*European Heart Journal Supplements* (2001) **3** (*Supplement E*), E2–E5

# The role of the exogenous pathway in hypercholesterolaemia

**J. Shepherd**

*Royal Infirmary, Glasgow, Scotland, U.K.*

The concentration of plasma cholesterol is regulated by endogenous and exogenous pathways of cholesterol metabolism. In the endogenous pathway, cholesterol is synthesized by the liver and extrahepatic tissues, and enters the circulation as a component of lipoproteins, or is secreted into bile. In the exogenous pathway, cholesterol from dietary and biliary sources is absorbed in the intestine and ultimately enters the circulation as a component of chylomicrons. A new class of drugs, the selective cholesterol absorption inhibitors, offers a different approach to current strategies available for the management of hypercholesterolaemia. Ezetimibe, the first of these new compounds, inhibits intestinal absorption of dietary and biliary cholesterol, and lowers total cholesterol and low-density lipoprotein cholesterol (LDL-C) levels in humans. By inhibiting cholesterol absorption, and thereby possibly reducing the cholesterol content of chylomicrons, ezetimibe may also decrease the potential atherogenicity of chylomicrons and their remnants. Combination therapy with ezetimibe and statins, which inhibit cholesterol synthesis, provides broader control of lipid levels by impacting both the exogenous and endogenous pathways of cholesterol metabolism. Such combination therapy may be a convenient and more practical option for LDL-C reduction.
**(Eur Heart J Supplements 2001; 3 (Suppl E): E2–E5)**


**Key Words:** Exogenous cholesterol pathway, hypercholesterolaemia, cholesterol metabolism, cholesterol absorption inhibition, ezetimibe, statins.

## Introduction

The concentration of plasma cholesterol depends on the integrated balance of the endogenous and exogenous pathways of cholesterol metabolism[1–3]. Pharmacological interventions to reduce plasma cholesterol levels can target either or both of these pathways. The statins impact the endogenous pathway. They reduce cholesterol by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the enzyme that catalyses the rate-limiting step in the synthesis of cholesterol. This reduction in cholesterol synthesis in the liver ultimately leads to an up-regulation of low-density lipoprotein (LDL) receptors, resulting in an increased clearance of LDL particles from plasma and a reduction in plasma LDL cholesterol (LDL-C) levels[1,4,5]. The statins lower LDL-C concentrations by as much as 60%, although decreases of 20–30% are more common[1,6–8]. However, they have a dose-response curve of limited applicability[9,10], and at high doses can be associated with elevations in aminotransferase levels[11,12]. The selective cholesterol absorption inhibitors, however, affect the exogenous pathway of cholesterol metabolism[13,14]. Ezetimibe, the first drug in this novel class, inhibits the absorption of dietary and biliary cholesterol from the intestine by blocking the transport of cholesterol through the intestinal wall[14].

The present article further details the exogenous and endogenous pathways of cholesterol metabolism, and discusses the role of the chylomicron in cholesterol metabolism and its potential role as an atherogenic particle. The roles of the liver and the intestine in net cholesterol balance are reviewed. Finally, a dual pharmacological approach utilizing the statins and ezetimibe to manage hypercholesterolaemia is discussed.

## The pathways of cholesterol metabolism

Plasma cholesterol concentrations are maintained by biosynthesis through the endogenous pathway and absorption of dietary and biliary cholesterol through the exogenous pathway (Fig. 1). In the endogenous pathway, cholesterol is synthesized by the liver and extrahepatic tissues and secreted into plasma, whereas the intestine is the primary site of the exogenous pathway of dietary cholesterol uptake[1–3]. Alteration of either pathway will affect the concentration of plasma cholesterol.

*Correspondence*: Professor James Shepherd, MB, ChB, PhD, Department of Pathological Biochemistry, University of Glasgow and Royal Infirmary, 84 Castle Street, Glasgow, Scotland, G4 0SF, U.K.

