Targeting Two Sources of Cholesterol – An Advanced Treatment Approach to Lipid-lowering Management

a report by

Dr Alberico L Catapano

Professor of Pharmacology, University of Milan

Dr Alberico L Catapano is Professor of Pharmacology at the University of Milan in Italy. He is Director of the Lipids and Lipoproteins Laboratory as well as Director of the Centre for the Study of Atherosclerosis at the Bassini Hospital, also in Milan. He has been an invited speaker at numerous medical and scientific conferences and is frequently invited to serve as the scientific secretary or member of the organising committee at these meetings. Dr Catapano has authored more than 150 scientific publications and edited 12 books on lipids and lipoproteins. He is a member of the editorial board for several peer-review journals, including *Aging*, *Atherosclerosis*, *Journal of Cardiovascular Pharmacology*, *Nutrition*, *Metabolism* and *Cardiovascular Disease*. Dr Catapano's research interests are varied and include the aetiology of atherosclerosis, gene expression in endothelial cells, metabolism of lipoproteins, biochemical and molecular defects in atherogenesis, mechanism of action of lipid lowering drugs, drugs and atherosclerosis and postprandial lipaemia.

Introduction

Hypercholesterolaemia plays a key role in the development and progression of atherosclerosis and is a proven risk factor for coronary heart disease (CHD).[1–4] Therapeutic interventions to lower cholesterol levels both in primary and secondary prevention trials show a clear reduction in the incidence of CHD and stroke.[5–11]

3-hydroxy-3-methylglutaryl co-enzyme A (HMG-CoA) reductase inhibitors or statins (even when administered at high doses), although widely used in lipid lowering therapy, are frequently insufficient to achieve guideline-recommended low-density lipoprotein cholesterol (LDL-C) goals for many patients with hypercholesterolaemia in everyday clinical practice.[12] According to a recent study, a large proportion of high-risk hyperlipidaemic patients receiving statins alone were not at goal even when physicians were free to use any statin and titrate according to their professional judgment.[13] Over half (52%) of patients did not achieve LDL-C goal on the initial dose of statin and 86% of these patients had still not reached their goal after six months.[13] A wide therapeutic gap therefore exists between target LDL-C levels and those typically achieved in clinical practice.[14]

The therapeutic gap will increase in light of recent amendments to the National Cholesterol Education Program Adult Treatment Program III (NCEP ATP III) guidelines, which recommend even more aggressive reductions in lipid levels for patients at medium, high and very high risk of CHD.[15] The more aggressive cholesterol treatment goals advocated by the revised guidelines call for a more advanced approach to maximise the cardiovascular (CV) benefits associated with lower LDL-C levels.

There are two main sources of cholesterol, which are similar in size – production of cholesterol, mainly from the liver, and absorption of cholesterol in the intestine. Approximately 50% of the cholesterol pool is absorbed and recirculated through the intestine, while the remainder is excreted in the faeces.[16,17] The intestinal pool is composed of dietary cholesterol (30%) and biliary cholesterol (50%), with a smaller amount of cholesterol coming from sloughed epithelial cells (20%).[17] A recent and more effective therapeutic strategy is therefore to treat both sources of cholesterol simultaneously with a complementary mechanism of action by co-administering ezetimibe, a novel agent inhibiting cholesterol absorption in the intestine, together with a statin, which inhibits cholesterol production in the liver.[16,18,19]

Ezetimibe can be effectively co-administered with any dose of any statin and, compared with single inhibition of cholesterol production afforded by statins alone, provides consistently greater reductions in LDL-C through dual inhibition of both cholesterol production and absorption.[20–23] Ezetimibe co-adminstered with any dose of any statin provides superior LDL-C lowering efficacy with improved LDL-C goal attainment.[24–26]

The purpose of this review is to summarise the pivotal role of both the liver and intestine in the overall balance of cholesterol in the body and describe the clinical impact and relevance of inhibiting both sources of cholesterol either by using ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of any statin.

