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Editorial

Combined lipid lowering drug therapy for the effective treatment of hypercholesterolaemia

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Every day we consume approximately 300 mg of cholesterol and its esters and 100 g of triglyceride in our diet.¹ This mixes in the intestinal lumen with about 900 mg of biliary cholesterol and thereafter the total package is reduced by digestion to free cholesterol, fatty acids and mono- and diglycerides which become incorporated, through the detergent effects of bile acids, into water soluble micelles for transport to absorption sites on the luminal surfaces of small intestinal enterocytes (Fig. 1). Triglyceride absorption is virtually complete whereas only about 50% of the cholesterol finds its way into the intestinal mucosa, the remainder being lost in the faeces. Within the enterocyte, cholesteryl esters are rapidly reconstructed by the action of the enzyme acyl Coenzyme A cholesterol acyltransferase (ACAT) and incorporated, with triglyceride, into large lipid-rich chylomicron particles containing about 1% protein. These appear in abundance in the intestinal mucosal cells following a fatty meal and are transported through omental lacteals to the thoracic duct from which they ultimately spill into the bloodstream via the left subclavian vein. Their onward journey through the systemic circulation exposes them to lipoprotein lipase within adipose tissue and striated (skeletal and cardiac) muscle. This enzyme mobilises and delivers the energy-rich triglyceride fuel to these sites, leaving behind a potentially atherogenic cholesteryl ester-containing remnant, which optimally, is rapidly assimilated by the liver via a

specific and highly efficient receptor-mediated process. The half-life of the chylomicron in the circulation is therefore measured in minutes.

In the fasting state, responsibility for lipid fuel transport through the plasma becomes the province of very low density lipoprotein (VLDL), elaborated and secreted by the liver (Fig. 1). Again, muscle and adipocyte lipoprotein lipases extract the triglyceride from this particle, leaving behind another potentially atherogenic remnant called low density lipoprotein (LDL). Mirroring the fate of the chylomicron remnant, LDL is extracted from the plasma (albeit more slowly) by the specific action of highly efficient LDL receptors located primarily on hepatocytes. The expression of these receptors is modulated by regulatory pools of cholesterol within the liver cells. When intracellular cholesterol levels fall the receptors are activated, and draw sterol from the circulation into the liver where it is used, inter alia, for the production of more VLDL and for the generation of bile acids. The half-life of LDL in the circulation is in the order of 3–4 days.

From the earlier discussion it is apparent that corporeal cholesterol homeostasis is critically dependent on the interplay between two specific membrane transport processes. One, located on the brush border of the intestinal mucosa, is the gate keeper for cholesterol absorption while the other, on hepatocyte membranes, modulates the rate of cholesterol extraction from the plasma prior to its elimination into the faeces via the bile. Two articles, published in this issue of the Journal (references X and Y), demonstrate the effectiveness of concerted pharmacologic modulation of these processes in controlling the level of cholesterol in the bloodstream.

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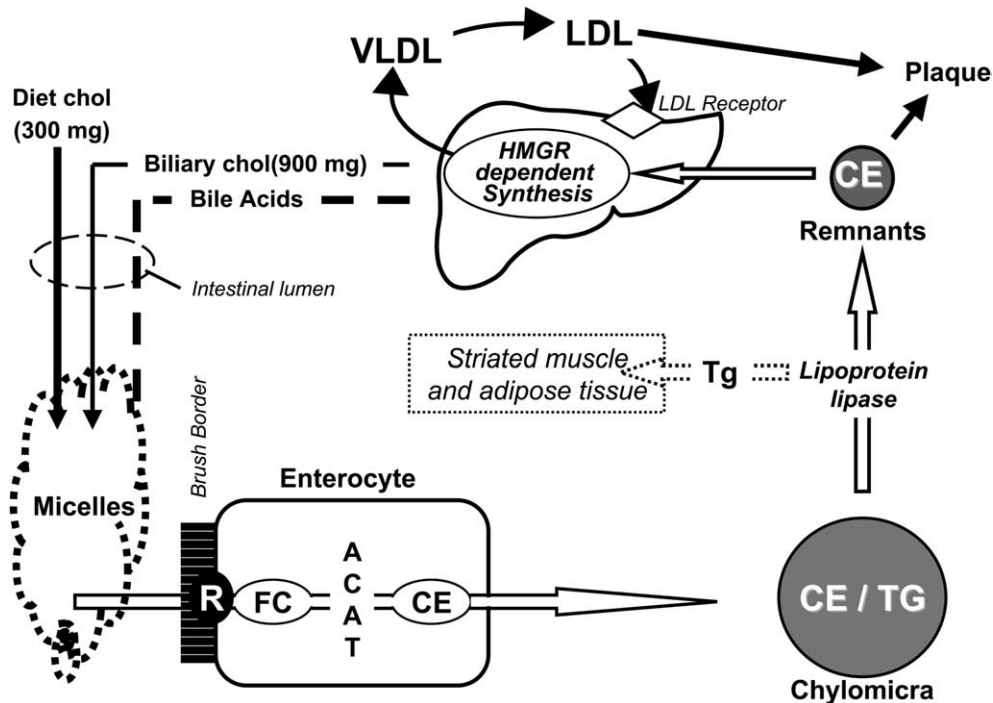


