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# Microsomal triglyceride transfer protein inhibition–friend or foe?

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**SUMMARY**

**This article sets out the clinical context of the research presented by Samaha *et al.* in an accompanying article in this issue. Hyperlipidemia is a common and important risk factor for cardiovascular disease. Current lipid-lowering therapies, particularly statins, lead to substantial decreases in cardiovascular disease morbidity and mortality, but use has been limited by safety or efficacy issues. The way has, therefore, been paved for the pharmaceutical development and clinical investigation of new lipid-lowering therapies. The clinical trial by Samaha *et al.* examines the safety and efficacy of microsomal triglyceride transfer protein inhibition for lowering lipids. Joy and Hegele explore the difficulties of translating microsomal triglyceride transfer protein inhibition into clinical practice because of the trade-off between efficacy and potential adverse effects. They also stress the need for outcome studies, rather than biochemical or surrogate studies, as the final arbiter for the clinical use of this new treatment.**

As evidence from clinical trials for a link between cardiovascular events and LDL-cholesterol levels is overwhelming, guidelines for cardiovascular disease (CVD) prevention emphasize reduction of this cholesterol subtype as a key preventative measure. Despite the impact of LDL-cholesterol-lowering therapies, primarily statins, on clinical cardiology, all agents have exhibited various limitations. Adverse effects, including myopathy and elevated transaminase levels, have been recorded in small but clinically important subgroups in trials involving patients with coronary artery disease or post-acute coronary syndrome.[1] Moreover, drug efficacy has been inadequate in some patients, particularly diabetics with or without CVD and patients with genetic dyslipidemias.[2] Indeed, up to 40% of high-risk and 80% of very-high-risk individuals do not achieve their LDL cholesterol goals (<2.6 mmol/l [<100 mg/dl] and <1.8 mmol/l [<70 mg/dl], respectively).[2] Tolerability issues have prompted the search for new LDL-cholesterol-lowering agents that have different mechanisms of action from that of statins. Problems with efficacy are being addressed by investigating the effect of administering statins in combination with other agents.

A concern regarding combination therapies lies with the paucity of cardiovascular outcome-related evidence for their effectiveness. Combination drugs such as Vytorin® (simvastatin plus ezetimibe, a cholesterol absorption inhibitor; Merck-Schering-Plough Pharmaceuticals, Kenilworth, NJ) reduce plasma LDL-cholesterol levels very effectively; unfortunately clinical trials have yielded minimal evidence of a reduction in hard cardiovascular end points. Whether equivalent LDL-cholesterol reduction by combination therapy will translate into CVD end point benefits comparable to those achieved by high-dose statin monotherapy remains unclear. The Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study[3] attempted to clarify this issue. In that trial, 720 patients with heterozygous familial hypercholesterolemia were randomly assigned simvastatin alone or simvastatin plus ezetimibe. Despite the fact that plasma LDL-cholesterol levels achieved with the combination therapy were much lower than those achieved by monotherapy, carotid intima–media thickness (cIMT) did not differ between the two treatments after 2 years.[4] Leaving aside concerns about delayed disclosure of the study results,[4] these findings raise the important clinical issue of whether LDL-cholesterol lowering by a nonstatin agent confers additional protection from CVD.

Apart from the small ENHANCE sample size, there are several reasons not to overturn the LDL hypothesis on the basis of its findings. First, this study evaluated a specialized, nonrepresentative patient demographic; individuals with heterozygous familial hypercholesterolemia make up only approximately 0.2% of the population. Second, some technical questions have arisen

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about the measurement of cIMT. The ultrasonographic device used in the ENHANCE trial was not the most up to date and could have had lower sensitivity and resolution than other instruments. These features are critical, as the treatment-related differences in cIMT are in the order of hundredths of a millimetre. Third, as most patients with familial hypercholesterolemia are not statin-naive, any study of cIMT reduction would leave little scope to measure treatment-related benefit. We feel, therefore, that the ENHANCE trial was an inconclusive study with some notable limitations. The definitive answer on whether the statin–ezetimibe combination provides CVD benefit awaits larger trials. Meanwhile, the search continues for new efficacious and well-tolerated drugs.