The Liver and Intestine – Sources of Cholesterol

The average adult body contains approximately 140g of sterol, mainly in the form of cholesterol.[27] This pool of cholesterol is derived from two major sources – synthesis of cholesterol by the liver (and extrahepatic sites) and absorption by the intestines.[16,18] Approximately 700mg to 1,400mg per day of cholesterol enters the body's cholesterol pool from synthesis (700mg to 1,000mg) and intestinal absorption (up to 400mg per day).[27,28] The cholesterol pool usually changes little because cholesterol input is balanced mainly by cholesterol output via excretion in bile/faeces; skin excretion, steroid hormone synthesis and other mechanisms play a minor role.[27,28]

The liver plays a central role in balancing cholesterol from all sources and also plays a pivotal role in regulating plasma LDL-C levels.[29] The hepatic pool of cholesterol is derived from local biosynthesis and from chylomicron remnants and lipoproteins. Cholesterol biosynthesis is regulated by the rate-limiting enzyme HMG-CoA reductase, which catalyses production of mevalonic acid from HMG-CoA and represents the single therapeutic target for statins. Cholesterol produced by the liver is either secreted in bile (principal route) or incorporated into lipoproteins (mainly LDL and very low-density lipoprotein (VLDL)) and secreted into plasma.

Intestinal cholesterol absorption represents another major route for the entry of cholesterol into the body; thus, this source can influence the plasma LDL-C concentration.[18] The cholesterol pool in the intestine comes from cholesterol in the diet and the majority from biliary excretion. Approximately 50% of the intestinal cholesterol pool is reabsorbed by the intestines[30] and recirculated through the body (via the enterohepatic circulation), with the remainder excreted in faeces.

While the precise molecular transport mechanisms of cholesterol absorption are not completely delineated, cholesterol absorption in the intestine is believed to involve a complex triphasic process (see *Figure 1*) – intraluminal phase (digestion/hydrolysis of dietary lipids and micellar solubilisation of cholesterol), membrane transport phase (cholesterol release from micelles at brush border membrane and uptake into enterocytes) and an intracellular phase (re-esterification, incorporation into nascent chylomicrons and secretion into lymph).[30,31] Although some cholesterol translocation across the brush border membrane occurs by passive diffusion, several sterol transporters have also been implicated in this process, including Niemann-Pick C1-like 1 protein (NPC1L1) aminopeptidase N (CD13), annexin-2/caveolin-1 (ANX2/CAV1) and adenosine triphosphate- (ATP)-binding cassette (ABC) transporters (ABCG5 and ABCG8).[31–33] Inhibition of cholesterol absorption with novel agents such as ezetimibe has thus become an important and attractive therapeutic target, particularly since postprandial lipoproteins (cholesterol-rich chylomicron remnants) appear to be particularly atherogenic, with the ability to enter the arterial wall and promote atherogenesis.[34]

Treating Two Sources of Cholesterol – Production and Absorption

In the past few years, an innovative progression in cholesterol-lipid lowering therapy has occurred. It is now recognised that treating both cholesterol production in the liver and absorption in the intestine, either by administering ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of statin, results in superior LDL-C-lowering efficacy and more patients achieving or obtaining below LDL-C treatment goals compared with inhibition of a single cholesterol source with statins alone.

Statins (e.g., simvastatin, lovastatin, fluvastatin, atorvastatin, rosuvastatin and pravastatin) deliver only single inhibition of cholesterol production in the liver by modulating HMG-Co A reductase, the rate-limiting step in cholesterol synthesis, but do not impact effectively intestinal cholesterol absorption.[35] As a result, hepatocytes become depleted of cholesterol and respond by increasing LDL-C clearance from the blood (via upregulation of hepatic LDL-C receptors) and decreasing entry of LDL-C into the circulation.[36,37] These actions, in turn, give rise to lower plasma LDL-C levels.

Ezetimibe is a novel, orally active and selective inhibitor of intestinal absorption of dietary and biliary cholesterol as well as plant sterols.[18,38,39] Ezetimibe is the first in a class of lipid-lowering agents with a mechanism of action that is very different from other lipid lowering therapies, including bile acid sequestrants. By inhibiting cholesterol absorption at the level of the brush border of the intestine, ezetimibe reduces the amount of chylomicron cholesterol circulated to the liver. In response to reduced cholesterol delivery, the liver reacts by upregulating LDL-C receptors, which in turn leads to increased clearance of cholesterol from the blood.[19]

