LDL receptor gene mutations is not yet completely understood but several lines of evidence support the hypothesis that the upregulation of the wild-type LDL receptor allele would be greater in patients with familial hypercholesterolaemia who were carrying a receptor-negative mutation than in those patients who were heterozygous for a receptor-defective mutation.[75,76] Further studies are needed to elucidate these controversial results.

Several studies have addressed the effect of a genetic variation at the apo E locus and the variability in plasma lipoprotein responses to different HMG-CoA reductase inhibitors. The greater LDL-C-lowering effect with HMG-CoA reductase inhibitors associated with the E2 allele is controversial. Some authors have reported some correlation in familial hypercholesterolaemia and non-familial hypercholesterolaemia patients,[77-79] and others have shown an independent response to apo E polymorphism.[80]

4.2.7 Pleiotropic Effects of Simvastatin Related to Cardiovascular Benefit

The predominant benefits of HMG-CoA reductase inhibitors on CHD risk reduction are mainly due to their effects on LDL-C levels, but the effects of HMG-CoA reductase inhibitors on triglycerides and HDL-C levels may also contribute to the risk reduction. The analysis of some trials has also suggested that HMG-CoA reductase inhibitors have some additional effects that may be partly responsible for the reduction of risk. These effects, also known as pleiotropic effects, include improvement in endothelial function, stabilisation of atheroscle-

rotic plaque, reduction of oxidative stress and reduction of vascular inflammation (see table IV).[81,82] These beneficial actions occur rapidly and yield potentially important anti-ischaemic effects as early as 1 month after the beginning the therapy. The clinical significance of these pleiotropic effects is uncertain, and it remains to be determined which of these effects accounts for the clinical benefits of HMG-CoA reductase inhibitors in cardiovascular disease. While some of the effects have also been observed in familial hypercholesterolaemia patients treated with LDL-apheresis,[18,22] the effects related to simvastatin in familial hypercholesterolaemia patients will be described in this review.

The effect of long-term treatment with simvastatin on endothelial function has been evaluated in 25 patients with familial hypercholesterolaemia.[21] The dose of simvastatin was titrated from 40 to 80 mg/day to achieve the goal of a 30% reduction in serum LDL-C. After 1 year of treatment, the LDL-C levels were reduced by 43%, and this reduction was associated with a beneficial and sustained effect on endothelial function and decrease of soluble E-selectin plasma levels.[21] Similar results were obtained in a randomised study comparing atorvastatin (80 mg/day) and simvastatin (40 mg/day) plus cholestyramine in 32 patients with severe primary hypercholesterolaemia. Patients receiving simvastatin plus cholestyramine showed an improvement of 150% in flow mediated vasodilation, which was similar to that observed in the atorvastatin group.[67] Moreover, the impaired myocardial flow reserve, observed in familial hypercholesterolaemia patients without evidence of ischaemia, can be reversed by long-term therapy with moderate doses of simvastatin.[83]

Table IV. Additional effects of simvastatin that are probably related to cardiovascular benefits

Patients with familial hypercholesterolaemia[21,35,83-85]
Improves of endothelial function
Improves myocardial flow reserve
Reduces LDL oxidation
Increases paraoxonase activity
Reduces electronegative LDL particles
Reduces vascular inflammation
Patients without familial hypercholesterolaemia[81,82,86-90]
Atherosclerotic plaque stabilisation
Inhibits thrombus formation:
reduces platelet activity
reduces PAI-1 expression by vascular cells
Reduces vascular inflammation

LDL = low density lipoprotein; **PAI-1** = plasminogen activator inhibitor-1.

In addition to the cholesterol-lowering effects of simvastatin, it has antioxidant properties *in vivo* and *in vitro*, which could play an important role in preventing atherosclerosis.[86] In one study in familial hypercholesterolaemia patients, simvastatin (20 mg/day) significantly increased paraoxonase activity to values close to those seen in the normal population. The increased paraoxonase activity was associated with a reduction in lipid peroxide concentration. This effect was independent of the paraoxonase polymorphisms.[84]

Many oxidative modifications in LDL particles increase the negative charge of these particles, and they can be identified and isolated in the plasma of normal volunteers following intense exercise and glycation of LDL particles. There is a general consensus about the cytotoxicity of these particles on endothelial cells.[91] In a study designed to evaluate the effect of simvastatin (40 mg/day for 6 months) on the electronegative LDL proportion in familial hypercholesterolaemia patients,[85] the drug reduced the proportion of electronegative LDL particles by approximately 40% compared with baseline values, but the proportions remained higher than in the healthy control patients. However, the susceptibility of LDL to oxidation was not affected by simvastatin treatment. It is possible that some methodological aspects could explain the differences observed in other reports regarding this issue.

