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Lipids and CVD: improving practice and clinical outcome

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SPONSORED SUPPLEMENT

Introduction

This supplement is a report from the inaugural meeting of the Cardiometabolic Forum, jointly organised by the British Journal of Cardiology and HEART UK – The Cholesterol Charity. The meeting was held at the Royal Pharmaceutical Society, London, on 24th November 2011. Meeting chairs were Dr Dermot Neely (Royal Victoria Infirmary, Newcastle upon Tyne) for HEART UK, and Dr Henry Purcell (Royal Brompton Hospital, London, and Editor) for BJC.

We hope this supplement will provide readers with an independent overview on recent developments in our knowledge of cholesterol metabolism and its implications for clinical practice.

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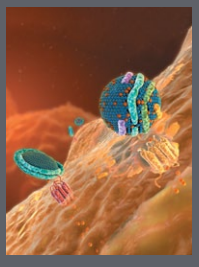
Sponsorship statement

This supplement has been sponsored by Roche Products Limited. It Is based on the proceedings of the inaugural meeting of the Cardiometabolic Forum, held at the Royal Pharmaceutical Society, London, on 24th November 2011. The Cardiometabolic Forum is an academic group jointly set up by The British Journal of Cardiology and HEART UK – The Cholesterol Charity. The Forum was responsible for developing the scientific programme, inviting the speakers and chairing the meeting. It approached Roche Products Limited for sponsorship and Roche Products Limited underwrote the costs of the meeting, the speakers' travel expenses and honoraria, and the writing, development and distribution of this supplement. Roche Products reviewed this supplement for ABPI compliance before publication but otherwise had no input into the content of either the meeting or this supplement.



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Lipids and cardiovascular disease: re-thinking targets

Kausik K Ray

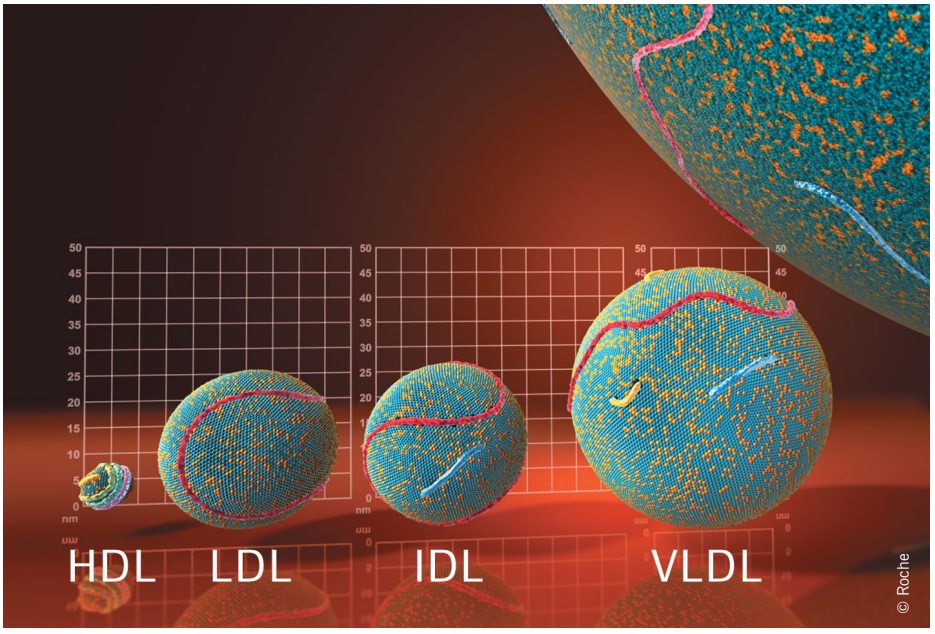
Introduction

Worldwide, cardiovascular disease remains the leading cause of death and a major cause of disability affecting quality of life.[1] Elevated cholesterol is one of the key risk factors accounting for a substantial proportion of this disease burden. In developed countries, at least one-third of all cardiovascular disease is attributable to five risk factors: smoking, excessive alcohol intake, elevated blood pressure, elevated cholesterol and obesity.[2] In particular, elevated cholesterol accounted for 56% of all cases of coronary heart disease (CHD) and 18% of cases of ischaemic stroke (2002 data).[2]

Improved management of risk factors and better care, especially in the secondary prevention setting, has undoubtedly been successful in reducing cardiovascular disease mortality in the UK over the last few decades.[3] Better care of patients after myocardial infarction (MI) has also increased the longevity of these patients.[3] However, these gains are now seriously challenged by the impact of the global epidemics of obesity and type 2 diabetes, arising from overconsumption and an increasingly sedentary society. As clinicians, we need to rise to this challenge to improve management.

Improving guideline implementation

Improved control of cholesterol, one of the key risk factors associated with cardiovascular disease, is one priority. Statin therapy is clearly recognised in guidelines as the cornerstone of treatment for managing dyslipidaemia.[4] However, implementation is still less than optimal. In the primary care setting, EURIKA (European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice) showed that less than one-half of treated dyslipidaemic patients attained both total and low-density lipoprotein (LDL) cholesterol targets.[5] Similarly, in the secondary prevention setting, the EUROASPIRE



(European Action on Secondary and Primary Prevention by Intervention to Reduce Events) III survey showed that only 55% of patients across Europe achieved total cholesterol targets. It has to be pointed out that control was somewhat better in the UK (72% of patients achieved total cholesterol targets) compared with the average for all countries.[6]

More aggressive statin therapy, in accordance with local guidance, can further improve LDL cholesterol lowering. However, LDL cholesterol lowering alone does not eliminate the risk of cardiovascular events.[7]

Considering other lipid targets: HDL cholesterol

The INTERHEART Study, a global case–control study, highlighted the relevance of both atherogenic apolipoprotein (apo) B-containing lipids, including LDL cholesterol, intermediate-density and very low-density lipoproteins, and atheroprotective lipoproteins, such as apoA-I contained in high-density lipoprotein (HDL) cholesterol to coronary risk. The study showed that, after smoking, the ratio of apoB/apoA-I was the most important contributor to population-attributable MI risk, accounting for almost one-half (49.2%) of this risk. Individuals with apoB/apoA-I ratios in the highest quintile had over three-fold increase in population attributable MI risk.[8] In INTERSTROKE, there was also a strong association between apoA-I and HDL cholesterol levels and the risk of ischaemic stroke.[9] These data clearly emphasise that achieving the right balance between atherogenic and atheroprotective lipoproteins can favourably impact the atherosclerotic process and reduce cardiovascular events.