While the precise molecular mechanism(s) by which ezetimibe reduces cholesterol absorption is still being delineated, experimental evidence suggests that ezetimibe may interact with several cholesterol transport proteins in the brush border membrane (see *Figure 1*). These transporters facilitate the movement of cholesterol from bile acid micelles in the intestinal lumen across the brush border membranes into enterocytes. Recent studies indicate that ezetimibe may interact with the cholesterol transport protein NPC1L1 expressed in the intestine as well as in the liver and other cell types.[40] Furthermore, in mice lacking the NPC1L1 protein, ezetimibe was unable to affect cholesterol absorption.[40] Ezetimibe may also prevent cholesterol absorption by inhibiting ANX2/CAV1, which is required for the uptake of cholesterol from micelles into enterocytes.[33] Interestingly, ezetimibe has also been shown to block the uptake of oxidised LDL by human macrophages through inhibition of both NPC1L1 and ANX2/CAV1,[41] suggesting that the actions of this agent may extend beyond the intestinal epithelium. Aminopeptidase N (CD13) in the brush border membrane may represent an additional molecular target for ezetimibe. Ezetimibe has been shown to bind to aminopeptidase N, thereby blocking the endocytosis of cholesterol from micelles in the intestinal lumen.[32]

The Impact of Treating Two Sources of Cholesterol on LDL-C (Lowering Efficacy and Allowing Patients to Reach Their Goal)

The use of two lipid-lowering compounds (ezetimibe co-administered with a statin) with a complementary mechanism of action provides a powerful new approach to prevent and treat atherosclerosis. Treating two sources of cholesterol (rather than one source with statins alone) results in a substantially greater overall LDL-C lowering efficacy as well as in more patients attaining or receiving below LDL-C goals.

Ezetimibe/Simvastatin as a Single Tablet

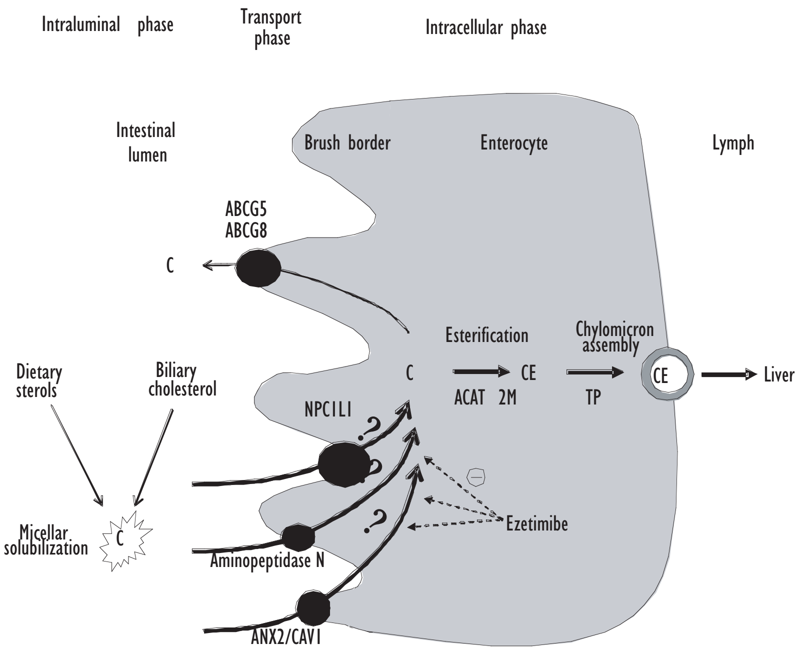
Ezetimibe/simvastatin as a single tablet was superior to atorvastatin alone at reducing plasma LDL-C at every dose comparison studied, according to a double-blind, randomised, forced-titration study.[24] Adult patients with hypercholesterolaemia experienced significantly greater reductions in LDL-C when they received the typical starting dose of ezetimibe/simvastatin 10mg/20mg (50%) compared with atorvastatin 10mg (37%) after six weeks of treatment (p<0.001). Importantly, the reduction in LDL-C levels seen with ezetimibe/simvastatin was comparable with the 50% reduction in LDL-C levels that has been shown to be required for reversal of atherosclerosis, according to the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study.[42] In addition, ezetimibe/simvastatin resulted in significantly more patients achieving LDL-C goal (less than 100mg/dl) whether compared with atorvastatin or simvastatin alone.[25,26]

Furthermore, compared with patients receiving atorvastatin alone, more patients treated with ezetimibe/simvastatin reached the more aggressive LDL-C target (less than 70mg/dl), as recently recommended by the National Cholesterol Education Program (NCEP) for very-high-risk CHD patients.[26] Approximately 23% of patients receiving atorvastatin 40mg alone and 36% of patients receiving atorvastatin 80mg alone reached the optional LDL-C treatment target of less than 70mg/dl, compared with 57% of patients treated with ezetimibe/simvastatin (10mg/40mg) and 64% of patients receiving ezetimibe/simvastatin (10mg/80mg).

