Introduction

The advent of the statins, competitive inhibitors of HMG CoA reductase and thus of cholesterol synthesis, has revolutionized the treatment and prevention of coronary heart disease. The reduction in coronary heart disease events in dyslipidaemic subjects largely reflects the extent to which these drugs lower LDL cholesterol, although additional mechanisms have been proposed in normolipidaemic individuals[1]. A meta-analysis of the five major statin trials showed an overall reduction in LDL cholesterol of 28%, which resulted in a 31% decrease in coronary heart disease events[3]. The latter value is 10% less than expected from the decrease in LDL cholesterol that occurred, judging from the Proportional Hazards analysis of the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT) where cholestyramine was used to lower LDL[3]. This discrepancy may reflect differences in design and duration between the CPPT and statin trials but does not support the notion that statins reduce coronary heart disease events by actions (‘pleiotropic effects’) which are additional to their LDL-lowering properties. Hence any factors which adversely affect the latter would be expected to diminish the benefits of statin therapy in the prevention of coronary heart disease, at least in hypercholesterolaemic subjects.

Extrinsic factors

The variations in response to statins between individuals that occur in a routine clinical setting are commonly due to extraneous influences. First and foremost among these is poor compliance as manifested by erratic consumption or discontinuation of the drug regimen. Simons et al.[4] conducted a large survey in Australia which showed that 30% of patients discontinue taking statins within 6–7 months of starting them, despite the good tolerability and excellent safety profile of this class of drug, with one exception (see below). Even higher discontinuation rates were observed with lipid-regulating drugs which had significant side effects, such as bile acid sequestrants and nicotinic acid.

Background diet is also important in increasing the proportion of patients achieving the target levels of LDL cholesterol stipulated in current guidelines. An additive but not synergistic effect of a low fat, low cholesterol intake has been shown in patients treated with statins[5,6].

Time of administration is another factor, the optimal time for most statins being the evening, reflecting the diurnal rhythm of HMG CoA reductase activity; reductions in LDL cholesterol are significantly less when they are taken in the morning[7]. This does not apply to atorvastatin, which has a much longer duration of action than other statins[8].

Concomitant drug therapy is another possible cause of variability of response to statins which, apart from pravastatin, are metabolized via the cytochrome P450 3A4 or 2C9 pathways[9]. A reduced LDL cholesterol-lowering effect could be expected when statins are given concomitantly with cytochrome P450 inducers such as carbamazepine, phenytoin and rifampicin, which accelerate their metabolism via that pathway. In contrast, increased blood levels of statins occur when their metabolism is impaired by cytochrome P450 inhibitors such as amiodarone, cyclosporin and diltiazem, which can occasionally lead to rhabdomyolysis. Pharmacokinetic interaction may also explain the increased frequency of rhabdomyolysis observed when gemfibrozil is given together with a statin, especially cerivastatin. The latter compound has recently been withdrawn by the manufacturer following 31 fatal cases of rhabdomyolysis in the U.S.A, 12 of which were associated with...
concomitant use of gemfibrozil[10]. Most of the remaining cases had been on a high dose of cerivastatin alone, which suggests that this particular compound is inherently more myotoxic than other statins.

Intrinsic factors

Intrinsic or genetically-determined factors are those responsible for the inter-individual variations in response seen under clinical trial conditions, where extrinsic influences such as variations in diet and compliance have been minimized. The extent of residual inter-individual variability in LDL cholesterol-lowering during statin therapy is considerable, and seems to be largely independent of the dose and drug used[11]. For example in a large trial of simvastatin 80 mg daily the mean reduction in LDL cholesterol was 46%[12]. However, decreases in the top 5% of responders ranged from 63–76% whereas in the bottom 5% changes ranged from −23% to +20%, the latter despite 6 months of treatment. Similarly, poor or diminishing responses over periods of up to 1 year have been observed in a minority of hypercholesterolaemic patients on simvastatin[13] and lovastatin[14]. The fact that this occurred also with pravastatin suggests that the waning of LDL-lowering efficacy in such individuals is not due to increased metabolism of these drugs via induction of the cytochrome P450 pathway but rather to a compensatory increase in HMG CoA reductase of sufficient magnitude to counteract their inhibitory effect on cholesterol synthesis[15]. It remains to be shown whether this phenomenon reflects genetic variation in HMG CoA reductase per se or in the sterol regulatory element-binding proteins (SREBPs), which regulate its expression.