Atherosclerosis is an inflammatory process which occurs over many decades. The initial trigger for this process is the accumulation of apoB-containing lipoproteins in the artery wall.[10] These then undergo oxidation, with the end products (oxidised LDL) then stimulating further processes involved in atherosclerosis. As a result, monocytes are attracted to the endothelial layer, attach to the endothelium, and migrate into the subendothelial space, where the monocytes differentiate into macrophages. Macrophages take up the modified LDL, becoming foam cells, and also release a

Table 1. Key atheroprotective activities of high-density lipoprotein (HDL)

- Reverse cholesterol transport
- Anti-inflammatory activity
- Anti-oxidative activity
- Anti-apoptotic activity
- Endothelial repair
- Anti-thrombotic activity
- Anti-infectious activity

number of chemicals, including cytokines and interleukin-1, leading endothelial cells to express adhesion molecules, which, in turn, bind monocytes to the endothelium, thus, continuing the cycle of atherosclerosis. Macrophages and foam cells secrete growth factors, which lead to cell proliferation and matrix production, as well as metalloproteinases, which lead to matrix degeneration. Thus, macrophages and foam cells contribute to lesion growth, plaque instability and ultimately clinical events.

Evidence from *in vitro* and *in vivo* studies points to HDL having a number of important atheroprotective properties that can help in slowing this process. HDL comprise a heterogeneous population of lipoproteins that differ by size, shape and composition. Essentially, HDL have the same structure as LDL, with a surface monolayer of phospholipids and free cholesterol and a hydrophobic core consisting mainly of cholesteryl esters, as well as some triglyceride.[10,11]

HDL play a key role in reverse cholesterol transport, the process by which excess cholesterol is transferred from macrophage foam cells in the arterial wall or peripheral tissues to the liver for excretion into the bile. However, HDL have other potentially atheroprotective functions including anti-inflammatory, anti-oxidative, and anti-thrombotic activities (**table 1**).[11] HDL also play a role in stabilising atherosclerotic plaque.[12] An analysis of four intravascular ultrasound studies involving 1,455 patients showed that both LDL cholesterol lowering and HDL cholesterol raising were relevant to atheroma progression.[13]

The epidemiological evidence base for the association of HDL cholesterol and cardiovascular risk is indisputable. The largest analysis to date, the ERFC (Emerging Risk Factors Collaboration) in more than 300,000 individuals without cardiovascular disease at baseline, provides the strongest evidence (**figure 1**). After adjustment for both lipid and non-lipid risk factors, each 0.38 mmol/L (15 mg/dL) increment in HDL cholesterol was associated with 22% reduction in CHD risk. A significant relationship was also shown for HDL cholesterol and risk of ischaemic stroke. However, the relationship between the level of HDL cholesterol and coronary risk appeared to plateau at 1.6 mmol/L (~61 mg/dL).[14] The jury is still out on whether raising HDL cholesterol levels beyond this value confers additional clinical benefit.

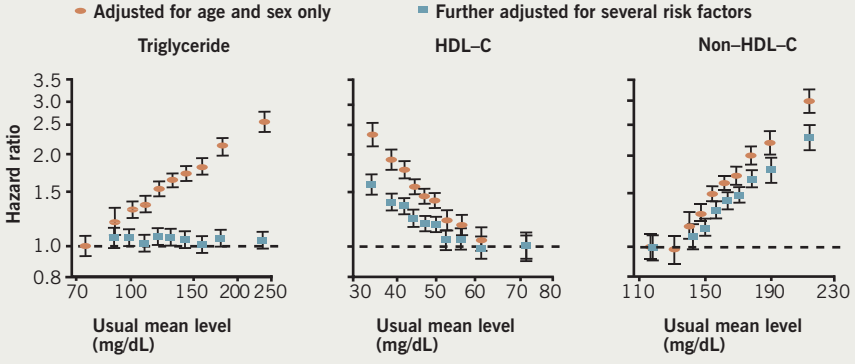
Current guidelines identify HDL cholesterol as a strong cardiovascular risk factor but refrain from identifying HDL cholesterol as a target for intervention given the lack of outcomes data.[15] HDL cholesterol is incorporated in SCORE risk estimation charts as it has been shown to contribute to risk as the individual variable but not as the ratio.[15] Clinically, HDL cholesterol can be readily measured in non-fasting samples as a simple marker of cardiovascular disease risk. Non-HDL cholesterol (or apoB) is a preferable measure of atherogenic apoB-containing lipoproteins to LDL cholesterol, and also readily measured in non-fasting samples (**see practice point**). Considering management strategies for low HDL cholesterol may be relevant in the overweight individual with the metabolic syndrome.

Relevance of inflammatory biomarkers?

There has been much debate about incorporation of inflammatory factors in risk estimation. Because C-reactive protein (CRP) is present in atherosclerotic plaques, it has been proposed that it may have a causal role in cardiovascular disease. Indeed, another comprehensive analysis by the ERFC showed that CRP levels were linearly associated with an increased risk of cardiovascular events, although more modestly than previously believed.[16] It is, however, unlikely that CRP is causal as genes associated with elevations in CRP are not associated with increased risk of CHD, suggesting that CRP is a marker of risk rather than a target for treatment.[17] However, this does preclude the potential causal role of inflammation with upstream factors such as interleukin 1 or 6, as progression from a stable to unstable atherosclerotic plaque culminating in the clinical event undoubtedly involves inflammation and the complex interplay of genetic and environmental risk factors.

The balance of evidence from epidemiological and mechanistic studies supports the HDL hypothesis. Whether raising HDL cholesterol levels translates to reduction in cardiovascular outcomes is being tested by several ongoing major prospective studies (see review on pages S14–S16) and answers should be available within the next two to four years. Finally, outstanding questions remain as to whether HDL cholesterol levels or the biological activities of HDL (i.e. its functionality) are more important. The HDL cholesterol

Figure 1. Emerging Risk Factors Collaboration (ERFC) analysis in individuals without prior cardiovascular disease established the importance of high-density lipoprotein (HDL) cholesterol (HDL-C) levels to coronary risk



Reproduced with permission from *JAMA* 2009[14]

hypothesis remains an intriguing concept, for which we hope to have definitive answers in the near future

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Key messages

- Achieving the right balance between atherogenic lipoproteins (as in LDL) and atheroprotective lipoproteins (as in HDL) is key to reducing cardiovascular risk
- HDL has been shown to have a number of atheroprotective properties
- Epidemiological data confirm HDL cholesterol as an independent risk factor for cardiovascular disease
- Ongoing clinical trials will help to determine whether HDL cholesterol is a target or only a risk factor

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Practice point

Non-HDL-C, LDL-C and apoB: what do they measure?