1520-765X/01/0E0002+04 $35.00/0

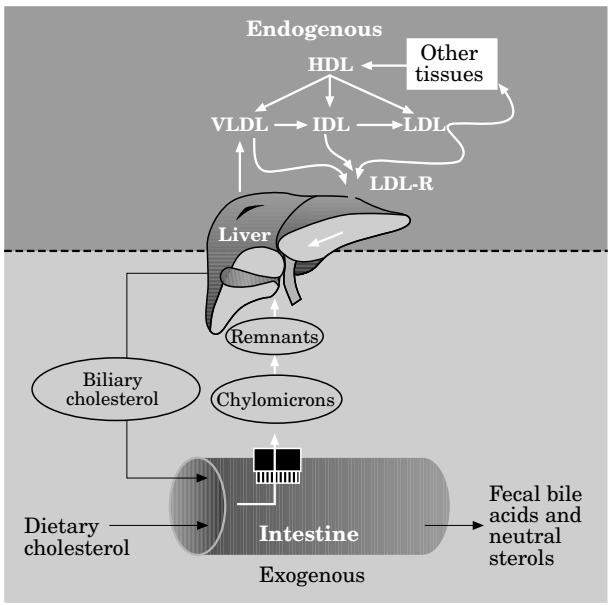


***Figure 1*** **The endogenous and exogenous pathways of cholesterol metabolism. HDL=high-density lipoprotein; VLDL=very-low-density lipoprotein; IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor.**

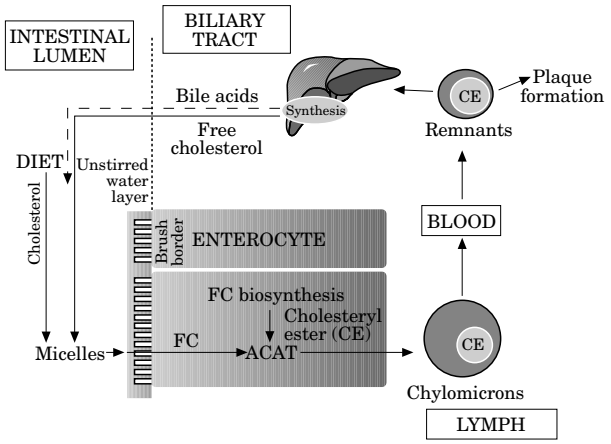


***Figure 2*** **Exogenous pathway of cholesterol metabolism. ACAT=acyl CoA: cholesterol acyltransferase; CE=cholesteryl ester; FC=free cholesterol.**

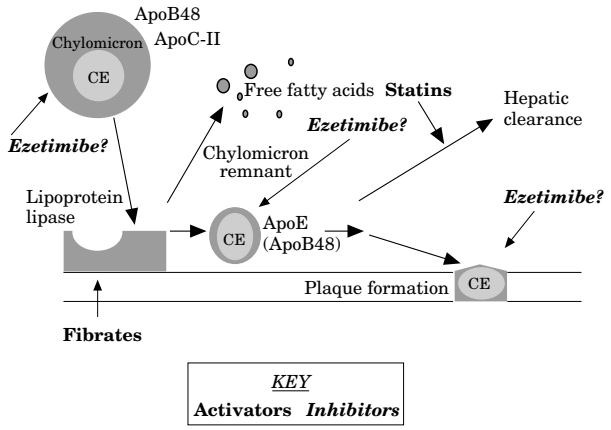


***Figure 3*** **Atherogenic potential of chylomicrons: benefits of inhibiting exogenous cholesterol absorption. CE=cholesteryl ester.**

Cholesterol from the liver can be secreted into the bile or can be incorporated, as the free or esterified form, into lipoproteins, namely very-low-density lipoprotein (VLDL) and LDL, which are then secreted into plasma. Elevated levels of cholesterol in the liver will lead to an increased production of VLDL and/or LDL, as well as down-regulation of the LDL receptor. The increase in lipoprotein production and the decrease in LDL clearance can both lead to an elevation in plasma cholesterol level.

