Cardiovascular disease (CVD) is the leading cause of death worldwide. More than 18 million deaths per year, or 2 in every 5, are consequent to CVD. In developed, and especially in developing countries this figure is expected to rise, so that, by 2020, ischaemic heart disease and cerebrovascular events will be the number one and number two causes of death, respectively.

The primary risk factors for CVD are hypertension, smoking, obesity, diabetes and dyslipidaemia. Of these hypercholesterolemia, and importantly raised low density lipoprotein (LDL) cholesterol, is the most important. In experimental models, it is virtually impossible to cause atherosclerosis in the absence of hypercholesterolemia (raised LDL cholesterol or remnants). The continuous and graded association between plasma cholesterol and coronary heart disease (CHD) has been clearly demonstrated in observational and prospective controlled clinical studies. For example, in the Multiple Risk Factor Intervention Trial (MR FIT) the overall 6-year risk of CHD in subjects with total plasma cholesterol ≥6.5mmol/l was approximately 4 times greater than those with cholesterol ≤4.7mmol/l. In younger subjects aged between 35 and 40 years, the risk was increased by a factor of 8. Conversely in observational studies, a decrease in plasma cholesterol of 0.6mmol/l (approximately 10%) was associated with a time-related decreased incidence of ischaemic heart disease (IHD) of more than 50% in men at age 40 years and approximately 30-40% in those up to age 65.
The INTERHEART study was a standardised case-control study of acute myocardial infarction in 52 countries that compared cardiovascular risk factors in 15,152 case individuals to 14,820 matched controls. Nine risk factors accounted for 90% of population attributable risk (PAR) for coronary artery disease (CAD) (Table 1). Of these, raised ApoB/ApoA1, which indicates the ratio of LDL to high density lipoprotein (HDL) cholesterol, contributed the greatest risk.

<table>
<thead>
<tr>
<th>Table 1. Risk factors for coronary artery disease (the INTERHEART study)</th>
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<tbody>
<tr>
<td><strong>Adverse risk factors</strong></td>
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<tr>
<td>ApoB/ApoA1 ratio</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Psychosocial factors</td>
</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Abdominal obesity</td>
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<tr>
<td><strong>Protective factors</strong></td>
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<tr>
<td>Regular alcohol consumption</td>
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<tr>
<td>Daily consumption of fruit and vegetables</td>
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<tr>
<td>Regular physical activity</td>
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</tbody>
</table>

Lipid lowering with statins

The early statin trials showed that reducing cholesterol by approximately 30% would reduce the risk of CAD events by approximately 30% across a broad range of patients with and without excess risk for CAD (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Early statin trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>Primary prevention</td>
</tr>
<tr>
<td>AFCAPS/TEXCAPS</td>
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<tr>
<td>WOSCOPS</td>
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<tr>
<td>CARE</td>
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<tr>
<td>Secondary prevention</td>
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<tr>
<td>LIPID</td>
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<tr>
<td>4S</td>
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<tr>
<td>Mixed</td>
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</tbody>
</table>

CV: cardiovascular; CHD: coronary heart disease; MI: myocardial infarction; HDL: high density lipoprotein cholesterol; ACS: acute coronary syndrome; CAD: coronary artery disease

It is estimated that 80 to 100 million people worldwide are currently on statin therapy, and undoubtedly millions of lives have been saved by this class of lipid-lowering molecules since their introduction almost 4 decades ago. In 2001, statins were declared ‘the new aspirin’, with some asking why everybody should not be on a statin!

In a prospective meta-analysis of data from 90,056 individuals in 14 randomised trials of statins it was shown that for every 1 mmol/L reduction in LDL on statin therapy there was a 12% reduction in overall mortality, 29% reduction in coronary mortality, 23% reduction in coronary events (myocardial infarction or coronary death), 24% reduction need for coronary revascularisation and 17% reduction in fatal or nonfatal stroke. Overall, each 1 mmol/L reduction in LDL was associated with 21% reduction in any such major cardiovascular event, equivalent to 48 fewer events per 1000 individuals.
with pre-existing CHD at baseline and 25 fewer per 1000 with no history of CVD.\textsuperscript{10}

Within the range of cholesterol levels represented in 26 statin studies published by 2009, there was no evidence of any threshold beyond which these risk reductions were diminished. Meta-analysis found that the size of the proportional reduction in major vascular events was directly proportional to the absolute LDL reduction achieved. Benefit continued to increase with more intensive statin therapy, even if LDL cholesterol was already lower than 2mmol/L, suggesting that more intensive reduction of LDL cholesterol by 2-3mmol/L would reduce CV risk by around 40-50%. Furthermore, in general, there was no evidence of any significant increased health risks associated with intensive statin treatment or main-tenance of LDL levels in the lower range. In light of these results, it was concluded that the primary goal for patients at high risk of occlusive vascular events should be to achieve the largest LDL cholesterol reduction possible.\textsuperscript{11}

Nevertheless, especially in those at high risk, despite significantly reducing the risk, statins alone cannot eliminate the risk of CV events and there are limits to the levels of LDL that are achievable with statin monotherapy, even with higher doses. As a general rule, each doubling of statin dose only results in a further 6% reduction in cholesterol.