Non-HDL cholesterol

= the sum of cholesterol in all atherogenic apolipoprotein B (apoB) containing lipoprotein particles (i.e. low-density lipoprotein [LDL] + intermediate-density lipoprotein [IDL] + very-low-density lipoprotein [VLDL])

= Total cholesterol – HDL cholesterol

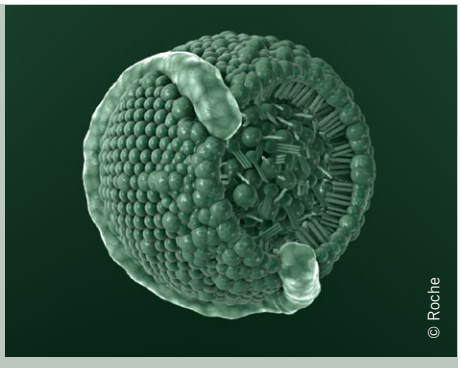
LDL cholesterol

= cholesterol in LDL

Calculated using Friedewald's formula (invalid if non-fasting or if triglycerides [TG] >4.5 mmol/L)

ApoB

= the total number of atherogenic apoB lipoprotein particles in LDL + IDL + VLDL



Useful in diagnosis but no advantage over non-HDL cholesterol in risk assessment[14]

How can we improve clinical diagnosis of dyslipidaemia?

Dermot Neely

Introduction

Abnormalities in plasma lipoprotein concentrations are found in seven of out every 10 patients with premature coronary disease, with a familial disorder in more than half of these cases, highlighting the importance of accurate diagnosis and scope for early treatment of affected families.[1] Clinical assessment, incorporating review of phenotypic features, personal and family history, physical signs and laboratory tests, is fundamental to diagnosis.

In the first instance, it is important to exclude secondary causes of dyslipidaemia. Diabetes mellitus, untreated hypothyroidism, nephrotic syndrome, obesity and cholestasis are all associated with hyperlipidaemia and must be excluded by baseline biochemical tests (**table 1** and see also the **case scenario** on page S11).

In addition, a wide range of medications are commonly implicated as a cause of dyslipidaemia, including:

- atypical antipsychotics, corticosteroids and ciclosporin, which increase cholesterol and triglycerides
- beta blockers, HIV/antiretroviral drugs, oestrogens and retinoids, which increase triglycerides
- anabolic steroids, which lower high-density lipoprotein (HDL) cholesterol.

For many people with primary dyslipidaemia, cholesterol is relatively easy to manage once diagnosed. However, clinicians must consider the possibility of a familial aetiology, especially in those patients with a strong family history of coronary heart disease (CHD).[2] Such disorders are commonly underdiagnosed in practice. With early diagnosis and instigation of appropriate lipid-lowering therapy and therapeutic lifestyle changes, major cardiovascular complications can be prevented.

Familial hypercholesterolaemia

In the absence of secondary causes, a strong family history of premature CHD is suggestive of an atherogenic familial lipid disorder (**table 2**). Of these, familial hypercholesterolaemia (FH) is the best recognised, with an estimated prevalence in Caucasians of one in 500 (0.2%).[3,4] This means that in the UK, about 110,000 people have FH.[4] Almost all affected people are heterozygotes (HeFH). Homozygous FH is extremely rare (~one in one million).[2]

Low-density lipoprotein (LDL) cholesterol levels in individuals with HeFH are typically double normal levels, in the range of 5–10 mmol/L.[2] HeFH increases the risk of premature CHD dramatically, with a cumulative risk of 50% in men by age 50 and 30% in women by age 60.[4] If affected individuals are not diagnosed and treated, 50% of men and 15% of women will have died by age 60. However, if individuals are diagnosed and treated they can look forward to a normal life expectancy.[2]

FH is due to an autosomal genetic defect affecting the LDL-receptor pathway.[5] Normally LDL-derived cholesterol acts at several levels, to suppress transcription of the LDL-receptor gene. This allows cells to regulate the number of LDL-receptors to provide sufficient cholesterol for metabolic needs. When cholesterol levels in the cell increase, the production of LDL-receptors is decreased. FH may be caused by mutations in genes coding for the LDL-receptor (LDLR), apolipoprotein (apo) B100 (the LDL-receptor ligand), and a protease known as PCSK9 (proprotein convertase subtilisin/kexin type 9), which is involved in the regulation of LDL-receptor recycling.[5]

The finding of tendon xanthomas confirms the diagnosis of FH. Although these are found in fewer than 30% of cases, greater than 80% of such cases will have a disease defining mutation in LDLR, APOB or PCSK9 genes (**figure 1**).[4] Studies have also shown that the

Table 1. Key tests to exclude secondary causes of dyslipidaemia

Test	Reason for test
Renal profile (sodium, potassium, creatinine, estimated GFR)	Exclude renal failure
Liver profile (total protein, albumin, ALP, ALT, GGT)	Exclude cholestasis
Thyroid profile	Exclude hypothyroidism
Fasting glucose	Exclude diabetes
Dipstick urinary protein	Exclude nephrotic syndrome

Key: ALP = alkaline phosphatase; ALT = alanine transaminase; GFR = glomerular filtration rate; GGT = gamma-glutamyl transpeptidase

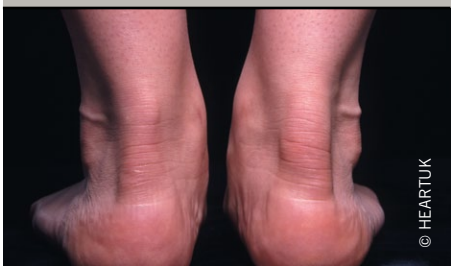
Table 2. Prevalence of common genetic dyslipidaemias in people of European origin. Derived from the ESC/EAS guidelines[2]

Dyslipidaemia	Abnormal lipids	Prevalence
Familial combined hyperlipidaemia (FCH)	↑ LDL cholesterol, triglycerides (VLDL) or both	1:100
Heterozygous familial hypercholesterolaemia (HeFH)*	↑ LDL cholesterol (typical range 5–10 mmol/L in FH) ↑ apo B	1:500
Polygenic hypercholesterolaemia		1:50
Familial hypertriglyceridaemia	↑ triglycerides (VLDL)	1:100

* Note homozygous familial hypercholesterolaemia is very rare (~one in one million births)

Key: apoB = apolipoprotein B; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein

Figure 1. Tendon xanthomas, characteristic of familial hypercholesterolaemia



presence of this clinical sign is associated with a significant increase in cardiovascular disease risk across all age groups.[6] The National Institute for Health and Clinical Excellence (NICE) guidelines recommend cascade screening involving a combination of genetic testing and LDL cholesterol measurement for definitive diagnosis (**table 3**). If a familial FH mutation is not identified or genetic testing is not available, relatives of an FH patient can be diagnosed on the basis of sex- and age-specific LDL cholesterol thresholds (as recommended by NICE).[4] Diagnosis on clinical signs alone is less sensitive.

