New therapeutic developments in lipidology

Since the previous CME on lipidology was published in 2003 there have been many new and exciting developments in lipid-modifying therapy.

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At the time of writing there are some new lipid-lowering drugs on the market, but attempts to influence atherosclerosis by new mechanisms have unfortunately generally been unsuccessful so far. This article briefly reviews selected developments that may be of interest to the non-specialist practitioner.

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Lipid-modifying medications

The statin family has grown with the addition of rosvastatin and pitavastatin. Rosuvastatin is a highly potent statin and its effect when compared milligram for milligram with other potent statins is approximately double that of atorvastatin and 4 times that of simvastatin. Rosuvastatin also raises HDL cholesterol (HDLC) more effectively than most other statins, but there is currently no evidence that this translates into improved clinical outcomes when compared with treatment with other statins. Rosuvastatin has a low potential to interact with other drugs. Many studies with rosuvastatin addressing important questions in lipidology are still ongoing and the results are eagerly awaited. Pitavastatin was developed in Japan and is currently not marketed in South Africa. Generic statins have significantly reduced the costs of lipid-modifying therapy and allowed many more patients access to this important therapy.

Ezetimibe is the first in the new class of cholesterol absorption inhibitors. It blocks cholesterol uptake in the intestine by inhibiting the action of Nieman-Pick C1-like 1 protein. Ezetimibe monotherapy (10 mg/day) lowers LDL cholesterol (LDLC) by about 20% with minor effects on plasma triglycerides (TG) and HDLC. In combination with statins its effects are additive, with no significant increase in adverse events. Ezetimibe is generally well tolerated and certainly much easier to take than cholestyramine, which was previously prescribed to patients intolerant of statins or not at their LDLC goal despite maximal statin therapy. The utility and safety of ezetimibe has been called into question recently, following the publication of 2 studies. In one study the addition of ezetimibe 10 mg to simvastatin 80 mg in patients with heterozygous familial hypercholesterolaemia (FH) did not translate into different carotid intima media (IMT) measurements compared with simvastatin alone over a 2-year period. This has raised concerns that ezetimibe may not improve cardiovascular outcomes despite lowering LDLC effectively. Most patients in the above study had previously received aggressive lipid-lowering therapy and did not have very thick IMT. In retrospect they were probably not the ideal cohort to study, as starting lipid-lowering therapy may have resulted in an early large decrease in IMT as lipid-rich plaques resolve.

In a study of aortic stenosis the patients randomised to ezetimibe + simvastatin had more cancer-related deaths than the placebo group. This finding has not been confirmed in a review of two ongoing studies and is probably a statistical aberration, but only data from even more subjects will dispel all concerns.

The results of outcome studies looking at hard clinical endpoints with ezetimibe are eagerly awaited. These studies will also provide more long-term safety data and assist in finally clarifying whether ezetimibe use is associated with an increased risk of cancer or not. In the authors’ opinion ezetimibe remains a valuable additional, but not a first-line, lipid-lowering agent. Statins have a well-established safety and efficacy record and should therefore always be the first choice when cardiovascular risk reduction is required. Ezetimibe should be used when the LDLC remains unacceptably high despite maximal statin dosages or when patients have intolerable side-effects from statins.

Phytosterols are naturally occurring compounds in plants that are structurally similar to cholesterol. Phytosterols (or their saturated forms known as phytostanols) can reduce serum cholesterol by interfering with micelle formation and cholesterol absorption. Incorporated into foods such as margarine (the only product available in South Africa) or dairy plant sterols (or stanols) lower the LDL cholesterol nearly as effectively. Most patients in the above study had previously received aggressive lipid-lowering therapy and did not have very thick IMT. In retrospect they were probably not the ideal cohort to study, as starting lipid-lowering therapy may have resulted in an early large decrease in IMT as lipid-rich plaques resolve.