Inter-individual variability in response to statins occurs to a similar extent in patients with heterozygous familial hypercholesterolaemia as in those with non-familial hypercholesterolaemia[16], including a group of familial hypercholesterolaemia patients all having the same mutation[16]; this suggests that differences in receptor-mediated LDL catabolism are not the explanation.

Influence of interaction between the absorptive and synthetic cholesterol pathways

The cholesterol circulating in plasma lipoproteins is derived both from the diet and endogenous synthesis. Dietary intake averages 200–600 mg daily on a Western diet and this mixes in the duodenum with up to twice that amount of cholesterol secreted in bile. Both sources of cholesterol must become incorporated into mixed micelles, as a result of the actions of pancreatic enzymes and bile salts, before undergoing absorption in the jejunum. Recent studies suggest that uptake by enterocytes is mediated by a saturable transport mechanism[17].

Plant sterols and stanols not only compete with cholesterol for micellar solubilization but probably also for this uptake pathway. In contrast with cholesterol, however, their further absorption is prevented by two or more ATP-binding cassette transporters. It has been proposed that these selectively mediate the efflux of plant sterols back into the intestinal lumen[18]. This proposal is based on the loss of this selectivity in phytosterolaemia, a rare disorder characterized by increased absorption of plant sterols and premature atherosclerosis, which has recently been shown to be due to mutations of ATP-binding cassette transporters G5 or G8[19].

In the final stage of absorption cholesterol is incorporated into chylomicrons which are converted to remnant particles after their entry into plasma and exposure to lipoprotein lipase. These chylomicron remnants are subsequently taken up by receptors in the liver and the cholesterol which they contain acts to down-regulate the activity of HMG CoA reductase, thereby reducing the rate of endogenous cholesterol synthesis[20]. Conversely, reduced influx of cholesterol via the absorptive pathway results in up-regulation of HMG CoA reductase and increased synthesis.

The role of genetic factors in determining inter-individual differences in response to dietary cholesterol both in animals and man has been reviewed elsewhere[21]. Briefly, most people fed high intakes of cholesterol in the diet show a modest rise in plasma cholesterol while a minority shows either a marked rise or no change. Replicate studies suggest that these patterns of response to dietary cholesterol are reproducible, leading to the terms hypo- and hyper-responders. Further studies have shown that hyper-responders had low basal rates of cholesterol synthesis before being put onto the high cholesterol diet, whereas hypo-responders had higher basal rates of cholesterol synthesis. Furthermore, people whose plasma cholesterol on their normal diet was in the high range tended to be more efficient absorbers of cholesterol in percentage terms than those whose plasma cholesterol was at the low or normal end of the range. Hence, people with a high serum cholesterol, and those who show an exaggerated response to dietary cholesterol, tend to hyper-absorb dietary cholesterol and have a low rate of cholesterol synthesis, whereas people who absorb the least have a lower serum cholesterol despite having a higher rate of synthesis.

Role of apolipoprotein E4

The most likely explanation for the above findings is that genetically-influenced differences in cholesterol absorption efficiency determine both the magnitude of the rise in plasma cholesterol and the extent to which the rate of cholesterol synthesis is down-regulated when the cholesterol content of the diet is raised. Probably the most frequently studied factor in this context is apolipoprotein E (apoE).
The existence of apoE polymorphism in humans is well documented and three major alleles have been described, E2, 3 and 4. The normal apoE genotype, 3/3, is possessed by two-thirds of the population, whereas about 20% have the E3/4 genotype. A small minority, probably less than 5% have the E4/4 genotype, except in Finland where there is an increased prevalence of the E4 allele. Sarkinnen et al. [22] examined the effect of a low fat diet without and with the addition of 300 mg of cholesterol on the serum cholesterol of three groups of Finns, with apoE 3/3, 3/4 or 4/4 genotypes. All three groups showed a decrease in serum cholesterol on the low fat diet, with the greatest fall in the E4/4s and the least in the 3/3s, the 3/4s being intermediate. With the addition of 300 mg of cholesterol daily to the low fat diet, the subsequent rise in serum cholesterol in the E4/4s was greater than in 3/4s and 3/3s. This suggests that individuals homozygous for E4 show exaggerated responses to removal of cholesterol and saturated fat from the diet as well as to the addition of cholesterol alone, compared with people with other phenotypes.

