Clinical Medicine 2013, Vol 13, No 6: 618–20

Lipid management: maximising reduction of cardiac risk

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Introduction

Cardiovascular disease (CVD), particularly coronary artery disease (CAD), is the leading cause of death and disability in the western world and contributes substantially to healthcare budgets.[1] Lipid modification therapies (LMTs) have revolutionised contemporary approaches to primary and secondary prevention of CVD.

What should we measure?

Total cholesterol has a log linear relationship with CAD with no apparent threshold below which risk diminishes. However, total cholesterol incorporates both the atherogenic components–low-density lipoprotein (LDL), intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL) cholesterol (collectively known as non-high-density lipoprotein cholesterol [non-HDL-C] – and the protective factor high-density lipoprotein (HDL) and its measure HDL-C. Therefore, measurements of either apolipoproteins (apo) (one apo B per LDL, IDL and VLDL particle, or apo A as a measure of the number of HDL particles) or cholesterol content (non-HDL-C and HDL-C) are more informative. Collective evidence demonstrates that CAD risk per 1 standard deviation (SD) is identical for apo B and non-HDL-C and 30% stronger than for LDL-C; apo A and HDL-C offer similar magnitudes of protection.[2] As measurement of LDL-C requires a fasting sample, is calculated (TC-HDL-C – (TG/5), where TC-HDL-C is total cholesterol HDL-C and TG is triglyceride) rather than directly measured and incompletely captures atherogenic risk, non-fasting non-HDL-C (TC-HDL-C) is the preferred measure of atherogenic risk.[3] Both non-HDL-C and apo B can be obtained from non-fasting samples, but the latter is more expensive, less available and not standardised. The European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines recommend non-HDL-C as a secondary target when HDL-C is low or TG is high, or both. Several statin trials now suggest that non-HDL-C is a better marker of on-treatment risk than LDL-C.[4] Finally, among subjects with a family history of premature CVD or elevation in lipoprotein a (Lp(a)), the ESC/EAS recommend measuring Lp(a) levels, with levels of >50 mg/dl identifying high-risk groups.

Lifestyle adjustment

Cardiovascular disease prevention begins with lifestyle change: smoking cessation, alcohol consumption, blood pressure, diet and exercise (which affect body mass index and blood glucose), should be addressed. The National Institute for Health and Care Excellence (NICE) guidelines recommend a diet with total fat intake of <30% and saturated fats <10% of total energy intake, dietary cholesterol of <300 mg/day and replacement of saturated fat with mono- and poly-unsaturated fats. Such measures reduce cholesterol modestly, but response varies considerably between individuals.

Risk assessment

Lipid modification therapy is indicated as part of primary prevention for adults with a predicted 20% or greater 10-year risk of developing CVD. Several risk equations exist: Framingham, QRISK (UK specific) and SCORE (European). LMT must be initiated simultaneously with lifestyle advice for those with established CVD. Chronic kidney disease (CKD) and Lp(a) levels do not contribute to many risk engines, but can potentially reclassify an intermediate- into a high-risk individual.

Statin therapy

Statins are the cornerstone of LMT and more than 20 trials conducted in settings ranging from primary prevention and stable CAD to acute coronary syndromes (ACS) and stroke demonstrate that statins prevent fatal and non-fatal CVD events and reduce all-cause mortality.[5,6] Meta-analyses of individual trials demonstrate an approximate 23% reduction in CVD events per 1 mmol/l reduction in LDL-C, with a log linear relationship with no threshold below which benefit ceases. The benefit is observed equally across a range of baseline lipids and demographic groups.[7]

Recent trials have focused on more (vs less) intensive statin therapy; for example, the median on-treatment LDL-C in the intensive arm (atorvastatin 80 mg) of the PROVE- IT trial was 1.6 mmol/l vs a LDL-C of about 2.4 mmol/l (pravastatin 40 mg) resulting in 16% CVD risk reduction.[8] Similarly, in stable CAD (TNT and IDEAL trials) a 0.6 mmol/l greater reduction in LDL-C (the average on-treatment LDL-C was approximately 2 mmol/l) resulted in significant reductions in CVD events with intensive therapy (atorvastatin 80 mg). In contrast, the AZ (ACS patients) and the SEARCH (stable CAD patients) trials failed to demonstrate a benefit of simvastatin 80 mg vs 20 mg, largely because of the very small incremental reduction in LDL-C.[7,9] Importantly, the risk of myopathy with simvastatin 80 mg was 2,000-fold higher than with atorvastatin 80 mg, resulting in the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) warning against the use of simvastatin 80 mg. The Medicines and Healthcare Products Regulatory Agency (MHRA) guidance warns against co-prescription of a number of cardiovascular drugs, including calcium antagonists and amiodarone, with simvastatin at doses above 20 mg. To date, trials have not been designed to assess the benefit of any specific LDL-C target, hence guidance on specific targets is based on extrapolations from trial data and the absolute risk of the patient, with lower LDL-C goals advised for those at highest risk – for example, established CVD. NICE recommends an LDL-C goal of 2 mmol/l for such high-risk patients, whereas the ESC/EAS recommend a lower target of 1.8 mmol/l (and 2.5 mmol/l for high-risk primary prevention patients).