Fig. 1 Cholesterol homeostasis in man. Each day approximately 1200 mg of cholesterol and its esters transits the human intestine, 300 mg being derived from dietary sources and 900 mg from endogenous synthesis. Following deacylation by cholesterol esterase, the liberated cholesterol becomes incorporated into bile acid-rich micelles, which present it for absorption to the brush border of intestinal enterocytes. Within the enterocyte the free sterol is reesterified through the action of ACAT and subsequently packaged with dietary triglyceride into chylomicra, which ultimately are secreted into the bloodstream. There the triglyceride fuel is liberated into striated muscle and adipose tissue through the lipolytic action of lipoprotein lipase, leaving a cholesteryl ester risk 'remnant' particle which delivers the residual sterol to the liver. Chylomicron remnant particles may also be atherogenic and lead to arterial subintimal plaque formation. In the fasting state, triglyceride transport through the plasma falls upon VLDL whose lipolysis, analogous to that of the chylomicron, produces a cholesteryl ester risk remnant called LDL. This particle is cleared from the bloodstream by specific LDL receptors or hepatocyte membranes. When clearance is reduced, LDL accumulates in the plasma and becomes a potent progenitor of the atherosclerotic plaque. The atherogenicity of plasma lipoproteins is therefore heavily dependent on the rates of intestinal cholesterol absorption and of plasma LDL clearance into hepatocytes.

Modulation of cholesterol absorption: serendipity takes a hand

Despite intensive investigation, the specific membrane transport system responsible for the regulated assimilation of cholesterol across the intestinal mucosa has, until recently, remained elusive. Then, serendipity took a hand. Just over a decade ago, investigators at the Schering-Plough Research Institute in Kenilworth, NJ, went on the trail of an effective inhibitor of ACAT (see Fig. 1) and identified a new compound,² eventually called ezetimibe, which suppressed the intestinal absorption of cholesterol by more than 50% despite having no inhibitory effect on ACAT. Although its exact molecular target still remains to be defined, the pharmacologic profile of ezetimibe differs entirely from that of all other known lipid lowering agents and is uniquely dependent on its specific, high affinity binding to a structural protein on the brush

border of intestinal enterocytes. The efficacy of this binding process is clearly evident in the results of the study from Knopp et al. (ref X). Daily administration of 10 mg of ezetimibe to hypercholesterolaemic adults (with LDL cholesterol between 3.36 and 6.47 mmol/l) produced, over a 12 week treatment period, a mean 18% reduction in their circulating LDL levels, irrespective of race, age, gender or vascular risk factor profile; and this benefit, given the relative limitation of the small numbers of subjects studied ($n=827$), was not compromised by drug tolerability problems or altered metabolism of steroid hormones or fat soluble vitamins.

Interestingly, in addition to producing a significant and sustained decrease in plasma LDL cholesterol, there was also a measurable fall in the plasma concentration of apolipoprotein B (the main structural protein in VLDL and LDL) and in the circulating mass of triglyceride. The number of