Other haemostatic and inflammatory variables have been measured in hypercholesterolaemic patients undergoing treatment with simvastatin including the suppression of monocyte tissue factor expression[87] and the reduction of the expression of interleukin (IL)-6, IL-8 and monocyte chemoattractant protein-1 mRNA in peripheral blood mononuclear cells and their levels in serum.[88] The addition of simvastatin to smooth muscle cells and endo-

thelial cells in culture reduced plasminogen activator inhibitor-1 released by both types of cells and increased tissue plasminogen activator released by endothelial cells.[89] In addition, a beneficial reduction of blood thrombogenicity has been reported in patients with hypercholesterolaemia after 3 months of therapy with simvastatin 20 mg/day or pravastatin 40 mg/day. In the same study, the normalisation of endothelium function was also observed.[90]

Finally, a study involving high-resolution magnetic resonance imaging has demonstrated that an effective and maintained lipid-lowering regimen using simvastatin will not only abolish the progression but will even induce the regression of previously existing human carotid and aortic atherosclerotic lesions.[92]

5. Tolerability and Safety of Simvastatin in Familial Hypercholesterolaemia

Familial hypercholesterolaemia is a chronic disorder requiring long-term therapy. Therefore, medication used in this disorder must be effective, safe and tolerable. The high doses of HMG-CoA reductase inhibitors commonly used in familial hypercholesterolaemia are usually well tolerated by most patients. Constipation, dyspepsia, diarrhoea and nausea are the most frequent adverse events associated with HMG-CoA reductase inhibitor therapy. In general, these symptoms are often mild and few patients discontinue therapy. Other adverse events described are headache, asthenia and sleep disturbances. However, less frequent but more serious adverse events associated with HMG-CoA reductase inhibitors are asymptomatic transaminase elevation and myopathy.

Short- and long-term clinical trials have clearly demonstrated that simvastatin is well tolerated, and few patients stopped medication because of adverse events. In the 4S trial (using conventional doses of simvastatin 20–40 mg/day)[28] the rate of discontinuation was 6% for both placebo and simvastatin groups. In the HPS trial[33] fewer than 0.5% of patients who received simvastatin 40 mg/day stopped therapy, and this was also the case in the placebo group. The frequency of discontinuation of medication was slightly higher in the Worldwide Simvastatin Expanded Dose Program (WSEDP) trial.[37] In this study, approximately 3.5% of patients receiving simvastatin 40 or 80 mg/day discontinued therapy because of a clinical adverse event. However, there were no discontinuations due to serious drug-related clinical adverse events. The incidence of drug-related clinical adverse events (18%) was similar in both groups, and fewer than 2% of patients in the 80 mg/day group had abnormal laboratory tests.

The rate of treatment discontinuation among familial hypercholesterolaemia patients was similar to that observed in non-familial hypercholesterolaemia patients. Only 2 out of 42 patients stopped taking medication because of adverse effects after 6 years of simvastatin (20–80 mg/day) treatment.[36] In the larger Express study, the percentage of patients discontinuing the study was 5.7%, and only five patients discontinued therapy because of laboratory adverse events.[38]

5.1 Elevation of Transaminase Levels

The elevation of hepatic transaminases during HMG-CoA reductase inhibitor therapy occurs in 0.5–2.0% of patients,[93] and it is not well known if this effect constitutes hepatotoxicity. Usually, the rise in transaminases is mild and returns to normal values when the dose is reduced or treatment stopped. In a large cohort of patients treated with simvastatin, fewer than 3.5% of patients developed mild and transitory elevations in serum transaminases, and about 1% showed a persistent elevation greater than three times the upper limit of the normal range (ULN).[94] In the WSEDP trial,[37] the incidence of elevation of transaminases greater than three times the ULN value was similar in both simvastatin groups (0.5% in the whole study population), and no patient developed symptomatic hepatic disease. All transaminase elevations were reversible after discontinuation of simvastatin. In the HPS trial,[33] fewer than 1.5% of patients allocated to simvastatin showed elevated alanine aminotransferase values between 2 and 4 times ULN, and in

fewer than 0.1% this elevation was persistent. Finally, the incidence of sustained elevations in liver enzymes greater than three times the ULN was very low (1%) in the Express study, using simvastatin 80 mg/day.[38]