Exogenous cholesterol is derived from bile and from dietary sources, which predominantly comprise animal and dairy food products. In the intestinal lumen, if the cholesterol is esterified, the ester is cleaved from the cholesterol moiety by pancreatic cholesteryl ester hydrolase, which is produced by the exocrine pancreas. Free cholesterol, along with other lipids and fat-soluble vitamins, is then solubilized into micelles and is subsequently absorbed by enterocytes by a mechanism that is not completely understood. After absorption, the free cholesterol is re-esterified to cholesteryl ester by acyl CoA:cholesterol acyltransferase (ACAT), and is packaged with other lipids into chylomicrons, which are secreted into the mesenteric lymph and ultimately into plasma[15]. Once in circulation, chylomicrons are hydrolyzed by lipoprotein lipase at the endothelial surface of vessels and are reduced to chylomicron remnants[16]. These chylomicron remnants can then be removed from the circulation by the liver or, if they are small enough, may be able to penetrate the endothelial surface of the arterial wall, where they may contribute to plaque formation[17] (see Fig. 2 for schematic presentation).

## Chylomicron remnants and atherosclerosis

Data from pre-clinical and clinical studies strongly support the concept that chylomicron remnants may dramatically affect the risk of atherosclerosis and coronary heart disease[18–21]. Significant accumulation of chylomicron remnants may occur in certain primary and secondary lipid disorders, as well as in normolipidaemic individuals with coronary heart disease[22]. Blocking the exogenous pathway by selectively inhibiting the uptake of cholesterol at the level of the brush border, as has been demonstrated by ezetimibe[23], may reduce the cholesteryl ester content of chylomicrons and their remnants. Consequently, plaque formation may be reduced at the level of the arterial wall (Fig. 3). If hepatic clearance of lipoproteins is activated with statins by up-regulation of LDL receptors, removal of chylomicron remnants from the circulation will also be enhanced since they contain apolipoprotein E, which

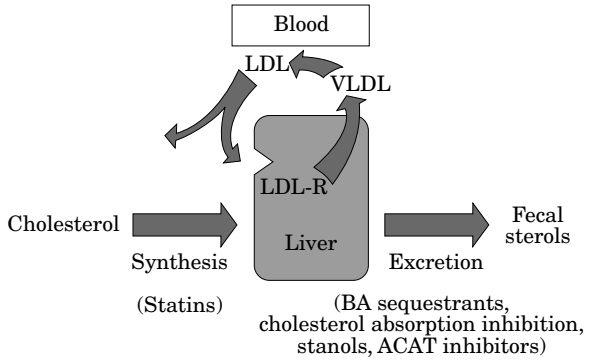


***Figure 4*** **Liver regulates corporeal cholesterol metabolism. ACAT=acyl CoA: cholesterol acyltransferase; BA=bile acids; LDL=low-density lipoprotein; LDL-R=low-density lipoprotein receptor; VLDL=very-low-density lipoprotein. (Courtesy of J. Dietschy, Southwestern Medical Center, Dallas, TX, U.S.A.)**

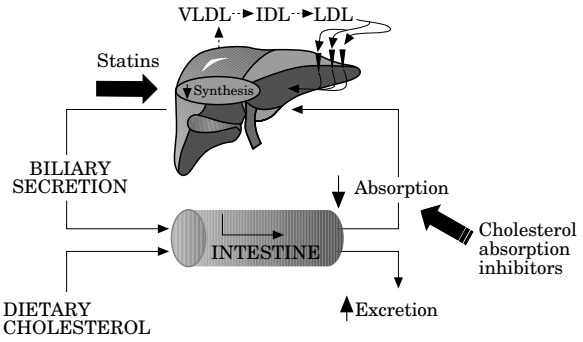


***Figure 5*** **Complementary actions of statins and selective cholesterol absorption inhibitors. IDL=intermediate-density lipoprotein; LDL=low-density lipoprotein; VLDL=very-low-density lipoprotein.**

can bind to the LDL receptor. Hence, there are two options available to regulate plasma cholesterol: block its uptake into the body with agents such as selective cholesterol absorption inhibitors, or promote its removal from the circulation by blocking the endogenous pathway with agents such as statins.

Ezetimibe may reduce the cholesterol content of chylomicrons and decrease the potential atherogenicity of chylomicrons and their remnants. A single 10-mg . $kg^{-1}$ dose of an ezetimibe analogue was administered to a small group of cholesterol-fed cynomolgus monkeys and blood samples were collected 4–5 h into the postprandial period. The single dose of the ezetimibe analogue significantly decreased the concentrations of postprandial chylomicra cholesteryl esters by 69% ($P<0{\cdot}05$), with no significant effect on the triglyceride content[24].