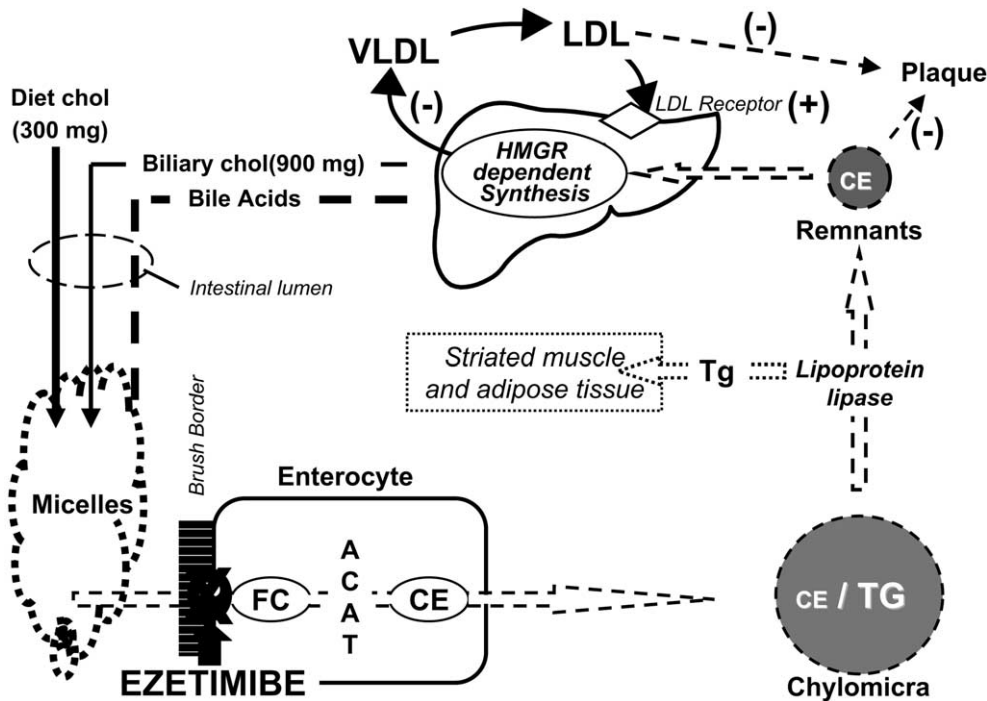


Fig. 2 Proposed actions of ezetimibe, a novel cholesterol absorption inhibitor. Ezetimibe is believed to act by inhibiting the specific transfer of cholesterol across the brush border of the intestinal enterocyte. As a consequence, less sterol is available for packaging into chylomicra and delivery to the liver. Hepatocyte regulatory cholesterol pools therefore become depleted, limiting the potential for cholesterol-enriched VLDL secretion and promoting the hepatic uptake of LDL from the circulation. This should lead to reduced atherogenicity of plasma lipoproteins due to: (a) fall in plasma LDL; and (b) diminished chylomicron cholesteryl ester transport through the plasma compartment.

VLDL and LDL particles in the bloodstream is therefore reduced by ezetimibe therapy, indicating that secretion of VLDL and uptake of LDL by the liver have both been changed (Fig. 2). The trigger for these actions presumably is the reduced flow of chylomicron cholesterol from the intestine to the liver. It is tempting to speculate that, by suppressing this transport process, the drug may also diminish the atherogenicity of circulating chylomicron remnant particles (Fig. 2). All of these proposals warrant further detailed investigation.

The upshot of Knopp's publication is therefore that 10 mg of ezetimibe per day lowers LDL cholesterol by 17–18% without the need for dose titration and in the apparent absence of any safety concerns. Those committed to the management of vascular risk factors can now access a new, well tolerated and unpretentious cholesterol lowering agent with a placebo-like safety profile and no Cytochrome P450 metabolism or likelihood of drug–drug interaction.³ Such an agent is well placed to manage cardiovascular risk for example, in elderly subjects who may present with mild hypercholesterolaemia and in whom polypharmacy makes the

safety of additional drug prescribing of paramount importance.^{4,5}

Tomorrow's world: dual therapy for hypercholesterolaemia with cholesterol absorption and synthesis inhibitors

Consideration of the intricacies of cholesterol homeostasis in man (Fig. 1) brings immediately into focus the wisdom of combining cholesterol absorption inhibition with suppression of endogenous cholesterol synthesis in the management of moderate to severe hypercholesterolaemia. The 3-hydroxy-3-methylglutaryl CoA reductase inhibitors or statins, have revolutionised cholesterol management in clinical practice and proven their effectiveness and safety in the prevention of vascular disease in adults of all ages.⁶ Nevertheless, clinical practice surveys have shown that doctors either through inexperience, over-caution, or a concern for thrift, fail to capitalise on the full potential of these agents. Consequently, not all patients who deserve treatment actually receive it, and those who do are often managed inadequately.^{7–9} Few clinicians are