An alternative and compelling molecular target for LDL-cholesterol reduction is microsomal triglyceride transfer protein (MTP). This protein transfers triglyceride to nascent apolipoprotein B (apoB), directing the formation of chylomicrons and VLDL in enterocytes and hepatocytes, respectively.[5] As VLDL is the precursor to LDL, inhibiting MTP should reduce plasma LDL levels. The importance of MTP is seen in patients with the rare disorder abetalipoproteinemia, in which mutations in the *MTTP* gene produce nonfunctional MTP and a virtual absence of apoB-containing lipoproteins.[6,7] Although these patients have 'clean' arteries, they also have compromised intestinal fat absorption, accompanied by fatty engorgement of enterocytes and steatorrhea. Fat-soluble vitamin deficiency in individuals with abetalipoproteinemia leads to neuropathy, night blindness, coagulopathy and rickets or osteomalacia. Compromised triglyceride transfer to VLDL leads to hepatic steatosis that can progress to cirrhosis. Considering the severe consequences of absent MTP in abetalipoproteinemia, careful evaluation of pharmacological MTP inhibition is warranted.

Two human trials have evaluated the MTP inhibitor AEGR-733 (Aegerion Pharmaceuticals Inc., Bridgewater, NJ). In 2007, Cuchel and colleagues demonstrated a 50.9% decrease in LDL-cholesterol levels with a 1.0 mg/kg dose of AEGR-733 in six patients with homozygous familial hypercholesterolemia.[8] However, MTP inhibitor treatment was associated with increased serum transaminase levels and hepatic steatosis.[8–10] These adverse effects might be tolerable for patients with homozygous familial hypercholesterolemia when considered as a trade-off against their high CVD mortality risk and the effect that serial LDL apheresis—currently the mainstay treatment—can have on their quality of life. The introduction of MTP inhibition in patients with milder hypercholesterolemia and lower CVD risk, however, raises more-subtle questions.

Reporting in *Nature Clinical Practice Cardiovascular Medicine*, Samaha and colleagues study the safety and efficacy of low-dose AEGR-733 in a randomized, double-blind, placebo-controlled trial involving 85 patients with moderate hypercholesterolemia.[11] Patients followed a low-fat diet and were randomly assigned ezetimibe 10 mg daily plus placebo (ezetimibe alone), AEGR-733 at escalating doses of 5 mg, 7.5 mg, and 10 mg daily for 4 weeks each plus placebo (AEGR-733 alone), or ezetimibe 10 mg daily plus AEGR-733 using the same dose-titration regimen (combination therapy). After 12 weeks, ezetimibe alone reduced LDL-cholesterol levels by 21%, while AEGR-733 alone resulted in dose-dependent LDL-cholesterol reductions of 19–30%. The combination showed dose-dependent LDL-cholesterol reductions of 35–46% and significant decreases in levels of proatherogenic apoB and lipoprotein (a). AEGR-733 was, however, also associated with significant decreases in antiatherogenic HDL cholesterol and apolipoprotein A-I (apoA-I). Although the mechanisms underlying the effects of MTP inhibition on HDL and apoA-I remain to be elucidated, decreases in HDL cholesterol levels have also been observed in liver-specific $Mttp^{-/-}$ mice; this implies a critical but undefined role for MTP in the determination of HDL cholesterol levels.[9] Possible explanations include the fact that substrates for HDL assembly are partly derived from the lipolysis of triglyceride-rich lipoproteins;[12] ApoA-I production rate has been shown to directly correlate with LDL pool size.[13] Furthermore, in patients with abetalipoproteinemia, apoA-I production rate is decreased and apoA-I catabolic rate is increased, which produces low apoA-I levels.[14] In addition to concerns about HDL cholesterol reduction, 16% of patients receiving AEGR-733 discontinued treatment because of elevated serum transaminase levels. This study provides proof-of-concept for the efficacy of low-dose MTP inhibition but highlights several potential safety issues.

Samaha and colleagues did not examine hepatic fat; however, based on earlier results,

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**Competing interests**
The authors declared no competing interests.

some liver fat accumulation is likely.[8] The long-term risks of MTP inhibition could include hepatic steatosis, insulin resistance, cirrhosis, steatorrhea and fat-soluble vitamin deficiency. The difficulties of complying with a low-fat diet and possible steatorrhea mean that the discontinuation rate observed by Samaha and colleagues might underestimate rates seen with long-term clinical use. The trade-off between risks and benefits of MTP inhibition is probably more marginal for patients with milder hypercholesterolemia than for those with homozygous familial hypercholesterolemia, emphasizing the need to evaluate hard clinical outcomes for MTP inhibitors. As seen in the ENHANCE trial, safety and efficacy data from small studies of biochemical or imaging surrogate end points provide a 'way station' *en route* to the outcome study, which is the final arbiter of cumulative benefit-to-risk ratio and will determine whether MTP inhibition is friend or foe.

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