Co-administering Ezetimibe Together with a Statin

In patients with hypercholesterolaemia not at goal on statin therapy alone, the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial[43] demonstrated that co-administering ezetimibe (10mg) with any dose of statin reduced LDL-C levels by an additional 20% to 25% and improved LDL-C goal attainment from 20% on statin monotherapy to 71% with dual inhibition therapy. Similarly, co-administering ezetimibe together with on-going statin therapy also produced a marked reduction in LDL-C compared with statin alone, a reduction that resulted in significantly more patients achieving NCEP treatment goals (71.7% compared with 18.9% on statin alone, p<0.001).[44]

Figure 1: Overview of the Principal Steps in the Intestinal Absorption of Cholesterol (C)



The intraluminal phase involves the digestion/hydrolysis of dietary lipids and micellar solubilisation of cholesterol. The membrane transport phase involves cholesterol release from micelles at the brush border membrane and uptake into enterocytes via several sterol transporters, including Niemann-Pick C1-like 1 protein (NPC1L1), aminopeptidase N (CD13) and annexin-2/caveolin-1 (ANX2/CAV1). The brush border membrane also contains adenosine triphosphate- (ATP)-binding cassette (ABC) transporters (ABCG5 and ABCG8), which primarily move plant sterols and, to a lesser extent, cholesterol out of the enterocytes. The intracellular phase involves esterification, incorporation into nascent chylomicrons and secretion into lymph for transport to the liver. Several enzymes and proteins within the enterocyte are involved in the intracellular phase, including acyl CoA:cholesterol acyltranserase (ACAT), which enhances intracellular cholesterol esterification and microsomal triglyceride transfer protein (MTP), which assembles intestinal chylomicrons. Ezetimibe may inhibit cholesterol absorption by interacting with several cholesterol transport proteins present in the brush border membrane, including NPC1L1, ANX2/CAV1 and aminopeptidase N (CD13). Based on information extracted from Turley S D and Dietschy J M[18], Smart E J et al.,[33] Kramer W et al.[32] and Sudhop T et al.[31]

The Impact of Treating Two Sources of Cholesterol on Outcomes

Although treating two sources of cholesterol through dual inhibition provides superior LDL-C lowering efficacy with improved LDL-C goal attainment, one key clinical question remains to be addressed – do the lower LDL-C levels achieved with dual inhibition of cholesterol production and absorption ultimately translate into reduced CV or renal events and a slower rate of progression of atherosclerosis? This question is currently being assessed in several major CV outcomes studies, including Ezetimibe and Simvastatin in Hypercholesterolaemia Enhances Atherosclerosis

Regression (ENHANCE), Improved Reduction of Outcomes: Vytorin™ Efficacy International Trial (IMPROVE IT), Simvastatin and Ezetimibe in Aortic Stenosis Study (SEAS) and Study of Heart and Renal Protection (SHARP). These major end-point trials collectively involve more than 21,000 patients.

Conclusions

A wide therapeutic gap exists between target LDL-C levels and LDL-C levels typically achieved in actual clinical practice – a gap that will certainly widen with traditional therapy of single inhibition in light of recent amendments to the NCEP ATP III guidelines. The new aggressive cholesterol treatment goals call for a more advanced therapeutic approach to maximise the CV benefits associated with lower LDL-C levels. One logical approach is to target both cholesterol production in the liver and absorption in the intestine. By administrating ezetimibe/simvastatin as a single tablet or co-administering ezetimibe together with any dose of any statin, superior LDL-C-lowering efficacy and a substantially greater proportion of patients achieving or obtaining below LDL-C treatment goals can be expected. Treating two sources of cholesterol through dual inhibition should therefore be considered as a more advanced therapeutic option for all hypercholesterolaemic patients whose LDL-C levels are not appropriately controlled approximately two to three months after initiating statin monotherapy. Four large-scale CV end-point trials involving more than 21,000 patients are currently underway to determine the impact of dual inhibition on patient outcomes. ■