Augmenting statin-induced lipid-lowering with ezetimibe

Serum cholesterol levels are dependent on the interaction between cholesterol synthesis in the liver and absorption of cholesterol from the intestinal lumen, occurring primarily in the duodenum and proximal jejunum. Approximately 25% of the cholesterol entering the intestinal lumen is derived from dietary lipid intake, whereas the remaining 75% is derived from biliary cholesterol excretion from the liver.

Statin therapy reduces plasma LDL by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the rate limiting step in hepatic cholesterol synthesis. A direct result of reduced hepatic cholesterol synthesis is increased expression of LDL receptors on hepatocytes, leading to increased removal of LDL from the plasma. Conversely, this is also accompanied by a compensatory increase in absorption of cholesterol from the intestine, which may also downregulate hepatic cholesterol reduction.

Uptake of cholesterol from the intestinal lumen into the enterocyte is facilitated by transport proteins. These include the Niemann-Pick C1-like protein (NPC1L1), which works in conjunction with the adaptor protein 2 (AP2) complex and clarithrin. Cholesterol from the intestinal lumen incorporates into the enterocyte cell membrane and binds to the sterol-sensing domain of NPC1L1. This cholesterol/NPC1L1 complex is then internalised into the cell from where it can be transferred into the plasma. NPC1L1 expression on enterocytes is increased when intracellular cholesterol levels are low. Ezetimibe is a selective inhibitor of NPC1L1 in the jejunal brush border and can thereby help to reduce serum cholesterol levels by reducing intestinal absorption.\textsuperscript{12} Adding ezetimibe to statin therapy can achieve a further 18%-24% reduction in plasma LDL cholesterol.

The incremental reduction in LDL is also associated with an incremental improvement in cardiovascular outcomes. In the IMPROVE-IT study, over a mean duration of 6 years follow-up in patients who had been hospitalised following acute coronary syndrome, combination treatment with simvastatin plus ezetimibe was associated with a mean time-weighted average LDL cholesterol level of 1.4mmol/l in comparison with 1.8mmol/l with simvastatin alone.\textsuperscript{13} The primary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, unstable angina requiring rehospitalisation, coronary revascularization, or nonfatal stroke) was reduced by a small, but statistically significant 2% (event rate 32.7% vs. 34.7%; hazard ratio [HR] 0.936; 95%CI 0.89-0.99; \(p = 0.016\); number needed to treat [NNT] = 50). Benefits were similar regardless of lower or higher baseline LDL levels. When plotted against LDL-lowering vs CV outcomes data from other statin studies, the outcomes from IMPROVE-IT falls on a trajectory consistent with what would be
expected from the further reduction in LDL cholesterol (Fig. 1).

Although statins have been shown to possess anti-inflammatory, immunomodulatory, antithrombotic, vascular and other non-LDL-C-lowering effects, it is uncertain what role these play in cardioprotection. The results from IMPROVE-IT are supportive of previous observations that reductions in cardiovascular risk are directly associated with LDL lowering, regardless of whether statin or non-statin lipid-lowering therapy has been used, and, where statins have been prescribed, the pleiotropic effects do not appear to contribute any additional benefit.13-15

What proportion of patients achieve LDL goals?