Another Finnish study provided an explanation for this phenomenon in that people with an E4 allele, who are often hypercholesterolaemic to start with, absorb cholesterol more efficiently and have lower synthetic rates than those with a normal phenotype [23].

Clinical consequences

What are the clinical implications of these putative genetic influences? One of the many subgroup analyses conducted on the results of the Scandinavian Simvastatin Survival Study (4S) involved the Finnish cohort who were divided into quartiles according to their serum cholestanol:cholesterol ratio [23]. Cholestanol was used as an index of cholesterol absorption and correlated very closely with the serum level of campesterol, another marker of cholesterol absorption, as shown in Fig. 1. Those in the lowest quartile of the cholestanol to cholesterol ratio were regarded as hypoabsorbers, those in the highest quartile as hyperabsorbers. As in previous studies, an inverse correlation between cholesterol absorption and synthesis is evident, synthesis being indicated by the ratio of lathosterol to cholesterol.

Values of serum cholesterol were similar in each quartile at baseline and remained so in those on placebo throughout the trial. However, when the subgroup treated with simvastatin was examined, it was found that the reduction in serum cholesterol in Q4, the high absorbers and low synthesizers, was less marked than in Q1, who absorbed less and synthesized more. The probable reason for this differential effect was that subjects in the fourth quartile showed a less marked decrease in their lathosterol:cholesterol ratio when on simvastatin than did those in the first quartile. Thus, people whose cholesterol synthesis rate was low to start with showed a lesser decrease in synthesis when treated with simvastatin than those people whose rate was initially high.

Using mevalonic acid rather than lathosterol as an index of cholesterol synthesis, Naoumova et al. [25] also found that a poor response to statins was associated with a low basal rate of cholesterol synthesis. The possibility that this phenomenon was due to inheritance of the apoE4 allele, presumably via an associated increase in cholesterol absorption, is supported by data from four of the 11 studies [26, 29, 31, 36] shown in Table 1. However, despite a definite trend towards a lessened response to statins in those with an E4 allele in most of the other studies, the differences were not statistically significant and further data are needed to substantiate or refute this explanation. Genetic variability in the expression of ATP-binding cassette transporters loci in the small intestine provides an alternative albeit hypothetical explanation for inter-individual differences in cholesterol absorption.

In their subgroup analysis of 4S, Miettinen et al. [37] also examined the reduction in risk of coronary events according to quartiles of the cholesterol:cholesterol ratio. The relative risk of coronary heart disease was reduced by 38–25% in simvastatin-treated subjects in the first, second and third quartiles but it was not reduced in those in the fourth quartile. Therefore people with a high cholesterol to cholesterol ratio at the start of the trial, the high absorbers/low synthesizers, showed no reduction in coronary events when treated with simvastatin and had the same relative risk of recurrent coronary heart disease as placebo-treated subjects.
Therapeutic approaches to enhancing statin responsiveness

As discussed above, evidence from both experimental animals and man strongly suggests that down-regulation of HMG CoA reductase resulting from increased absorption of intestinal cholesterol is associated with below average decreases in LDL cholesterol on statin therapy. The fact that this phenomenon has been observed under controlled trial conditions suggests that it is genetically determined rather than a reflection of a high intake of dietary cholesterol, although the latter may well be a contributory factor under free living conditions. The possible role of the apoE allele has already been mentioned but there are many other steps in cholesterol absorption at which genetic variation could influence absorptive efficiency[21]. For example in sitosterolemia, mutations of ATP-binding cassette transporters result in increased absorption of cholesterol as well as of plant sterols[49], with a consequent down-regulation of HMG CoA reductase and lack of response to simvastatin[38]. The likelihood that hyper-absorption is the primary defect and that down-regulation of HMG CoA reductase is a secondary phenomenon is further supported by the data of Miettinen et al.[24,37], already cited, which showed that hyper-absorbers in the Finnish cohort of 4S had less cholesterol absorption by this means decreases LDL cholesterol by more than 30%, despite a compensatory increase in hepatic cholesterol synthesis, but side effects preclude the long-term use of neomycin for this purpose. A new and apparently safe cholesterol absorption inhibitor, ezetimibe, which acts on the mucosal rather than on the micellar phase of absorption, is currently undergoing clinical trials. Preliminary data show that a dose of 10 mg daily reduces LDL cholesterol by about 20%/40%, as shown in Fig. 2.

