New approaches to residual atherosclerosis risk

Professor Derick Raal interprets new evidence

Learning objectives

You will learn:

• The role of LDL-cholesterol in the timeline of atherosclerosis development
• Current approaches to targeting lipids, the coagulation cascade and the inflammatory process - all of which are key to eliminating/reducing residual atherosclerotic risk
• The patients for whom PCSK9 inhibitor therapy should be considered
• Considerations of managing inflammation and thrombotic factors to reduce residual risk.

Introduction

In this review, Professor Derick Raal addresses current lipid management, the availability of new agents and the scientific evidence that influences modern clinical approaches to the prevention of cardiovascular morbidity and mortality.

Pivotal to this discussion is, firstly, the understanding of the lengthy timeline of atherosclerosis development (Figure 1) and the role of the major risk factor – low-density lipoprotein (LDL)-cholesterol. “The pivotal role of LDL-cholesterol has been shown in many studies, including the INTERHEART study in which South Africa participated, emphasising that raised LDL-cholesterol contributes the most risk to an individual’s likelihood of developing acute vascular injury.”

Figure 1. Atherosclerosis timeline

Growth mainly by lipid accumulation
Smooth muscle and collagen
Thrombosis, haematoma

Endothelial dysfunction

From first decade

From third decade

From fourth decade
Value of LDL-cholesterol reduction

In a meta-analysis done by the Cholesterol Treatment Trialists (CTT) Collaboration, which included 174 000 patients treated in 22 trials with statin therapy, it was shown that for every 1 mmol/l reduction in LDL-cholesterol, there was a 21-24% reduction in major coronary artery disease (CAD) or vascular events, and a 12% reduction in overall mortality.

“But statins do not fix everything despite being remarkable drugs,” Professor Raal noted. This reality has led to the development of the clinical concept of residual risk (Figure 2). To eliminate residual risk, three clinical targets need to be addressed – the lipids, the coagulation cascade and the inflammatory process. Managing these risk factors offers real potential to reduce remaining atherosclerotic risk.

Figure 2. Residual risk

Clinical target 1: Reducing residual risk by targeting lipids and overall dyslipidaemia

Combination therapy

In the IMPROVE-IT trial, adding ezetimibe to simvastatin provided further benefit and a significant reduction in cardiovascular death, myocardial infarction (MI), hospitalisation for unstable angina and the need for revascularisation.

If ezetimibe is added to even more powerful statins, this combination can reduce LDL-cholesterol by between 60 and 70% (Figure 3).
Alirocumab was subsequently launched as a 75mg and 150mg single injection, which maintains cholesterol-lowering for approximately two weeks before returning slowly to baseline.

“This is not true for all patients of course; in molecularly diagnosed familial hypercholesterolaemia (FH), as shown in the SAFEHEART study, less than 10% of patients reached the LDL-cholesterol target for very high-risk individuals of 1.8mmol/l on this combination therapy after five years.”

PCS99 inhibitors

The proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors have progressed rapidly from discovery to everyday clinical practice; they are available globally and will hopefully soon be available in South Africa too. “There are currently two monoclonal antibodies to PCSK9 that are available to treat dyslipidaemia not responsive to current therapies; they are alirocumab and evolocumab,” Professor Raal said.

Mechanism of action of PCS99 inhibitors

The PCSK9 inhibitors essentially ‘mop-up’ the PCSK9 produced by the liver and this allows LDL receptors to be recycled and not destroyed in a lysosome-induced process (Figure 4).6

Figure 3. Reduction in LDL-cholesterol with combination lipid-lowering therapy

Figure 4. The role of PCSK9 inhibition6
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In the initial proof of concept study of PCSK9 inhibition, a single injection of alirocumab in healthy volunteers produced a 60% reduction in LDL-cholesterol levels (Figure 5). Alirocumab was subsequently launched as a 75mg and 150mg single injection, which maintains cholesterol-lowering for approximately two weeks before returning slowly to baseline.

**Why do we need PCSK9 inhibitors?**

**PCSK9 inhibitors in heterozygous FH**

Patients with FH are real-situation ‘proof of concept’ of the effectiveness of PCSK9 inhibitors, as heterozygous FH (HeFH) patients have about 50% of normal LDL receptors and homozygous patients have very few receptors. These agents are very effective in these patients and the ODYSSEY FH I and FH II clinical trials of HeFH patients highlight the LDL-cholesterol lowering ability of these agents (in this case, alirocumab) (Figure 6).  