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Squalene synthase acts more distally than HMGCoA-reductase (the target of statins) in the biosynthesis of cholesterol. Inhibition of squalene synthase decreases intracellular cholesterol and upregulates LDL receptors, resulting in decreased LDLc levels. Squalene synthase inhibitors held the theoretical promise of having fewer side-effects than statins, as they do not deplete the mevalonate pool and so should not interfere with isoprenoid synthesis. Lapakquistat was in an advanced state of development (phase III trials) when it was discontinued. Concerns about transaminits at high doses and commercial viability are the likely reasons for discontinuing development.

Homozogous FH is a particular problem in South Africa with its founder populations. Currently available treatment is not sufficiently effective and premature heart disease remains the norm. LDLc apheresis (or plasmapheresis) is effective but available to a few patients only. New exciting treatments on the horizon are ApoB antisense oligonucleotides (mipomersen) that inhibit apoB100 production in the liver and mitochondrial triglyceride transfer protein (MTP) inhibitors that inhibit hepatic and intestinal assembly of lipoproteins. Both agents are currently undergoing clinical trials and, if the initial promise is fulfilled, will be significant therapeutic advances.

Nicotinic acid (niacin) in high doses is an effective lipid-modifying drug. It lowers TG, LDLC and Lp(a) while also raising HDLC effectively. Nicotinic acid is also supported by favourable outcome data and its use is theoretically very attractive as it modifies most aspects of the lipid profile left untreated by statins.3 Despite all these positives nicotinic acid has never gained widespread acceptance. This is mainly because of the nearly universal side-effects of flushing and pruritus. The dosage form currently available in South Africa (immediate release 100 mg tablets) also imposes a large pill burden as effective doses are around 1.5 - 3.0 g/d. Sustained release nicotinic acid was associated with fulminant hepatitis in a few cases. The newer extended release forms of nicotinic acid (not available in South Africa) have not been reported to cause hepatitis and reduce the pill burden and flushing. The mechanism of the flush has been elucidated recently: nicotinic acid releases prostaglandin D2 and E2 from macrophages and Langerhans cells in the skin and this stimulates prostaglandin receptors, leading to vasodilatation. Agents that block the prostaglandin D2 subtype 1 receptor have been developed and are undergoing clinical trials (laropiprant) with early results indicating good safety and flush reduction but not abolition.4

The glucose raising effect of nicotinic acid has been a major concern and led to recommendations that the drug should be avoided in diabetes. Ironically, diabetic dyslipidaemia, with its low HDLC and raised TG, could potentially be greatly improved by nicotinic acid. More recently several studies have shown that nicotinic acid can be used in diabetics with only minor loss of glycaemic control that is easily treatable.7 Currently several large trials are re-examining nicotinic acid and there may be a resurgence in the use of this agent.

Low HDLC is an important cardiovascular risk factor, but the effect of pharmaceutical HDLC modification has been much less studied than that of LDLc lowering, mainly because most available lipid-lowering agents (except nicotinic acid and fibrates in hypertriglyceridaemia) have little influence on HDLC. The available data suggest that fibrates and nicotinic acid are beneficial in the right circumstances.5 Raising HDLC substantially has therefore become a very attractive new target for pharmaceutical companies. Inhibition of cholesterol ester transfer protein (CETP) raises HDLC very significantly, by preventing the transfer of cholesterol from HDL to triglyceride-rich lipoproteins. Several CETP-inhibitors have been developed, but torcetrapib, which was the furthest down the development pathway, was recently withdrawn when it was found that patients treated with this agent (in conjunction with atorvastatin) had a higher rate of cardiovascular events than those in the atorvastatin-only group.8 Subsequently there has been much debate whether the result reflects ‘dysfunctional HDL’ and would therefore be seen with all CETP-inhibitors or whether torcetrapib had an ‘off-target’ effect. Torcetrapib does raise BP and aldosterone levels somewhat and this may explain the increased mortality. Once again the dangers of relying on surrogate markers (high HDLC in this case) and the importance of clinical outcome studies have been demonstrated.