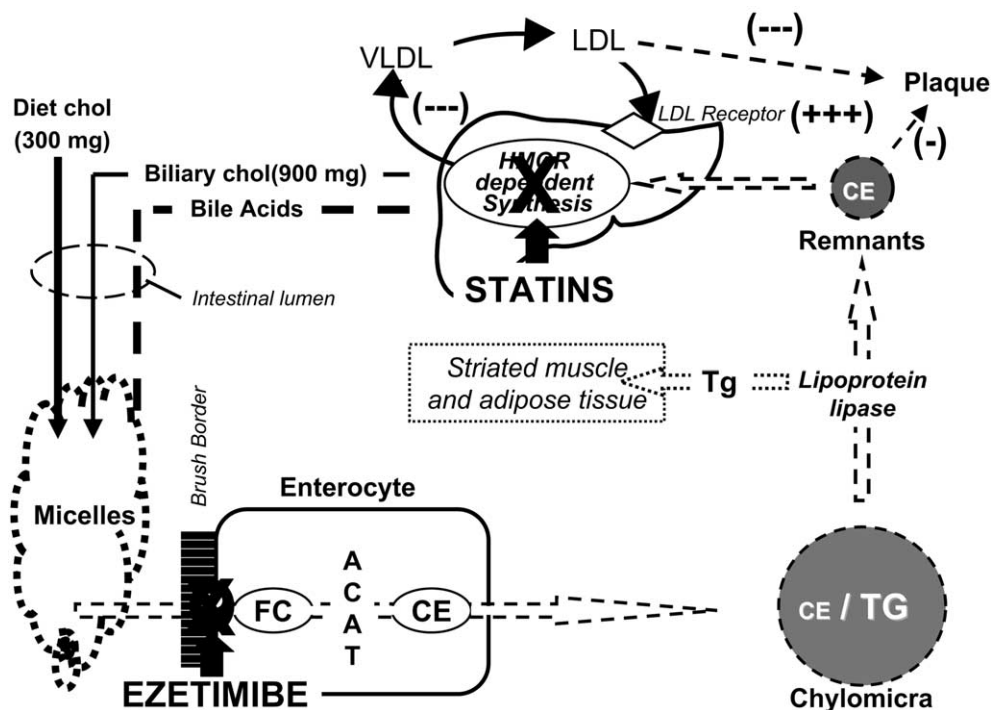


Fig. 3 Combination therapy with ezetimibe and statins. Supplementation of ezetimibe therapy with statins not only sets in motion the processes outlined in Fig. 2, but also inhibits hepatic overproduction of cholesterol which is triggered by reduced intestinal absorption of the sterol. Hepatic VLDL secretion is therefore doubly inhibited while receptor-mediated LDL clearance is further accelerated. The complementary actions of ezetimibe and low dose statin therapy therefore produce at least the same beneficial changes in the plasma lipoprotein profile as does the highest permissible dose of statin monotherapy.

prepared to prescribe statins to the maximum, even though flat-pricing strategies have made this an attractive option. While the exemplary statin safety record hardly justifies such caution, it is perhaps not surprising after the demise of cerivastatin on toxicity grounds 2 years ago.

In this issue of the Journal, Melani et al. (reference Y) have opened a new door to the management of moderate to severe primary hypercholesterolaemia by defining the benefits of coadministration of ezetimibe and low dose pravastatin. Their findings substantiate earlier data on the value of coprescription of ezetimibe with simvastatin,¹⁰ atorvastatin¹¹ or lovastatin.¹² Combining these treatments in all cases resulted in complementary and additive improvements in LDL cholesterol, HDL cholesterol, and triglyceride; and again these benefits are delivered without compromising safety. Ten milligrams of ezetimibe added to 10 mg of pravastatin lowered LDL cholesterol by a third (which is at least as effective as monotherapy with 40 mg of pravastatin), increased HDL cholesterol by 8% and reduced triglyceride by 23%, with an adverse event profile on par with that of the statin on its own. Not surprisingly, this combination brought more patients to European Guideline

goals¹³ than either drug administered alone and demonstrated convincingly the value of targeting simultaneously two distinct cholesterol regulatory mechanisms. (Fig. 3).

Although it is not fully proven that more aggressive reduction of LDL cholesterol, which brings greater number of patients to guideline targets, will lead to a commensurate further reduction in clinical events, it is likely that this will occur as LDL lowering therapy becomes more predictable and effective.¹⁴⁻¹⁶ It therefore makes good clinical sense to strive for safer and more effective LDL cholesterol lowering strategies in the expectation that clinical events will be further reduced as more patients are brought to guideline goal. Clinical outcome studies are urgently needed to confirm that coadministration of ezetimibe and statins delivers the tantalising promise that comes from the findings of Knopp et al.

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