It is remarkable how the treatment of lipid disorders has moved in just over a decade from the domain of a few interested secondary-care specialists to become a mainstream activity for all primary-care professionals. Clearly this represents an appreciation of the burden of atherosclerotic disease in society, the realisation of the central, causative role of abnormal lipid levels and the emergence of incontrovertible evidence of benefit from lipid-modifying trials.

The extent of dyslipidaemia in industrialized societies means that the burden of management logistically falls to primary care. Primary care must accept the challenge of identifying and treating patients at high global cardiovascular risk, help these individuals achieve target lipid goals and maximise long-term benefit by developing systems of care which ensure continuing target delivery and long-term compliance.

Identifying individuals for lipid-lowering treatment

There is broad consensus between modern international guidelines about who should be treated. The updated Joint British Societies’ guidelines for the prevention of cardiovascular disease (JBS2) provide typical advice.1 Treatment priority is given to a spectrum of high-risk individuals - people with established manifestations of cardiovascular disease (CVD), people with diabetes mellitus (whose current or future risk of CVD is high) and people whose 10-year risk of a CVD event exceeds 20%. The switch in focus from the estimation of risk of coronary heart disease to the risk of cardiovascular disease reflects recognition of the unifying pathology of atherosclerosis in the aetiology of ischaemic cardiovascular disease and emerging evidence of the especially high risk and potential for benefit in patients with existing cerebrovascular and peripheral arterial disease.2, 3, 4 The choice of the 10-year 20% CV risk threshold for people without established CVD or diabetes is challenging as many people exceed this threshold. In the UK, 23% of men and 8% of women aged 40-74 years - some 3.3 million people are candidates for treatment. The workload and cost implications are significant.

Despite favouring a 20% 10-year CVD threshold endorsed by current guidelines,5,6 The recent MEGA study from Japan further expanded this evidence to the Asian population.7 To widen the scope of lipid management further, however, would strain the twin constraints of affordability and practicality and currently a lifestyle approach is recommended. In the UK some individuals choose to buy simvastatin ‘over the counter’ in pharmacies although the uptake has not been significant.

What are the targets to aim for?

Lowering cholesterol and more specifically, low density lipoprotein cholesterol (LDL-C), lowers CV risk. Although it is clear that lipid-lowering agents have multiple actions (so called ‘pleiotropic’ effects), the message of the trials is that it is lowering of LDL-C that is the dominant effect.8 LDL-C is a closer pathophysiological measure of the cholesterol fractions which are oxidised and deposited in arterial walls than total cholesterol and is accordingly, a better target than total cholesterol. In the USA, health professionals ignore total cholesterol levels and concentrate almost wholly on LDL-C, with a new lower target of <1.8mmol/L for those at very high risk.9

Figure 1 (taken from JBS2) shows the before and after values of LDL-C in a number of clinical trials and their attributed CHD risk. All the lines point downwards showing that events are consistently reduced with lower levels of LDL-C.
The Cholesterol Trialists’ Collaboration estimated from clinical trials that every 1mmol/L lowering of LDL-C resulted in 12% fewer deaths, 19% fewer CHD events and 17% fewer strokes. These benefits are seen irrespective of age or starting cholesterol, LDL-C and HDL-C, thereby supporting the approach to treat according to CV risk and not absolute cholesterol values. The benefits are seen within one year but increase subsequently. With the availability of cholesterol-lowering medication that can effect more than 1mmol/L LDL-C reduction clinical trials have been able to explore whether ‘lower is better’.

Four well-conducted clinical trials have attempted to explore the value of driving LDL-C down to very low levels in high-risk people with CHD. A meta-analysis of their results confirms a significant 16% reduction in CHD death or non-fatal myocardial infarction in the more aggressively treated patients and it is this that has prompted the new lower target recommendations. At the moment, there appears to be no lower threshold at which LDL-C reduction ceases to confer benefit. Speculation suggests a level of 1.3mmol/L (the level we are born with) might be the lowest point and trials are already designed to test this.

The recommendations of JBS2 suggest that for individuals in the priority, high-risk group total cholesterol should now be < 4.0mmol/L and LDL-C should be < 2.0mmol/L (or 25% reduction in total cholesterol and 30% reduction in LDL-C, whichever gets to the lowest cholesterol level). The addition of the percentage calculations is designed to ensure that individuals at risk achieve sufficient cholesterol lowering to derive benefit, even if their baseline cholesterol levels are low. In practice, few of us make these calculations and most concentrate on the target figures alone.

**How to achieve and maintain target lipid values**

Cholesterol-lowering trials are invariably conducted in individuals who have already received some lifestyle input. The power of drugs sometimes makes us diminish the impact of lifestyle change and in particular, healthy eating. Compliance with a pattern of diet and lifestyle that optimises weight, reduces fat (particularly saturated and trans fats) and incorporates soluble fibre, plant sterols and soya protein will have the greatest impact on cholesterol levels.