There is no evidence for excess risk of liver or muscle side effects or for excess risk of cancers with low achieved LDL-C; side effects

may be dose-related but, in general, statins are safe and well tolerated even at high doses (except simvastatin) and side effects are usually fully reversible with cessation of therapy.[10,11] Myopathy and rhabdomyolysis are rare at standard doses (about 0.1% per year)[5] but the rates of myalgia are higher (about 4%).[12] Conditions that increase the likelihood of statin-induced myalgia or myopathy, such as alcohol excess, hypothyroidism, vitamin D deficiency and acute viral illness, should be ruled out. Medications may affect statin metabolism (eg gemfibrozil, cyclosporine, amiodarone, macrolides, antibiotics, verapamil, warfarin and protease inhibitors), and a high intake of grapefruit juice may have an impact on CYP3A4 in the liver. Asymptomatic increases in hepatic transaminases are dose dependent and reversible with down-titration or discontinuation. Hepatitis attributable to drugs is rare (0.001%).[13] As the evidence base for statins far exceeds any other LMT, intolerant patients should try at least one other statin at a lower dose. If this fails, suggest a weekly or twice weekly dose of a statin with a longer half-life, such as rosuvastatin 5 mg or atorvastatin 10 mg, before trying monotherapy with ezetimibe or bile acid sequestrants such as colesevalam.

In the JUPITER trial, it was observed that rosuvastatin increased the risk of developing diabetes mellitus (DM) compared with placebo.[14] In two large-scale meta-analyses of all randomised controlled trials, this observation was established as a class and dose effect, where statins increased the relative risk of DM by 9% at a standard dose and by 12% when comparing high with standard doses. In absolute terms, the risk is low and offset by the greater number of CVD events prevented, approximately five per case of DM (for statin vs placebo) or three CVD events per case of DM (for high vs standard dose). Therefore, in patients with high or existing cardiovascular risk, current clinical practice should not change, but initiation of therapy in low-risk subjects should be considered on a case by case basis, with annual blood glucose monitoring.[15]

Maximising cardiac risk reduction

Optimising evidence-based treatments remains a challenge; for example, data from EuroASPIRE III showed that although 80% of patients with CVD were treated with LMT, only 34% achieved lipid targets.[16] This represents a significant burden of residual but modifiable risk correctable by optimising the statin dose. Absolute risk depends on both the number of uncontrolled modifiable risk factors and the presence of non-modifiable risk factors such as DM and stage 3 CKD, hence any approach to CVD risk reduction should aim to optimise lifestyle and control all risk factors. Treatments need to be tailored to individual patients and clinicians should target high-risk subjects (with multiple risk factors) for more intensive therapies, lower lipid targets and, importantly, should recognise that LDL-C is a suboptimal target for assessing efficacy of LMT when HDL is low (for example, in patients with obesity, DM, CKD and those with high triglycerides) and instead use non-HDL-C.

Alternative lipid-modification strategies

The evidence base for other LMTs is small and they are generally less effective. Nevertheless, there is consistent data that in addition to statins, fibrates reduce CVD risk by about one-third when TG is >1.7 mmol/l and HDL-C is <1 mmol/l. Non-fatal events and revascularisation may be reduced but generally not CVD death. Ezetimibe and colesevelam each lower LDL-C by around 20% and are often used in addition to statins or as monotherapy for statin-intolerant subjects, but the evidence base is unclear. Niacin, which lowers LDL-C by 20%, raises HDL-C by 30% and lowers Lp(a) by 25%, has recently been withdrawn in several European countries because of a lack of contemporary outcomes data. Therapeutic options being licenced for rare conditions such as homozygous familial hypercholesterolaemia include mipomersen which is an antisense inhibitor of apo B, which reduces transcription of the protein scaffold, providing 30% lowering of LDL-C and the microsomal triglyceride transfer protein (MTP) inhibitor lomitapide, which reduces LDL-C by about 50% but does lead to an increase in hepatic fat. More exciting are the monoclonal PCSK9 antibodies given by subcutaneous injection every 2–4 weeks that increase LDL receptor survival time and reduce LDL-C by a further 70% in patients on optimal statin therapy.

Key points

Low-density lipoprotein cholesterol (LDL-C) has a log linear relationship to the risk of coronary artery disease (CAD) and there is extensive evidence from epidemiological, genetic and animal studies, and from trials of LDL-C modification, demonstrating an important link between LDL-C and CAD

LDL-C is the principal target for treatment of conditions associated with insulin resistance and/or the combination of high triglyceride (TG) and/or low high density lipoprotein cholesterol (HDL-C), but non-HDL-C or apolipoprotein B are better therapeutic targets and provide better pre-treatment risk prediction

Assessing absolute risk is crucial in ensuring that patients are optimally treated

Lifestyle adjustment and targeting of multiple risk factors is necessary to reduce residual risk among those with a high absolute risk of cardiovascular disease

Statins are generally safe and well tolerated. Myopathy and rhabdomyolysis are rare at standard doses and usually reverse fully with cessation of therapy

KEY WORDS: Low-density lipoprotein cholesterol (LDL-C), residual risk, side effect, statin, primary prevention, secondary prevention

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