References

1. *Steinberg D, Witztum J L, "Lipoproteins and atherogenesis. Current concepts",* JAMA *(1990);264: pp. 3,047–3,052.*
2. *Castelli W P, Anderson K, Wilson P W, Levy D, "Lipids and risk of coronary heart disease. The Framingham Study",* Ann. Epidemiol. *(1992);2: pp. 23–28.*
3. *Wilson P W, Garrison R J, Castelli W P, Feinleib M, McNamara P M, Kannel W B, "Prevalence of coronary heart disease in the Framingham Offspring Study: role of lipoprotein cholesterols",* Am. J. Cardiol. *(1980);46: pp. 649–654.*
4. *Stamler J, Wentworth D, Neaton J, "Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT)",* JAMA *(1986);256: pp. 2,823–2,828.*
5. *"The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease",* JAMA *(1984);251: pp. 351–364.*
6. *Shepherd J, Cobbe S M, Ford I, Isles C G, Lorimer A R, MacFarlane P W et al., "Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group",* N. Engl. J. Med. *(1995);333: pp. 1,301–1,307.*
7. *Collins R, Armitage J, Parish S, Sleight P, Peto R, "Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20,536 people with cerebrovascular disease or other high-risk conditions",* Lancet *(2004);363: pp. 757–767.*
8. *"Randomised trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)",* Lancet *(1994);344: pp. 1,383–1,389.*
9. *Downs J R, Clearfield M, Tyroler H A, Whitney E J, Kruyer W, Langendorfer A et al., "Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS): additional perspectives on tolerability of long-term treatment with lovastatin",* Am. J. Cardiol. *(2001);87: pp. 1,074–1,079.*
10. *Manninen V, Elo M O, Frick M H, Haapa K, Heinonen O P, Heinsalmi P et al., "Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study",* JAMA *(1988);260: pp. 641–651.*
11. *Frick M H, Elo O, Haapa K, Heinonen O P, Heinsalmi P, Helo P et al., "Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease",* N. Engl. J. Med. *(1987);317: pp. 1,237–1,245.*
12. *Goettsch W G, Yin D D, Alemao E, Klungel O H, Stalenhoef A F, Herings R M, "Statins are less effective in common daily practice among patients with hypercholesterolemia: the REALITY-PHARMO study",* Curr. Med. Res. Opin. *(2004);20: pp. 1,025–1,033.*
13. *Foley K A, Simpson R J Jr, Crouse J R III, Weiss T W, Markson L E, Alexander C M, "Effectiveness of statin titration on low-density lipoprotein cholesterol goal attainment in patients at high risk of atherogenic events",* Am. J. Cardiol. *(2003);92: pp. 79–81.*
14. *Neal R C, Jones P H, "Lipid-lowering: can ezetimibe help close the treatment gap?",* Cleve. Clin. J. Med. *(2003);70: pp. 777–783.*
15. *Grundy S M, Cleeman J I, Merz C N, Brewer H B Jr, Clark L T, Hunninghake D B et al., "Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines",* J. Am. Coll. Cardiol. *(2004);44: pp. 720–732.*
16. *Shepherd J, "Combined lipid lowering drug therapy for the effective treatment of hypercholesterolaemia",* Eur. Heart J.

(2003);24: pp. 685–689.