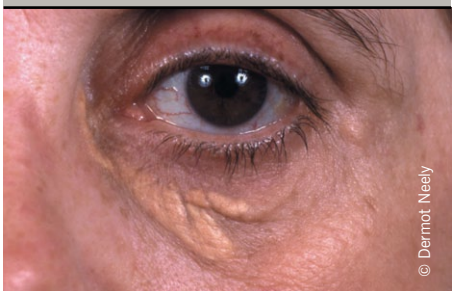
Underdiagnosis remains a major problem, with estimates suggesting that less than 25% of people with FH are diagnosed.[7] As FH is readily treatable with statins,[4] there is clearly a role for primary care in the diagnosis and identification of affected family members with FH. A nationwide, proactive, systematic approach to cascade testing is recommended in guidelines,[2,4] but commissioning support for implementation is lacking in most parts of the UK.

Combined hyperlipidaemia

A lipid profile defined by elevated LDL cholesterol, triglycerides or both can be suggestive of a number of dyslipidaemias. These include familial combined hyperlipidaemia (FCH), remnant hyperlipidaemia (Type III or familial dysbetalipoproteinaemia) and dyslipidaemia associated with the metabolic syndrome, as well as milder presentations of familial hypertriglyceridaemia (see the **case scenario** on page S8).

FCH affects about one in 100 people. The underlying mechanism involves overproduction of very-low-density lipoprotein (VLDL) and apoB. The genetic basis is complex and multifactorial and also influenced by environmental factors.[2] As there is considerable variability in presentation, diagnosis can often be missed in practice. FCH should be suspected if total cholesterol levels are in the range 6.5–8.0 mmol/L and/or triglycerides between 2.3 and 5.0 mmol/L (**table 4**). Elevated levels, either alone or in combination, in patients and other family members confer a 'variable phenotype'. ApoB is invariably elevated and is, therefore, a useful diagnostic tool, with levels >1.20 g/L, together with elevated triglycerides and family history of cardiovascular disease, strongly suggestive of diagnosis.[2] The finding of an apoB concentration that is unexpectedly low (apoB/total cholesterol ratio <0.15 g/mmol) raises suspicion of remnant hyperlipidaemia.[8] The presence of xanthelasma (**figure 2**) is not of diagnostic significance but represents an area of lipid-laden macrophages, which is predictive of an increased risk of CHD, atherosclerosis and mortality.[9]

Figure 2. Xanthelasma represent areas of lipid-laden macrophages. The presence of these is predictive of an increased risk of coronary heart disease, atherosclerosis and mortality



Lipid profiles

Clearly the full lipid profile is key to diagnosis of dyslipidaemia. The baseline lipid evaluation should comprise total cholesterol, triglycerides and HDL cholesterol.[2] Because total cholesterol involves measurement of both atherogenic (LDL-, intermediate-density lipoprotein [IDL]- and VLDL cholesterol) and anti-atherogenic (HDL cholesterol) lipid fractions, it is inadequate for monitoring treatment. Instead, LDL- and non-HDL cholesterol are preferred. Of the two, there is a strong case for preferential use of non-HDL cholesterol, given that 1) it is a simple calculation (non-HDL cholesterol = total cholesterol – HDL cholesterol); and 2) can be readily measured in non-fasting samples.[10] In contrast, LDL cholesterol must be measured in fasting samples as its calculation assumes a constant cholesterol/triglyceride ratio in VLDL of 0.45. This assumption does not

Table 3. Diagnostic criteria for familial hypercholesterolaemia in adults (Simon Broome Register Criteria)[4]

1	Total cholesterol >7.5 mmol/L or low-density lipoprotein (LDL) cholesterol >4.9 mmol/L in adults
2	Tendon xanthomas are present in the patient, first-degree relative or second-degree relative
3	DNA-based evidence of a mutation in LDLR, APOB or PCSK9
4	Family history of premature myocardial infarction (<50 years in second-degree relative or <60 years in first-degree relative)
5	Family history of elevated total cholesterol (>7.5 mmol/L in first- or second-degree relative)

Definite familial hypercholesterolaemia = 1 + 2 or 3; possible hypercholesterolaemia = 1 + 4 or 5

Table 4. Lipid profile associated with familial combined hyperlipidaemia[2]

↑ Total cholesterol (6.5–10.0 mmol/L)
↑ LDL cholesterol
↑ Triglycerides (2.3–6.0 mmol/L or higher)
ApoB/total cholesterol >0.15
VLDL cholesterol/total triglycerides <0.69*
Small, dense, LDL
Diagnosis is commonly based on the combination of apoB >1.20 g/L + triglycerides >1.5 mmol/L with a family history of premature cardiovascular disease[2]

* Determined by ultracentrifugation

Key: apoB = apolipoprotein B; LDL = low-density lipoprotein; VLDL = very-low-density lipoprotein

hold in non-fasting conditions or when the fasting triglyceride concentration exceeds 4.5 mmol/L.[2] Furthermore, the ratio is altered by statin treatment. Therefore, the main role for calculated LDL cholesterol is in assessment of suspected FH before treatment.

Non-HDL cholesterol represents the total sum of cholesterol in apoB-containing lipoproteins. This includes lipoprotein(a) (Lp[a]), which comprises a cholesterol-rich LDL particle with one molecule of apo B100 and an additional protein, apolipoprotein(a). Elevated Lp(a) is associated with increased risk of cardiovascular disease, particularly if levels exceed 50 mg/dL (500 mg/L or 125 nmol/L) where the risk of MI is increased two- to three-fold.[11] The association between elevated Lp(a) and increased cardiovascular disease risk was continuous and did not depend on LDL cholesterol levels. On this basis, a position statement from the European Atherosclerosis Society has recommended screening for elevated Lp(a), with consideration of nicotinic acid (niacin) in addition to statins in patients with elevated levels, aiming for a Lp(a) level <50 mg/dl.[11]

There has been much debate concerning the role of other novel risk factors such as systemic inflammatory biomarkers in risk assessment. However, current evidence suggests that these add little and are not currently recommended

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Key messages

- Diagnosis of dyslipidaemia should involve a thorough clinical assessment. Secondary causes of dyslipidaemia should be excluded
- LDL cholesterol is important in the diagnosis of familial hypercholesterolaemia; apoB is diagnostic in mixed dyslipidaemia
- Measurement of lipoprotein(a) should be considered in patients with a personal or family history of coronary heart disease
- Systemic inflammatory risk markers add little to risk assessment

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Case scenario

Differentiating familial causes of hypercholesterolaemia

Derek, a 40-year-old former RAF engineer, was referred to the lipid clinic after recent admission to the Rapid Access Chest Pain Clinic with burning central chest pain (exercise electrocardiogram [ECG] was negative). Simvastatin was initiated by the clinician but Derek later stopped this due to severe headache and fatigue.