5.2 Myotoxicity

The recent withdrawal of cerivastatin owing to fatal rhabdomyolysis focused attention on the safety of HMG-CoA reductase inhibitors, particularly with respect to myotoxicity, ranging from myalgia and mild myopathy to rhabdomyolysis. The precise mechanism of HMG-CoA reductase inhibitor-associated myotoxicity is complex and multifactorial, involving effects on cell membrane structures and functions, mitochondrial dysfunction and impaired myocyte duplication.[95-97] The risk of myotoxicity appears to be an HMG-CoA reductase inhibitor class effect and is also dose-related.[97] However, cerivastatin was associated with a 10-fold higher incidence of myotoxicity than any other HMG-CoA reductase inhibitor, suggesting that there may be differences between HMG-CoA reductase inhibitors. The rate of fatal rhabdomyolysis for cerivastatin monotherapy was 10–50 times higher than any other HMG-CoA reductase inhibitor, and increased to 80% when administered concomitantly with gemfibrozil.[98] Potential differences in myotoxicity between agents may relate to the physicochemical, pharmacokinetic and pharmacodynamic properties of individual drugs.

Differences in myotoxicity between the HMG-CoA reductase inhibitors may also be related to the CYP enzymatic pathway. Various CYP isoforms are responsible for the metabolism of all HMG-CoA reductase inhibitors other than pravastatin. The CYP3A4 isoform is the predominant isoform for the metabolism of simvastatin, atorvastatin and lovastatin.[39] Concomitant administration of HMG-CoA reductase inhibitors with drugs that inhibit or are metabolised by the CYP system (see table II for examples of such agents) may lead to potential interactions, resulting in increased plasma concentrations of HMG-CoA reductase inhibitors, which may increase the risk of adverse events. Macrolides, azole antifungal agents and cyclosporin lead to increased bioavailability of HMG-CoA reductase inhibitors, increasing the potential for myotoxicity.[39,99] The potential for interactions between HMG-CoA reductase inhibitors and fibric acid derivatives needs special attention, because of the increasing evidence supporting the beneficial effects of fibric acid derivatives on cardiovascular risk and the increasing use of combination therapy with HMG-CoA reductase inhibitor and fibric acid derivatives in the treatment of mixed hyperlipidaemia and in familial hypercholesterolaemia patients with high triglyceride levels.

The two largest trials using simvastatin – the 4S[28] and HPS[33] – have shown similar rates of myotoxicity in the simvastatin and placebo groups. In the HPS trial, patients were treated with simvastatin 40 mg/day or placebo for an average of 5.5 years, with similar adverse event rates, including myotoxicity (0.09%) in both groups. Additionally, in several trials in patients with familial hypercholesterolaemia or non-familial hypercholesterolaemia who were treated with simvastatin 80 mg/day for up to 12 months, the rate of myotoxicity was very uncommon compared with the rates in the general population. In the Express study,[38] drug-related myalgia was observed in 45 patients (8.9%), and only seven of these discontinued therapy. No cases of myopathy (muscle pain or weakness with creatine phosphokinase levels greater than 10 times ULN) were observed.

The prevention of myopathy associated with HMG-CoA reductase inhibitors is a very important issue in long-term treatment, especially in patients who require high doses of HMG-CoA reductase inhibitors, such as familial hypercholesterolaemia patients. In agreement with the document of the American College of Cardiology/American Heart Association/National Heart, Lung and Blood Institute clinical advisory on HMG-CoA reductase inhibitors,[100] it is important to pay close attention to factors that could contribute to increasing the risk for myopathy (see table V).

Table V. Risk factors for myopathy associated with HMG-CoA reductase inhibitors

Older age
Female sex
Renal or liver disease
Diabetes mellitus
Hypothyroidism
Multiple medications
Perioperative periods
Excessive alcohol consumption
Heavy exercise
Specific concomitant medication (e.g. fibric acid derivatives [especially gemfibrozil] or nicotinic acid)

A summary of guidelines for using simvastatin in familial hypercholesterolaemia patients is shown in table VI.

6. Economic Considerations of Treating Familial Hypercholesterolaemia

It is estimated that each year about 200 000 persons, worldwide, die of preventable early heart attack due to familial hypercholesterolaemia. Many of these patients can achieve normal or near-normal blood cholesterol levels with long-term high-dose HMG-CoA reductase inhibitor therapy, and they could probably live 15–30 years longer.