## Role of the liver in cholesterol metabolism

Cholesterol balance is maintained through hepatic and extrahepatic activity. Depending on diet, humans typically consume approximately 300–700 mg of cholesterol daily[3]. Approximately three times that amount (1000 mg) is secreted into bile and subsequently into the intestine. Thus, humans metabolize approximately 1300–1700 mg of cholesterol per day through their intestines.

The liver is an important organ for cholesterol production and might be regarded as the crossroads of cholesterol metabolism. The liver largely regulates corporeal cholesterol metabolism, maintaining cholesterol balance by responding to variations in cholesterol uptake and export[25] (Fig. 4). The liver can resecrete the cholesterol into bile or package the cholesterol into apolipoprotein B-containing particles, which are atherogenic. Thus, the hepatocyte cholesterol level can be affected in several ways, including decreasing cholesterol synthesis in the hepatocyte, reducing cholesterol uptake from the intestine or modifying cholesterol output to bile.

## A dual approach to managing hypercholesterolaemia

Statins are widely used in clinical practice to lower cholesterol levels. These compounds primarily affect the hepatic production of cholesterol, reducing the sterol pools the liver needs to make bile acids or cholesterol. Reducing the hepatic cholesterol stores up-regulates LDL receptors on liver cell membranes. These remove the cholesterol from the circulation, mainly in the form of LDL-C, resulting in a decrease in plasma cholesterol levels.

Another option for cholesterol-lowering therapy is to block the uptake of cholesterol from the intestine with a selective cholesterol absorption inhibitor such as ezetimibe. By inhibiting cholesterol absorption, less cholesterol would ultimately be delivered to the liver. This would also lead to an up-regulation of LDL receptors and increased clearance of LDL. However, one potential consequence of blocking cholesterol absorption could be an increase in hepatic cholesterol synthesis.

Therefore, blockade of cholesterol synthesis with one of the statins, and inhibition of cholesterol absorption with a selective cholesterol absorption inhibitor such as ezetimibe, would be expected to have an enhanced effect on removal of cholesterol from the circulation. Given the potential complementarity of these agents on the exogenous and endogenous pathways of cholesterol metabolism, this approach may be expected to provide greater reductions in LDL-C levels than with either agent alone (Fig. 5).

The expectation that combination therapy with a statin and ezetimibe would have an additive effect on LDL-C levels has been tested clinically. In one study[26], a group of patients given placebo (n=11) had little change in their LDL-C levels. Those given simvastatin

10 mg . day$^{-1}$ (n=12) or ezetimibe 10 mg . day$^{-1}$ (n=46) had statistically significant ($P<0{\cdot}01$ vs placebo) reductions in LDL-C levels from baseline (35% and 19%, respectively). However, patients given the combination of 10 mg of simvastatin and 10 mg of ezetimibe (n=11) achieved a reduction of 52% in LDL-C levels, which was an additional 17% reduction beyond that achieved with simvastatin (10 mg) monotherapy. The co-administration of ezetimibe and simvastatin was safe and well tolerated. Reported side effects were generally mild, non-specific and similar between treatment groups. No significant abnormalities in clinical laboratory test results, particularly in enzymes assessing muscle and liver injury, were associated with any of the treatments. Clinical studies evaluating the co-administration of ezetimibe with other statins are ongoing.

## Conclusion

Co-administration of a statin and a selective cholesterol absorption inhibitor such as ezetimibe should lower plasma cholesterol levels more than is possible with either treatment alone. This strategy promises a more tailored approach to the management of hypercholesterolaemia.

## References


[1] Witztum JL. Drugs used in the treatment of hyperdyslipidemias. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Gilman AG, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 9th edn. New York: McGraw-Hill International Book Co, 1996; chap 36: 875–97.

[2] Beisiegel U. Lipoprotein metabolism. Eur Heart J 1998; 19 (Suppl A): A20–3.

[3] Russell DW. Cholesterol biosynthesis and metabolism. Cardiovasc Drugs Ther 1992; 6: 103–10.