In theory, with combination therapy, it should be possible to reduce LDL by up to, or even beyond 70%. However, this is not what is seen either in clinical studies or in practice. In statin trials, more than 40% of patients assigned to high-dose therapy failed to achieve LDL levels lower than 1.8mmol/l.16 In patients with hereditary familial hypercholesterolemia (FH) the results are even worse. An analysis of 1249 patients with FH showed that only 21% attained LDL <2.5mmol/L. Among those not achieving LDL goal, 27% were on combination therapy of maximum statin dose plus ezetimibe.17

New cholesterol lowering treatments: PCSK9 inhibitors

Pro-protein convertase subtilisin/kexin 9 (PCSK9) is a serine protease that is highly expressed in the liver and intestine and which regulates degradation of the LDL receptor. Expression of PCSK9 reduces the clearance of LDL cholesterol, while inhibition increases activity of the LDL receptor, which in turn increases clearance of LDL. Although statins upregulate the LDL receptor, they also increase the activity of PSCK9, which may attenuate cholesterol clearance. Therefore, PCSK9 inhibition is an attractive target to enhance the LDL-lowering efficacy of statin treatment and various PCSK9 inhibitors are currently under development.18,19

The RUTHERFORD-2 study was a multicenter, double-blind, placebo-controlled trial in which 331 patients with heterozygous FH were randomised to the PCSK9 inhibitor, evolocumab, or placebo administered either every 2 weeks or

Figure 1. Plot of the IMPROVE-IT trial data and statin trials for change in low-density lipoprotein (LDL) cholesterol versus clinical benefit

Statin studies: a: GISSI Prevenzione; b: ALLHAT-LLT; c: ALERT; d: LIPS; e: AFCAPS/TexCAPS; f: CARE; g: LIPID; h: PROSPER; i: ASCOT-LLA; j: WOSCOPS; k: Post CABG; l: CARDS; m: HPS; n: 4S. Size of the box is proportional to the number of endpoints in the study.

At baseline, all patients were on stable lipid-lowering therapy and had a fasting LDL cholesterol concentration $\geq 2.6$mmol/l. After 12 weeks, LDL remained essentially unchanged in the placebo groups, whereas there were considerable reductions in the evolocumab groups of 59% with 2-weekly administration and 61% with monthly administration (Fig. 2). By week 12, 68% in the evolocumab 2-weekly group and 63% in the monthly group achieved LDL cholesterol goal of $<1.8$mmol/l, compared with only 2% in the placebo groups. The response to evolocumab was unrelated to the underlying genetic mutation. Treatment was well tolerated with no serious treatment-related adverse events.

Can we go too low?

LDL receptors efficiently maintain intracellular cholesterol levels. The LDL receptor has very high affinity for its ligand, such that LDL uptake would be sustained even at very low plasma LDL concentrations of around 0.25mmol/L. In some subjects with hypobetalipoproteinaemia or loss-of-function PCSK9 mutations LDL levels are lower than 0.4 mmol/l throughout life, without obvious detriment to normal growth and development or longevity. Furthermore, as mentioned earlier in this article, in clinical studies, lowering LDL cholesterol to below 1.8mmol/l was not only safe, but was also associated with proportional reductions in cardiovascular morbidity and mortality.

In two open-label, randomised trials enrolling 4465 patients who had completed a phase 2 or 3 trial of evolocumab, in comparison to standard therapy alone, a 61% reduction in LDL cholesterol was associated with 53% reduction in rate of cardiovascular events at 1 year. The absolute rates were 2.18% in the standard therapy group and 0.95% in the evolocumab group (HR 0.47; 95%CI 0.28-0.78; $p = 0.003$). The incidence of adverse events was similar in the two groups and was unrelated to LDL cholesterol levels achieved.

Similar results have been observed with another PCSK9 inhibitor, alirocumab. A total of 2341 patients at high risk for cardiovascular events who had LDL cholesterol $\geq 1.8$mmol/l and who were on maximum doses of statins with or without other lipid-lowering therapy were randomised to alirocumab or placebo administered every 2 weeks. After 78 weeks, in the post hoc safety analysis, a 62% reduction in LDL in the alirocumab group was associated with 48% reduction in major cardiovascular events. Absolute rates were 1.7% and 3.3% in the alirocumab and placebo groups, respectively (HR 0.52; 95%CI 0.31-0.90; $p = 0.02$).
Conclusions

Although the optimal treatment target for LDL-lowering therapy is unknown, results from clinical studies of both statin and non-statin lipid-lowering treatments indicate that targets should be aggressive and that lower is better if one is to prevent CV events. With current knowledge, a treatment target of at least 1.8mmol/l, and possibly lower, is recommended. Achieving these ambitious targets is likely to require combination therapy. Early studies suggest that PCSK9 inhibitors will be a useful addition to first-line treatment with statins. In addition to aggressive lowering, therapy needs to be administered earlier and proactively. This is especially true for patients with FH who reach their threshold for CHD early in life at age 20-40 years and after which prophylactic therapy is likely to have limited benefit.

Review written by Dr David Webb for deNovo Medica.

References


15. LaRosa JC. At the heart of the statin benefit. J Am Coll Cardiol 2005; 46(10): 1863.