The first economic analysis of familial hypercholesterolaemia stated that low-dose therapy with lovastatin could save money as well as lives in many familial hypercholesterolaemia patients.[101] Since that study, newer medications such as simvastatin have proved to be more effective and less expensive.[102] Cholesterol-lowering treatment after an event of CHD has been proven to be even more cost-effective in secondary prevention than initially estimated.[102] Treatment of high cholesterol in patients who have had a myocardial infarction is widely accepted as one of the most cost-effective interventions since the report of the 4S study. Cholesterol reduction for primary prevention in men and women with familial hypercholesterolaemia carries similar benefits to those of secondary prevention in non-familial hypercholesterolaemia patients.[24]

Table VI. Summary of simvastatin use in patients with familial hypercholesterolaemia

Major indication	To lower LDL-C levels
Approximate extent of LDL-C level reduction	41–50%
Absolute contraindication	Active or chronic liver disease
Efficacy	Reduced risk for coronary heart disease in patients without familial hypercholesterolaemia
	Atherosclerosis regression in patients with familial hypercholesterolaemia
Safety	Adverse effects are minimal in long-term therapy
Usual dosage[a]	20–80 mg/day

a In general, most patients with familial hypercholesterolaemia require 40–80 mg/day of simvastatin.

LDL-C = low density lipoprotein-cholesterol.

Some medical economic analyses have also taken into account quality of life of the years gained, avoiding the economic impact on society of lost income and lost taxes from wage-earning patients who die early. US data suggest that medication costs represent only 5% of the total economic burden of coronary artery disease compared with 39% for hospital costs and 47% for lost productivity.[103] Moreover, a significant reduction in cost of the therapy may be expected when generic medications of HMG-CoA reductase inhibitors (including simvastatin) become available.

7. Conclusions

Familial hypercholesterolaemia is associated with an accelerated development of atherosclerotic cardiovascular disease, mainly coronary artery disease. Drug therapy is recommended for all patients with familial hypercholesterolaemia; it must be initiated as soon as the disorder is diagnosed and must also be continued for the patient's entire life. Therapy selection for each patient should consider the age and sex of the patients, whether the patient may be pregnant (or wish to become pregnant), as well as known cardiovascular risk factors.

HMG-CoA reductase inhibitors are the treatment of choice in familial hypercholesterolaemia patients, and patients usually require high doses to achieve a therapeutic goal for LDL-C levels. The efficacy and tolerability of simvastatin at dosages up to 80 mg/day are well established in long-term therapy. High doses of simvastatin can achieve a reduction in

LDL-C levels of up to 50% with favourable effects on other lipoproteins, including HDL and triglyceride levels, leading to reduced risk for development of cardiovascular disease. Simvastatin in dosages up to 40 mg/day has also been tested in children and adolescents aged 10–18 years with familial hypercholesterolaemia, with good tolerability and without effect on pubertal development and growth.

Comparative data with other HMG-CoA reductase inhibitors in familial hypercholesterolaemia patients indicate that simvastatin is more effective than lovastatin, fluvastatin or pravastatin in reducing LDL-C levels. With respect to atorvastatin, the effect of simvastatin is nearly the same when they are used in similar doses. However, simvastatin is more effective than atorvastatin in raising HDL-C levels. Regression studies in familial hypercholesterolaemia patients using simvastatin and LDL-apheresis have demonstrated that a reduction of at least 45% in LDL-C levels is necessary to obtain an improvement in carotid artery intima-media thickness.

The most important adverse events are hepatotoxicity and myopathy. Both entities are rare in long-term therapy with simvastatin. Patients with familial hypercholesterolaemia usually require high doses of simvastatin, and the frequency of increase in transaminase and creatine phosphokinase levels with myopathy are very close to that observed with lower doses. A detailed benefit-risk assessment must be done in all patients requiring HMG-CoA reductase inhibitor treatment, with close attention to the presence of some factors that predispose to myotoxicity such as age, female sex, renal or liver disease, diabetes mellitus and multiple medications.

The overwhelming clinical evidence regarding the long-term use of HMG-CoA reductase inhibitor therapy in patients with familial hypercholesterolaemia together with the long-term safety data (particularly relating to simvastatin) provide support for the use of this drug as a first-line agent when pharmacological treatment is indicated. Early intervention with simvastatin treatment can be successfully implemented with favourable economic benefits.

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