[4] Faggiotto A, Paoletti R. Statins and blockers of the renin–angiotensin system. Vascular protection beyond their primary mode of action. Hypertension 1999; 34 (pt 2): 987–96.

[5] Moghadasian MH. Clinical pharmacology of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors. Life Sci 1999; 65: 1329–37.

[6] Farnier M, Davignon J. Current and future treatment of hyperlipidemia: the role of statins. Am J Cardiol 1998; 82: 3J–10J.

[7] Blum CB. Comparison of the properties of four inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A reductase. Am J Cardiol 1994; 73 (Suppl): 3D–11D.

[8] Nawrocki JW, Weiss SR, Davidson MH *et al*. Reduction of LDL cholesterol by 25% to 60% in patients with primary hypercholesterolemia by atorvastatin, a new HMG-CoA reductase inhibitor. Arterioscler Thromb Vasc Biol 1995; 15: 678–82.

[9] Illingworth DR. Management of hypercholesterolemia. Med Clin North Am 2000; 84: 23–42.

[10] Knopp RH. Drug treatment of lipid disorders. N Engl J Med 1999; 341: 498–511.

[11] Lennernäs H, Fager G. Pharmacodynamics and pharmacokinetics of HMG-CoA reductase inhibitors: similarities and differences. Clin Pharmacokinet 1997; 32: 403–25.

[12] Dujovne CA, Chremos AN, Pool JL *et al*. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: IV. Additional perspectives on the tolerability of lovastatin. Am J Med 1991; 91 (Suppl 1B): 25S–30S.

[13] van Heek M, Farley C, Compton DS *et al*. Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663. Br J Pharmacol 2000; 129: 1748–54.

[14] van Heek M, France CF, Compton DS *et al*. In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. J Pharmacol Exp Ther 1997; 283: 157–63.

[15] Dawson PA, Rudel LL. Intestinal cholesterol absorption. Curr Opin Lipidol 1999; 10: 315–20.

[16] Patsch J. Influence of lipolysis on chylomicron clearance and HDL cholesterol levels. Eur Heart J 1998; 19 (Suppl H): H2–6.

[17] Mamo JCL. Atherosclerosis as a post-prandial disease. Endocrinol Metab 1995; 2: 229–44.

[18] Proctor SD, Pabla CK, Mamo JCL. Arterial intimal retention of pro-atherogenic lipoproteins in insulin deficient rabbits and rats. Atherosclerosis 2000; 149: 315–22.

[19] Mamo JCL, Smith D, Yu KCW *et al*. Accumulation of chylomicron remnants in homozygous subjects with familial hypercholesterolaemia. Eur J Clin Invest 1998; 28: 379–84.

[20] Cohn JS. Postprandial lipemia: emerging evidence for atherogenicity of remnant lipoproteins. Can J Cardiol 1998; 14 (Suppl B): 18B–27B.

[21] Phillips C, Murugasu G, Owens D, Collins P, Johnson A, Tomkin GH. Improved metabolic control reduces the number of postprandial apolipoprotein B-48-containing particles in type 2 diabetes. Atherosclerosis 2000; 148: 283–91.

[22] Mamo JC, Proctor SD, Smith D. Retention of chylomicron remnants by arterial tissue; importance of an efficient clearance mechanism from plasma. Atherosclerosis 1998; 141 (Suppl 1): S63–9.

[23] Davis HR, Compton DS, Hoos L, Tetzloff G, Caplen MA, Burnett DA. Ezetimibe (SCH58235) localizes to the brush border of small intestinal enterocyte and inhibits enterocyte cholesterol uptake and absorption (Abstr). Eur Heart J 2000; 21 (Suppl): 636.

[24] van Heek M, Compton DS, Davis HR. The cholesterol absorption inhibitor, ezetimibe, decreases diet-induced hypercholesterolemia in monkeys. Eur J Pharmacol 2001; 415: 79–84.

[25] Dietschy JM. Theoretical considerations of what regulates low-density-lipoprotein and high-density-lipoprotein cholesterol. Am J Clin Nutr 1997; 65 (Suppl): 1581S–9S.

[26] Kosoglou T, Meyer I, Musiol B *et al*. Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor SCH 58235 and simvastatin (Abstr). Atherosclerosis 2000; 151: 135.