Non-pharmacological inhibitors of cholesterol absorption include plant sterols and stanols, as reviewed 2 years ago[41]. Plant sterols occur naturally in vegetable oils whereas plant stanols are found in tall oil, a side product of the manufacture of paper from conifers. The main plant sterols, sitosterol and campesterol, can be readily converted to their stanol counterparts, sitostanol and campestanol, by hydrogenation. All these compounds compete with cholesterol for incorporation into mixed micelles but the limited solubility of free sterols and stanols makes it difficult to dissolve them in fat spreads in high enough concentrations to be effective. This can be overcome by esterifying them with long chain fatty acids, which increase their lipid solubility and facilitate their incorporation into foods. The ester bond

![Figure 2](https://example.com/figure2.png)

**Figure 2** Decrease in LDL cholesterol during administration of ezetimibe 0.25–10 mg daily. Reproduced with permission[48]. ◆=Placebo; ■=ezetimibe 0.25 mg; △=ezetimibe 1 mg; ●=ezetimibe 5 mg; *ezetimibe 10 mg.
Combined inhibition of the absorptive and synthetic cholesterol pathways

Several studies have shown enhancement of the LDL-lowering effects of statins when inhibitors of cholesterol absorption are given concomitantly. As shown in Table 2, four studies utilized plant stanol esters [24] and the fifth, ezetimibe [46]. The effects are additive, resulting in incremental decreases in LDL cholesterol ranging from 10–20% compared with statin therapy alone. A preliminary report based on the Finnish cohort of 4S suggests that the additive effect of stanol ester on LDL-lowering by simvastatin was most marked in those with highest basal levels of indices of cholesterol absorption, plasma cholesterol and campesterol, and the lowest level of lathosterol, an index of cholesterol synthesis, but this remains to be confirmed [47]. However, the data in Table 2 clearly show that inhibition of cholesterol absorption exerts a favourable effect at any given dose of statin, which in most instances is similar to or greater than that achieved by doubling the dose of the latter, as we also confirmed recently [39]. Hence the combined use of statins and plant stanol esters or ezetimibe should help overcome suboptimal decreases in LDL cholesterol as well as enable lower doses of statins to be used, thereby reducing the incidence of dose-related side effects such as myopathy.

References


Table 2 Combined effects of cholesterol absorption inhibition and statin therapy

<table>
<thead>
<tr>
<th>Authors (reference)</th>
<th>Design</th>
<th>Subjects (n)</th>
<th>Methods</th>
<th>Results of combined therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gylling et al., 1996 [41]</td>
<td>PC</td>
<td>NIDDM (8)</td>
<td>Pravastatin 40 mg+marge ± stan est 3 g, 7 weeks</td>
<td>TC − 31% vs pravastatin alone</td>
</tr>
<tr>
<td>Gylling et al., 1997 [41]</td>
<td>O, UC</td>
<td>P-M and CHD (11)</td>
<td>Simvastatin 10–20 mg+stan est marge 3 g, 12 wk</td>
<td>LDL-C − 16% vs simvastatin alone</td>
</tr>
<tr>
<td>Vuorio et al., 2000 [44]</td>
<td>O, UC</td>
<td>FH (12)</td>
<td>Simvastatin 20-40 mg+stan est marge 2-2 g, 6 wk</td>
<td>TC and LDL-C − 14% and − 20% vs simvastatin alone</td>
</tr>
<tr>
<td>Blair et al., 2000 [44]</td>
<td>DB, PC, R</td>
<td>HC (167)</td>
<td>Statin and marge ± stan est 3 g, 8 wk</td>
<td>TC and LDL-C − 7% and − 10% vs statin alone</td>
</tr>
<tr>
<td>Kosoglu et al., 2004 [44]</td>
<td>DB, PC,</td>
<td>HC (23)</td>
<td>Simvastatin 10 mg ± EZE 10 mg, 2 wk</td>
<td>TC and LDL-C − 9% and − 17% vs simvastatin alone</td>
</tr>
</tbody>
</table>

Design: O=open, UC=uncontrolled, R=randomized, DB=double blind, PC=placebo controlled, \|=parallel group
Subjects: n=number, P-M=post-menopausal, CHD=coronary heart disease, FH=familial hypercholesterolaemia, HC=hypercholesterolaemic
Methods: wk=weeks, stan est =stanol ester, marge=margarine, g=grams of stanol, EZE=ezetimibe
Results: TC=total cholesterol, LDL-C=LDL cholesterol.