Once a drug is prescribed, one of the key issues is continuing compliance over the longer term with both lifestyle and pharmacological interventions. Central to success is the sort of educational and supportive relationship that is possible in primary care between healthcare professionals and the patient. New evidence from Scotland shows that treating to target in such a ‘therapeutic alliance’ is 2.5 times more likely to achieve target values than a ‘fire and forget’ approach.

Statins are the mainstay of treatment, are remarkably well tolerated and with emerging patent expiries (in the UK, already on simvastatin and pravastatin), generic price reductions are significant. Simvastatin, by virtue of its moderate potency, its good tolerability and extensive evidence base is a natural first choice and favoured by those that control the purse strings but may not always result in target values. Different statin strategies are used to achieve target values including up-titration at 4-6 week intervals, switching to more potent statins or using high doses of powerful statins to ‘get it right first time’. The relative LDL-C lowering efficacy of the dose ranges of four statins is shown in Figure 2.

Mean cholesterol levels in older adults in the UK are just under 6mmol/L and LDL-C levels typically around 4mmol/L. Getting to TC<4.0mmol/L and LDL-C <2.0mmol/L is therefore quite a step and the new targets will favour the use of higher dose and more efficacious statin therapy and increasingly (as in blood pressure control) combination therapy.

Ezetimibe is a specific cholesterol absorption blocker which acts in the small intestine to stem the absorption of dietary and biliary cholesterol. In monotherapy it reduces LDL-C by about 18% but because its action is complementary to statins, really large reductions in LDL-C (up to 60%) can be seen when they are used together. New evidence shows its incremental action even in triple therapy, in combination with a statin and fenofibrate. Other lipid-lowering drugs used in combination with statins are nicotinic acid, fibrates and specifically for lowering triglycerides, fish oil capsules.

**What about HDL-C and triglycerides?**

The data supporting HDL-C and triglycerides are largely epidemiological and, unlike the situation with LDL-C, it is difficult to know from current trial evidence whether specific modification of either results in preventing CV events. JBS2 approaches this dilemma by not setting specific target values for HDL-C and triglycerides but by recommending ‘desirable values’ - HDL >1.0mmol/L for men and > 1.2mmol/L for women and triglycerides < 1.7mmol/L.

Levels of HDL-C and triglycerides are dynamically linked and often track each other inversely. Raised triglycerides are associated with low levels of HDL-C in many individuals, typically in those with diabetes and those with abdominal obesity, glucose intolerance and other features of the metabolic syndrome. Raised triglycerides alter both LDL-C and HDL-C, producing...
smaller, denser varieties which are in turn more atherogenic.

Although many statins have a moderate triglyceride-lowering effect (equivalent to their LDL-C lowering effect) they do little to raise HDL-C. Fibrates and particularly nicotinic acid preparations both lower triglycerides and raise HDL-C. Some patients may benefit from combination therapy if HDL-C is low and triglycerides raised, even if a statin has reduced their total and LDL-C to target.

The HDL-C story will expand with the development of several new specific HDL-C elevating drugs currently in the pipeline. Cholesteryl ester transfer protein (CETP) inhibitors have shown early promise but safety remains a concern.

Developing structured care

Many surveys show that implementation of the evidence base for lipid modification is suboptimal. The existence of the ‘implementation gap’ between expectation and reality underlines the failure, in many practices, to develop systematic care pathways for patients needing CVD prevention interventions. The computer is central to the efforts of most practices, and appropriate coding, database construction, and the use of templates and call and recall systems all enhance the delivery of care. Much research has focused on the role of the primary-care nurse, and data from the Grampian region in Scotland show significant improvements in the level of interventions and even the death rate at 4.7 years in CHD patients attending nurse-led clinics.14

Nurses already have established roles in chronic disease management in asthma and diabetes in primary care. As the aims are similar, a logical step would be to expand practice diabetes clinics to become CVD prevention clinics. In the UK, restructuring of the remuneration contract for GPs (the Quality and Outcomes scheme - QOF) has led to levels of achievement in lipid-lowering that have been internationally applauded.15 In 2005-6, 78% of patients with CHD, 72% with stroke or TIA and 79% with diabetes achieved total cholesterol levels of <5mmol/L, the QOF target.

Much of the success of this primary care exercise in implementation has been ascribed to the development of structured care pathways and appropriate IT and audit support systems. Primary healthcare professionals however feel that the most important factor is that by utilising the characteristics of primary care practice they are able to establish an ongoing and special therapeutic relationship between themselves and their patients, to mutual advantage.

References


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