Derek was a non-smoker, physically active, a light drinker (4–6 units per week), was overweight (BMI 29.5 kg/m^2) and had well-controlled blood pressure (136/84 mmHg), and normal renal, hepatic and thyroid function. Fasting glucose was 4.7 mmol/L. There was no family history of cardiovascular disease. However, on examination, there was xanthelasma together with elevated fasting total cholesterol (8.1 mmol/L), although triglycerides were near normal range (1.8 mmol/L). On a repeat fasting test one month later, both were higher (8.4 mmol/L total cholesterol and 3.4 mmol/L triglycerides). HDL cholesterol was within normal limits (1.4 mmol/L).

This case scenario highlights the variable phenotype of the lipid abnormality in combined dyslipidaemia and the importance of family history. The first profile is suggestive of possible familial hypercholesterolaemia, the second suggests that a diagnosis of combined dyslipidaemia typically associated with metabolic syndrome may be more likely. At least two lipid profiles are required to make a diagnosis.

Improving dyslipidaemia management: focus on lifestyle intervention and adherence

Adie Viljoen

Introduction

The global epidemic of obesity and type 2 diabetes, largely due to overconsumption and sedentary lifestyle, is a major challenge facing clinicians. In the UK, as in the European Region, the prevalence of obesity is rapidly increasing, highlighting a growing health challenge.[1] In England (2003 data), 65% of males and 55% of females aged 16 years or more are either overweight or obese.[1] As a consequence, the prevalence of the metabolic syndrome, of which dyslipidaemia (elevated triglycerides and low plasma levels of high-density lipoprotein [HDL] cholesterol) and central obesity are key features,[2] is increasing.

Therapeutic lifestyle intervention underpins the management of dyslipidaemia, especially that associated with the metabolic syndrome. Indeed, the recent European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines on dyslipidaemia place emphasis on nutritional approaches, either alone or complementary to pharmacotherapy, in managing hypercholesterolaemia to reduce cardiovascular risk.[3] This is clearly supported by concordant evidence from observational studies and randomised trials showing associations between lifestyle factors, effects on lipids and other biomarkers and cardiovascular disease risk. In the case–control INTERHEART study, involving 52 countries worldwide, four out of the nine major factors determining risk for myocardial infarction (MI) were lifestyle components.[4] Three of these were protective, namely, physical activity, intake of fruit and vegetables and alcohol use, while smoking increased risk. Additionally, the other factors in the INTERHEART study associated with cardiovascular risk were also influenced by lifestyle: abdominal obesity, blood pressure, lipids, diabetes and stress. Cardiovascular risk increased cumulatively with an increasing number of risk factors. Clearly, targeting lifestyle factors should be fundamental to control of lipids and prevention of cardiovascular disease.

Diet

Dietary intervention favourably influences lipids and cardiovascular risk and should, therefore, be a cornerstone of treatment efforts. Observational studies have shown that traditional Mediterranean diets, including vegetables, fruits, fish, wholegrain cereals, legumes, unsaturated fats, moderate alcohol intake and limited consumption of red meat, improved lipids and glycaemic control and reduced cardiac mortality.[5-7] The Lyon Diet Heart study[8] tested whether converting to a Mediterranean diet, as well as substituting omega-3 canola oil and spread for added fats, could impact coronary event rates in MI survivors. Despite a similar coronary risk factor profile, subjects following the Mediterranean-style diet had significant and substantial reductions in coronary events (by at least 50%), as well as all-cause mortality, leading to early termination of the trial. It is a salient point that across the UK, two-thirds of adults do not consume the recommended five portions of fruit and vegetables a day.[9]

Improving the diet by substitution of saturated fats with unsaturated or monosaturated fats not only lowers low-density lipoprotein (LDL) cholesterol, but also benefits triglycerides and HDL cholesterol. For example, the PREDIMED study showed that a Mediterranean-style diet (including olive oil) raised HDL cholesterol (by 0.62 mmol/L) and lowered triglycerides (by 0.03 mmol/L), compared with a low-fat diet.[7] This dietary approach is clearly valuable for targeting patients with the metabolic syndrome. Recent guidelines recommend that saturated fat intake should be less than 10% of the total caloric intake, and even lower in patients with hypercholesterolaemia.[3] Trans-fatty acids, present in hydrogenated fats, should be eliminated from the diet as these

have unfavourable effects on LDL cholesterol, triglycerides and HDL cholesterol.[10]

There is growing support for the value of so-called 'functional foods' in the diet, as incorporated in recent ESC/EAS guidelines.[3] Consumption of plant sterols or stanols is consistently associated with lowering of LDL cholesterol levels by 7–10%.[3] Additionally, increasing intake of soluble (viscous) fibre, such as in oats, can produce modest reductions in total and LDL cholesterol (by about 0.13 mmol/L).[11] Overall, the combined effect of dietary changes can produce up to a 20–30% reduction in LDL cholesterol levels (**table 1**).[12-16]

Physical activity

Exercise is also a cornerstone for improving lipids, treating metabolic syndrome and reducing cardiovascular risk. While physical activity improves LDL cholesterol levels, there

Table 1. Effects of dietary changes on low-density lipoprotein (LDL) cholesterol[12,23-26]

Dietary component	Dietary change	Approximate reduction in LDL cholesterol (%)
Reducing saturated fat	from 15% to ~6% of calories	11%
Reducing dietary cholesterol	<300 mg/day*	5%
Weight reduction	5% weight loss	10%
Functional foods		
Viscous fibre	5–10 g/day	5%
Plant stenols/stanols	2–3 g/day	6–15%
Effect with combined dietary intervention		**20-30%**

*100 mg/day reduction of cholesterol reduces total cholesterol by ~1%

is also benefit in terms of lowering triglycerides and raising levels of HDL cholesterol.[3] Not all of the effect of exercise is due to exercise-mediated weight loss, as there is evidence that both weight loss and physical exercise act independently to improve lipids and cardiovascular risk.[17,18] Indeed, gaining weight or becoming physically inactive are among the main determinants for developing the metabolic syndrome.[19] Increasing the amount and intensity of exercise have all been linked with benefit on lipids and lipoproteins.[19,20]

Implementation and adherence issues

Therapeutic lifestyle intervention is clearly effective in managing dyslipidaemia to reduce cardiovascular risk. Despite this, clinicians and patients fail to do their best with lifestyle intervention. First, how lifestyle advice is implemented and monitored by clinicians is often less than ideal, as illustrated by EURIKA (European Study on Cardiovascular Risk Prevention and Management in Daily Practice), a pan-European primary prevention study. Although advice on a healthy diet (low in fat and rich in vegetables and fruit) was provided to the vast majority (>80%) of patients, only one-half received written dietary advice and only one-third were referred to a dietitian.[21] For patients, long-term adherence is the main issue. For example, in the Atherosclerosis Risk in Communities study including 12,744 subjects initially free of cardiovascular disease, only 0.1% of subjects maintained an ideal healthy lifestyle in the long-term.[22] We need to address issues with non-adherence to optimise the benefit of lifestyle intervention.