Other experimental approaches at HDL modification include infusions of artificial ‘HDL mimetics’ or infusion of recombinant Apo A1 Milano. The latter is a mutated variant of ApoA1 (the main structural protein of HDL) that is associated with low levels of HDLC but is atheroprotective. HDL delipidation is also being investigated as a possible therapeutic alternative. Patients undergo apheresis, HDL is isolated and chemically ‘stripped’ of the cholesterol it carries. The lipid-poor HDL is re-infused to the liver (reverse transport). This is an interesting concept, but invasive and likely to be very costly.

Therapies directed at other mechanisms of atherosclerosis

Probucol has antioxidant and anti-inflammatory properties. It was used fairly commonly as a lipid-modifying medication prior to the advent of statins, but is now hardly prescribed at all. Probucol has very limited effects on LDLc and the outcome data are mainly limited to small studies looking at angiographic restenosis. Probucol can also prolong the QT interval. Succinobucol is the monosuccinic acid ester of probucol. It does not prolong the QT interval and is a more potent antioxidant. Recently the results of a large outcome study have been reported in which succinobucol or placebo was prescribed to patients with the acute coronary syndrome in addition to standard treatment.9 The primary endpoint (CVD death, cardiac arrest, MI, stroke, unstable angina or coronary revascularisation) did not show any difference. The secondary endpoint that excluded unstable angina and revascularisation was significantly different in favour of active treatment. Succinobucol

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also reduced the rate of new diabetes significantly. On the negative side, there were more cases of new atrial fibrillation with active treatment, the bleeding risk was increased, there was a slight increase in admissions for heart failure and both LDLC and systolic blood pressure were modestly elevated. As with torcetrapib, it is possible that small ‘off-target’ effects that negatively affect cardiovascular risk abrogated the potential beneficial effect of the drug.

Acyl-coenzyme A: cholesterol acyltransferase (ACAT) is an intracellular enzyme that catalyses the formation of cholesterol esters from cholesterol and fatty acyl-coenzyme A. Inhibition of ACAT significantly lowers plasma cholesterol in animal models and may potentially be anti-atherosclerotic by inhibiting the formation of cholesterol ester in macrophages, which results in their transformation to foam cells. However, in a study assessing the effects of the ACAT-inhibitor pactimibe on coronary atherosclerosis using intravascular ultrasound (IVUS), pactimibe had a proatherogenic effect. The likely explanation for this is that macrophages were probably not able to export the free cholesterol, with subsequent toxicity and apoptosis.

Lipoprotein-associated phospholipase A2 (LP-PLA2) is an enzyme that is mainly found bound to apoB-containing lipoproteins. It is also found in high concentrations in the necrotic core of the atherosclerotic plaque. Its action promotes inflammation and may be cytotoxic. High levels of LP-PLA2 are associated with increased cardiovascular risk and suggestions have been made to incorporate LP-PLA2 measurement into cardiovascular risk assessment algorithms. More recently an inhibitor of LP-PLA2 (darapladib) has shown promising early results in an IVUS study where it prevented expansion of the necrotic core of coronary plaques when compared with placebo.

**Conclusion**

The last few years have seen a few new lipid-lowering medications successfully enter the market. At the same time several new classes of drugs that affect lipoprotein metabolism have shown adverse effects and were discontinued.

We are now able to lower LDLC adequately and safely in the majority of patients. The treatment of patients with severe genetic dyslipidaemias and statin intolerance still remains challenging. There is, however, an increasing realisation that even with very intensive LDLC lowering a significant ‘residual risk’ remains and many events go unprevented. This has led to the renewed interest in HDL modification and therapies that address other atherosclerotic mechanisms. Although some of these therapies are promising, none has advanced sufficiently to be marketed. Once again the importance of ‘getting the basics right’ in the prevention of atherosclerosis needs to be stressed, rather than trying to deal with the consequences. At an individual level we need to promote a healthy lifestyle to our patients from early on, while at a societal level we should strive to create conditions (e.g. food labelling, tobacco legislation) that make it easier to make healthy lifestyle choices.

**References**