17. *Bays H, "Ezetimibe",* Expert. Opin. Investig. Drugs *(2002);11: pp. 1,587–1,604.*
18. *Turley S D, "Cholesterol metabolism and therapeutic targets: rationale for targeting multiple metabolic pathways",* Clin. Cardiol. *(2004);27:III16-III21.*
19. *Patel S B, "Ezetimibe: a novel cholesterol-lowering agent that highlights novel physiologic pathways",* Curr. Cardiol. Rep. *(2004);6: pp. 439–442.*
20. *Ballantyne C M, Houri J, Notarbartolo A, Melani L, Lipka L J, Suresh R et al., "Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial",* Circulation *(2003);107: pp. 2,409–2,415.*
21. *Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A et al., "Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial",* Eur. Heart J. *(2003);24: pp. 717–728.*
22. *Gagne C, Bays H E, Weiss S R, Mata P, Quinto K, Melino M et al., "Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia",* Am. J. Cardiol. *(2002);90: pp. 1,084–1,091.*
23. *Kerzner B, Corbelli J, Sharp S, Lipka L J, Melani L, LeBeaut A et al., "Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia",* Am. J. Cardiol. *(2003);91:pp. 418–424.*
24. *Ballantyne C M, Blazing M A, King T R, Brady W E, Palmisano J, "Efficacy and safety of ezetimibe co-administered with simvastatin compared with atorvastatin in adults with hypercholesterolemia",* Am. J. Cardiol. *(2004);93: pp. 1,487–1,494.*
25. *Feldman T, Koren M, Insull W Jr, McKenney J, Schrott H, Lewin A et al., "Treatment of high-risk patients with ezetimibe plus simvastatin co-administration versus simvastatin alone to attain National Cholesterol Education Program Adult Treatment Panel III low-density lipoprotein cholesterol goals",* Am. J. Cardiol. *(2004);93: pp. 1,481–1,486.*
26. *Ballantyne C, Abate N, Zhong Y, King T R, Palmisano J, "Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia. the Vytorin Versus Atorvastatin (VYVA) Study",* Am. Heart J. *(2005); in press.*
27. *Cook R P, "Cholesterol. Distribution of sterols in organisms and in tissues", in: Cook R P (ed.),* Cholesterol. Chemistry, Biochemistry, and Pathology, *New York: Academic Press, Inc. (1958): pp. 145–180.*
28. *Illingworth D R, Duell P B, Connor W E, "Disorders of lipid metabolism", in: Felig P, Baxter J D, Frohman L A (eds)* Endocrinology and Metabolism, *New York: McGraw-Hill (1995): pp. 1,315–1,403.*
29. *Dietschy J M, Turley S D, Spady D K, "Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans",* J. Lipid Res. *(1993);34: pp. 1,637–1,659.*
30. *Turley S D, Dietschy J M, "Sterol absorption by the small intestine",* Curr. Opin. Lipidol. *(2003);14: pp. 233–240.*
31. *Sudhop T, Lutjohann D, von Bergmann K, "Sterol transporters: targets of natural sterols and new lipid lowering drugs",* Pharmacol. Ther. *(2005);105: pp. 333–341.*
32. *Kramer W, Girbig F, Corsiero D, Pfenninger A, Frick W, Jahne G et al., "Aminopeptidase N (CD13) is a molecular target of the cholesterol absorption inhibitor ezetimibe in the enterocyte brush border membrane",* J. Biol. Chem. *(2005);280: pp. 1,306–1,320.*
33. *Smart E J, De Rose R A, Farber S A, "Annexin 2-caveolin 1 complex is a target of ezetimibe and regulates intestinal cholesterol transport",* Proc. Natl. Acad. Sci. USA *(2004);101: pp. 3,450–3,455.*
34. *Huff M W, "Dietary cholesterol, cholesterol absorption, postprandial lipemia and atherosclerosis",* Can. J. Clin. Pharmacol. *(2003);10 Suppl A:26A–32A.*
35. *Shepherd J, "Lipids in health and disease",* Biochem. Soc. Trans. *(2004);32: pp. 1,051–1,056.*
36. *Knopp R H, "Drug treatment of lipid disorders",* N. Engl. J. Med. *(1999);341: pp. 498–511.*
37. *Steiner G, "The need for a different cholesterol lowering drug",* Can. J. Clin. Pharmacol. *(2003);10 Suppl A:4A–6A.*
38. *Van Heek M, Farley C, Compton D S, Hoos L, Alton K B, Sybertz E J et al., "Comparison of the activity and disposition of the novel cholesterol absorption inhibitor, SCH58235, and its glucuronide, SCH60663",* Br. J. Pharmacol. *(2000);129: pp. 1,748–1,754.*
39. *Lavoie M A, "Ezetimibe and cholesterol absorption",* Can. J. Clin. Pharmacol. *(2003);10 Suppl A:7A–12A.*
40. *Altmann S W, Davis H R Jr, Zhu L J, Yao X, Hoos L M, Tetzloff G et al., "Niemann-Pick C1 Like 1 protein is critical for intestinal cholesterol absorption",* Science *(2004);303: pp. 1,201–1,204.*
41. *Seedorf U, Engel T, Lueken A, Bode G, Lorkowski S, Assmann G, "Cholesterol absorption inhibitor Ezetimibe blocks uptake of oxidized LDL in human macrophages",* Biochem. Biophys. Res. Commun. *(2004);320: pp. 1,337–1,341.*
42. *Nissen S E, Tuzcu E M, Schoenhagen P, Brown B G, Ganz P, Vogel R A et al., "Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial",* JAMA *(2004);291: pp. 1,071–1,080.*
43. *Pearson T, Denke M, McBride P et al., "Ezetimibe added to statin therapy reduces LDL-C and improves goal attainment in patients with hypercholesterolemia (abstract)", American College of Cardiology 53rd Annual Meeting, New Orleans, (7–10 March 2004).*
44. *Gagne C, Bays H E, Weiss S R, Mata P, Quinto K, Melino M et al., "Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia",* Am. J. Cardiol. *(2002);90: pp. 1,084–1,091.*