The difficulties associated with maintaining a healthy lifestyle in the long term often mean that dyslipidaemic patients will require additional therapeutic intervention. Statin treatment remains the cornerstone of lipid-modifying treatment to prevent cardiovascular disease.[23] Consideration may be given to the need for additional treatment for lowering elevated triglycerides or raising low HDL cholesterol. Once again, non-adherence to treatment is a key issue, especially in the high-risk patient. In a study reviewing adherence with three treatments prescribed in the post-MI setting (statin, beta blocker and aspirin), one in five patients stopped one medication and one in eight stopped all three treatments within one month of discharge from hospital.[24] Furthermore, as is the case with all long-term therapy, there is progressive decline in adherence. In one study, less than half (~40%) of acute coronary syndrome patients were still taking statin therapy two years post-MI.[25] This in turn translates to poorer outcomes.[26]

Promoting a healthy lifestyle and improving adherence to lipid-modifying treatments should be priorities for improving outcome. This is especially relevant in the light of increasing numbers of individuals at risk of coronary heart disease and ever increasing economic restraint in healthcare budgets

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Key messages

- Therapeutic lifestyle intervention underpins the management of dyslipidaemia
- Functional foods also have a role in management of elevated LDL cholesterol
- Metabolic syndrome is reversible with targeted intervention
- Improving adherence with lifestyle intervention and pharmacotherapy is a priority

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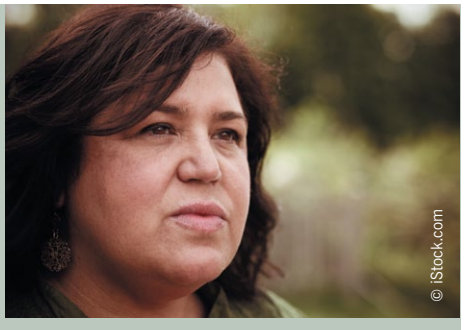
Case scenario

Consider secondary causes of dyslipidaemia

Hazel, a 49-year-old teaching assistant, was referred to the lipid clinic following admission with acute chest pain (subsequently considered non-cardiac, cardiac troponin negative). Her total cholesterol at the time of admission was 10.0 mmol/L. She had previously undergone thyroidectomy and radio-iodine ablation for papillary thyroid cancer. She had a history of treated hypertension (blood pressure [BP] 126/80 mmHg), was overweight (body mass index [BMI] 30.1 kg/m^2), physically active, a moderate drinker (10 units per week), recent ex-smoker and dietary assessment indicated scope for improvement. Both parents had type 2 diabetes and hypercholesterolaemia but no clinical cardiovascular disease. She was discharged on simvastatin 40 mg/day, aspirin 75 mg/day, levothyroxine 125 μg/day and lisinopril 5 mg/day. There was no evidence of stigmata associated with hyperlipidaemia.

At the clinic two months later her total cholesterol was 5.2 mmol/L (low-density lipoprotein [LDL] cholesterol 3.7 mmol/L, triglycerides 1.3 mmol/L, high-density lipoprotein [HDL] cholesterol 1.2 mmol/L) and thyroid profile was now within the target range for suppressive treatment (thyroid stimulating hormone [TSH] <0.05 mU/L, free thyroxine [FT4] 25.2 pmol/L). As post-ablation hypothyroidism was considered a possible cause of her dyslipidaemia on hospital admission, simvastatin was withdrawn to reassess her lipid profile. On repeat lipid testing one month later her total cholesterol was 6.3 mmol/L (LDL cholesterol 4.1 mmol/L, triglycerides 1.5 mmol/L and HDL cholesterol 1.6 mmol/L). Her Framingham 10-year cardiovascular risk was estimated at 13%. Hazel was advised to continue with therapeutic lifestyle interventions and return for repeat lipid testing in six months.



This case scenario highlights the importance of considering secondary causes of dyslipidaemia before instigating lipid-modifying treatment. Hazel's hypothyroidism due to radio-iodine ablation was the probable cause of dyslipidaemia. Following commencement of levothyroxine her cholesterol returned to more normal levels, and these were maintained after stopping statin therapy.

Translating evidence to practice

Jane Skinner

Introduction

Statins represent the cornerstone of treatment in guidelines for lipid management.[1] The clinical benefits have been confirmed by meta-analysis of major prospective studies which showed that statins reduced cardiovascular risk by about one fifth per mmol/L reduction in low-density lipoprotein (LDL) cholesterol, largely irrespective of the initial lipid profile, the presence of diabetes, or other presenting characteristics.[2,3] More intensive regimens produced further incremental benefit, compared with conventional-dose statin therapy.[4] Among patients at higher risk, such as those with pre-existing coronary heart disease (CHD) or with diabetes, the absolute clinical benefits were greater than in those at lower risk.[2] Furthermore, recent long-term follow-up of the Heart Protection Study shows that the cardiovascular benefits of statin therapy accrued as treatment continued and persisted for several years after the trial terminated. These data also provided reassurance that statins are safe, with no increase in cancer incidence or other safety concerns during extended follow-up.[5]

Current National Institute for Health and Clinical Excellence (NICE) guidance[1] recommends statin treatment for all adults with clinical evidence of cardiovascular disease. In the primary prevention setting, the guidance recommends systematic identification of adults (aged 40–75 years) likely to be at high risk of developing cardiovascular disease. Risk estimation is key to this process. Although preferable to clinical assessment alone, there are some outstanding concerns.

Improving risk estimation

Framingham-based risk assessment has been widely used and provides reasonable discrimination between individuals at higher or lower risk of cardiovascular disease. However, questions remain regarding its validity in contemporary populations, given differences between the Framingham study population (Caucasian US population) and the UK. For example, studies show that Framingham-based risk estimation can over-predict the absolute risk of cardiovascular disease in lower-risk populations, such as in South-East England.[6] Framingham-based risk estimation also does not take account of additional risk factors (**table 1**) leading to underestimation of risk in certain high-risk groups, such as socioeconomically deprived individuals.[7] As a consequence, statin treatment may be less available to those most in need.