In this phase III study, the patients referred to as the FH I group (n=486) included patients from Europe, USA and South Africa; while the smaller FH II group (n=249) were from Europe only. Homozygous FH patients were excluded from the study and HeFH patients in this study were included based on either genotyping or clinical criteria. All patients were receiving stable high-dose statin therapy (rosuvastatin 20-40mg, atorvastatin 40-80mg or simvastatin 80mg), with added ezetimibe in about 50% of patients. Despite this, those with prior cardiovascular events were not reaching their target of 1.8mmol/l and those at high risk were not reaching the 2.6mmol/l target.

On being treated with alirocumab 75mg or 150mg, if still not at target, 60% of patients in the FH I group and 68% of patients in FH II reached their LDL-cholesterol of target of <1.8mmol/l by week 24. “This was the first time these low levels of LDL-cholesterol were achieved in this group of heterozygous FH patients,” Professor Raal noted.
The PCSK9 inhibitors are clearly remarkable drugs that as subcutaneous injections can ‘mop up’ PCSK9 by some 60% and reduce cardiovascular events.

The turning point of plaque regression with PCSK9 inhibitors

Among the many phase II clinical trials, an IVUS study of a PCSK9 inhibitor provides important insights.9 In these 1 000 patients, including patients from South Africa, evolocumab therapy (420mg for 76 weeks) plus statins showed significant plaque regression in a greater percentage of patients (64% versus 47% on placebo), as measured by the percentage of atheroma volume and total atheroma volume. “The mean LDL-cholesterol value achieved was 0.95mmol/l and the lipid-level turning point for regression was in the region of 1.8mmol/l,” Professor Raal noted.

Cardiovascular disease outcome trials with PCSK9 inhibitors

Two large cardiovascular outcome trials have been published, involving some 43 000 patients and showing significant reductions in major adverse cardiovascular events (MACE).10,11

In the ODYSSEY Outcome trial, over a three-year period, alirocumab therapy resulted in an absolute risk reduction (ARR) of 1.8% in these patients following their acute coronary event (Figure 7). “The PCSK9 inhibitors are clearly remarkable drugs that as subcutaneous injections can ‘mop up’ PCSK9 by some 60% and reduce cardiovascular events,” noted Professor Raal.
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In which patients should clinicians consider prescribing PCSK9 inhibitors?

The use of these agents can and should be considered in the following groups of patients:

- Severe HeFH or non-FH patients who have not responded adequately to a statin plus ezetimibe
- The 70-95% of homozygous FH patients with defective LDL-receptor activity
- Patients with progressive CAD despite high-dose statin ± ezetimibe
- Patients unable to tolerate statins or effective doses of statins.

Dealing with residual risk when LDL-cholesterol levels are at target (≤2.5mmol/l)

There is considerable interest in addressing inflammation in order to reduce cardiovascular events – reducing the highly sensitive-CRP (hsCRP) levels. A recent study using a new agent, canakinumab\(^1\) (a human monoclonal antibody that inhibits interleukin-1β – a mediator of inflammation), has shown that this agent not only reduced hsCRP levels but also reduced the risk of MACE in post-MI patients with chronic kidney disease. Benefit was achieved in treated patients whose hsCRP levels reached <2mg/l (about 15% RRR). An observed clinical consequence of this approach is a slight increase in infections. “Reducing inflammation is currently an interesting approach, but further evidence is required before recommendations can be made.”

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* Figure 7. Primary efficacy endpoint: MACE

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* Based on cumulative incidence
Dealing with the thrombotic factors to reduce residual risk

There is a link between thrombotic risk and lipid risk represented by Lp(a), which has both atherogenic and prothrombotic effects. Lp(a) has been shown to be an independent risk factor for atherosclerotic cardiovascular disease, but to date, available agents do not lower Lp(a) sufficiently to derive benefit. A new agent, an Apo(a) antisense oligonucleotide, is currently in development and has achieved substantial reduction in Lp(a) in phase I and II trials.\textsuperscript{13}

The combination of aspirin and rivaroxaban in secondary prevention is useful and reduces cardiovascular events by approximately 25\%.

“The price of antithrombotic therapy is always increased bleeding, and individualisation of this approach is required in at-risk patients.”

Conclusions

In conclusion, Professor Raal pointed out that in his view, the most important approach is to deal with causative lipogenic risk, focusing on LDL-cholesterol; thereafter inflammation and other factors such as thrombotic disturbances will normalise.

Key learnings

- The addition of ezetamibe to a statin can reduce cholesterol by 60-70%.
- PCSK9 inhibitors are effective in treating dyslipidaemia in those not responsive to current therapies and HeFH patients, with trial data showing a reduction in cardiovascular events.
- Reducing hsCRP levels using canakinumab reduces risk of MACE in post-MI patients with chronic kidney disease.
- There is a link between thrombotic risk and lipid risk represented by Lp(a), which has both atherogenic and prothrombotic effects.

References

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