Table 1. Examples of additional risk factors not included in Framingham risk estimation

- Socioeconomic deprivation
- Systemic inflammatory conditions
- Chronic kidney disease
- South Asian ethnicity
- Left ventricular hypertrophy

The development of QRISK1 may offer advantages given that it is better validated to the UK population than the Framingham model, and also includes additional variables, which improve risk estimates (such as positive family history of premature cardiovascular disease).[8] Therefore, QRISK1 may be a more equitable tool to inform management decisions and help ensure treatments are directed towards those most likely to benefit. Further refinement (QRISK2) offers marginal differences in performance compared with QRISK1.[9]

One group that has been largely overlooked in risk estimation has been those with severe mental illness. In a recent observational study, such individuals were shown to be at higher risk of cardiovascular death, which is not totally explained by antipsychotic medication, smoking or social deprivation scores. However, it was noted that individuals receiving the highest doses of antipsychotics were at greatest cardiovascular risk.[10]

Ultimately, it is recognised that there is a continuum for cardiovascular risk, with increasing risk requiring increased intensity of risk factor modification. As a consequence, intervention has been targeted to high-risk

groups, in particular those with pre-existing cardiovascular disease and/or diabetes. Building on this concept, implementation of the National Health Service (NHS) Health Checks programme is providing a more comprehensive assessment of individual health as a baseline for deciding the most appropriate actions to reduce cardiovascular risk.[11] The programme provides a systematic holistic approach to measuring patients' risk, rather than assessing individual risk factors.

Evolving recommendations for statin therapy

Current guidance recommendations are based on clinical and cost-effectiveness. In both primary and secondary prevention settings, simvastatin 40 mg is recommended as first-line treatment, although if contraindications or potential drug interactions limit its use, a lower dose or alternative statin, such as pravastatin may be considered.[1] People with acute coronary syndromes (ACS) should be treated with a higher-intensity statin.[1] Such an approach is supported by evidence from a meta-analysis comparing intensive- and conventional-dose statin therapy in acute ACS patients,[12] and evidence that both high-dose simvastatin and atorvastatin were cost-effective.[1]

Issues arise when considering the best approach in secondary prevention patients (without diabetes) who fail to achieve

cholesterol targets (total cholesterol <4 mmol/L or for LDL cholesterol <2 mmol/L) on simvastatin 40 mg monotherapy. Guidelines recommend either titrating the dose of simvastatin to 80 mg or switching to a drug of similar efficacy and acquisition cost.[1] Furthermore, in patients with type 2 diabetes, cost-effectiveness analyses indicated that two-step titration (simvastatin 40 mg titrated first to simvastatin 80 mg and then, if indicated, switched to atorvastatin 80 mg) is cost-effective in patients who fail to achieve lipid targets, especially high-risk patients.[13] However, it should be borne in mind that these recommendations relate to data available in 2008. New evidence about statins questions this strategy. SEARCH (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine)[14] highlighted an increased risk of myopathy associated with simvastatin 80 mg compared with 20 mg, equating to an excess risk of four per 1,000 person-years during the first year of treatment. As a result, the Medicines and Healthcare products Regulatory Agency (MHRA) issued a warning regarding the use of simvastatin 80 mg.[15] Additionally, recommendations for the use of atorvastatin are likely to be revised given that generic atorvastatin will be available in 2012.

Local implementation

From a local perspective, agreeing guidelines for lipid management should involve a partnership between primary and secondary care. To achieve this there needs to be a realistic reconciliation of national guidelines and any new evidence to develop one local guideline, providing a consistent management approach that will benefit patients. Practical barriers to implementation need to be recognised and addressed. Finally, partnership also implies ownership, which is clearly essential to implementation. Local clinical 'champions' may assist in this process.

Healthcare systems face a major challenge in achieving cost-effective use of resources to prevent cardiovascular disease. As indicated by guidelines,[1] lifestyle modification is an important component of lipid management. Statins are the mainstay of pharmacotherapy; however, in the light of new evidence relating to the efficacy and cost-effectiveness of different statins, revisions of current guidelines are likely. Moreover, statins should not be considered in isolation, as other treatments may offer benefit in managing abnormal lipids associated with the metabolic syndrome (elevated triglycerides and low plasma levels of high-density lipoprotein [HDL] cholesterol). Partnership between secondary and primary care is essential for ensuring successful implementation at the local level

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Key messages

- Emerging evidence highlights the need for timely review of guidelines, taking into account new data on the efficacy, safety and cost-effectiveness of statins in different settings
- Statin therapy should not be recommended in isolation; clinicians also need to take account of lifestyle intervention and other preventive drug treatments
- At the local level, partnership between primary and secondary care ensures successful implementation

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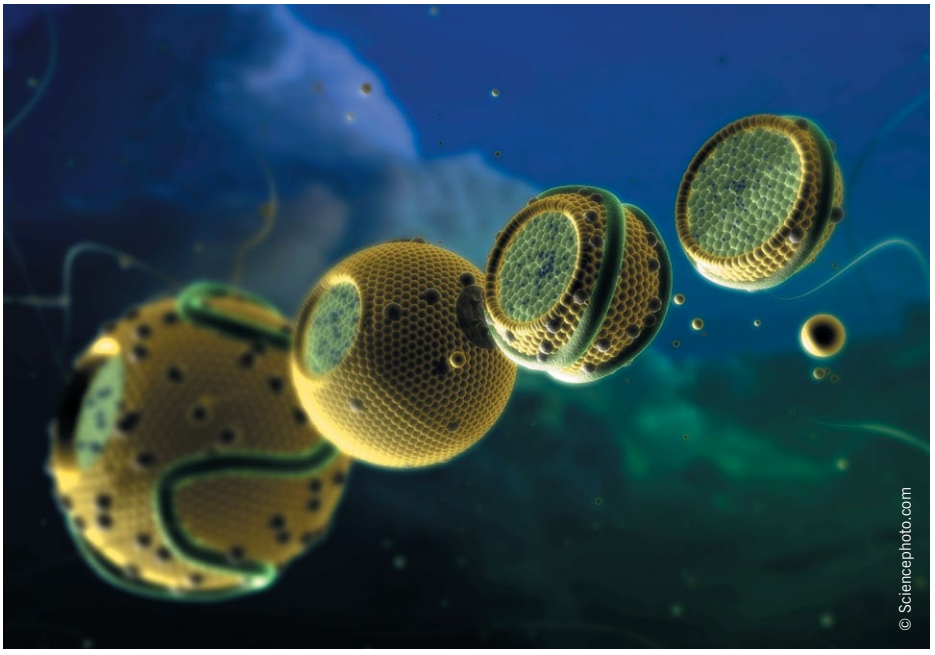
Addressing residual cardiovascular risk: what does the future hold?*

John Reckless

Introduction

There is conclusive evidence that lowering low-density lipoprotein (LDL) cholesterol levels with statins reduces the risk of cardiovascular disease events. However, it is also clear that a substantial residual cardiovascular risk persists, despite best treatment efforts.[1,2] Some of this residual risk will be determined by modifiable risk factors, such as lipids, hypertension, tobacco use and diabetes. Further reducing apolipoprotein (apo) B-containing atherogenic lipoproteins or increasing atheroprotective lipoproteins, specifically raising high-density lipoprotein (HDL) cholesterol,[2] are alternative proposed approaches to reducing this risk.



Other ways to reduce apoB lipoproteins

Based on regression analysis of major studies, further reduction of LDL cholesterol levels below current targets (<1.5 mmol/L or 57 mg/dL) may have potential.[3] Due to safety concerns with high-dose statin therapy, other approaches for reducing apoB levels are being investigated (**table 1**), although clinical outcomes data are so far not available.

Reducing apoB synthesis (e.g. mipomersen, a novel anti-sense oligonucleotide) may be one approach. In moderate hyperlipidaemia (mean LDL cholesterol 4.47 mmol/L) treatment with mipomersen (200–300 mg/week) was associated with ~45–60% reduction in LDL cholesterol and apoB-containing lipoproteins, and ~50% reduction in triglycerides, exceeding that observed with statins.[4] Mipomersen also reduced lipoprotein(a) (Lp[a]),[4] recognised as an additional cardiovascular risk factor.[5] However, the frequency of liver enzyme elevations and risk of hepatic steatosis (fatty liver) require further evaluation.[4]

The nuclear receptors known as peroxisome proliferator-activated receptors (PPARs) and liver X receptors (LXRs) are lipid-activated transcription factors that have emerged as key regulators of lipid metabolism and inflammation. Agents acting at these receptors are under investigation. Additionally, eprotirome (KB2115), a thyroid hormone analogue that is poorly taken up by heart and bone, can favourably modulate lipid profiles. In statin-treated patients, eprotirome produced dose-related reductions in LDL cholesterol levels (by up to ~30%). Similar reductions were also observed for triglycerides and Lp(a).[6]

Targeting LDL-receptor expression is another possibility. LDL is taken up through LDL-receptors on the cell surface. These LDL-receptors are either recycled back to the cell surface or are directed by proprotein convertase subtilisin/kexin type 9 (PCSK9) to degradation. A genetically upregulated PCSK9 is a cause of familial hypercholesterolaemia, while low PCSK9 activity protects against atheroma.[7,8] These data suggest that inhibition of PCSK9 may have therapeutic potential.

Inhibition of microsomal transfer proteins (MTP), which are involved in the assembly of hepatic very-low-density lipoprotein (VLDL) and gut chylomicron lipoprotein particles, may be another target. The oral MTP inhibitor lomitapide, given as monotherapy or in combination with ezetimibe, lowered LDL cholesterol and apoB levels by ~50% in patients with familial hypercholesterolaemia (FH) or moderate hypercholesterolaemia.[9,10] However, the clinical utility of these agents may be restricted by their potential to induce elevation of liver enzymes and hepatic steatosis,[9,10] although lomitapide was granted orphan drug designation in December 2010 for familial hyperchylomicronaemia.[11] To overcome these adverse hepatic effects, non-absorbable, enterocyte-selective inhibitors of MTP are under investigation.[12]

*This article contains information relating to a number of investigational agents which are currently unlicensed for medicinal use.

Table 1. Reducing low-density lipoprotein (LDL) cholesterol levels: potential options

Mode of action	Agents
Inhibition of hepatic cholesterol synthesis	Statins
Inhibition of cholesterol absorption leading to increased hepatic LDL-receptor expression	Bile acid sequestrants, ezetimibe
Inhibition of synthesis of apoB-containing lipoproteins	ApoB anti-sense oligonucleotides (e.g. mipomersen); microsomal transfer protein inhibitors (e.g. lomitapide)
Increasing LDL-receptor recycling	PCSK9 inhibitors

Key: apoB = apolipoprotein B; PCSK9 = proprotein convertase subtilisin/kexin type 9

Table 2. Raising high-density lipoprotein (HDL) cholesterol: potential options

Mode of action	Agents
HDL mimetics	ApoA-I mimetics, reconstituted HDL
PPAR agonism	Nicotinic acid
Redistribution of cholesterol between lipoproteins, aiming to increase recycling of cholesterol to the liver	CETP inhibitors

Key: apoA-I = apolipoprotein A-I; CETP = cholesteryl ester transfer protein; PPAR = peroxisome proliferator-activated receptor

Targeting non-LDL lipids

An alternative approach is to target non-LDL lipids. In post-hoc analyses of prospective trials in high-risk patients, elevated triglycerides or low plasma concentrations of HDL cholesterol have been associated with residual cardiovascular risk, even among patients achieving low LDL cholesterol.[13,14] The evidence for elevated triglycerides alone as a cardiovascular risk factor is contentious. In contrast, observational studies conclusively established HDL cholesterol as an important predictor of cardiovascular risk, independent of LDL cholesterol levels and other lipid and non-lipid factors.[15] The combination of low HDL cholesterol and elevated triglycerides, one of the defining features of the metabolic syndrome, is associated with increased cardiovascular risk.[16]

Targeting HDL cholesterol to reduce residual cardiovascular risk is, therefore, an attractive hypothesis. Nicotinic acid (niacin) is currently the only agent available that effectively raises HDL cholesterol, as well as lowering LDL cholesterol, triglycerides and Lp(a). In the Coronary Drug Project, treatment with nicotinic acid (immediate-release formulation 3 g/day) was associated with modest reduction in non-fatal myocardial infarction at the end of treatment and 11% reduction in all-cause mortality (p=0.0004) at 15 years (~9 years after the end of treatment).[17]

However, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes) study[18] was prematurely terminated 18 months ahead of schedule because extended-release nicotinic acid offered no additional benefits in these statin-treated patients with cardiovascular disease. A number of caveats need to be borne in mind; this event-driven trial was not sufficiently powered, achieved only a modest difference in HDL cholesterol and may have been compromised by the placebo containing a low dose of nicotinic acid (50 mg) to mask the study treatment. We need to wait for the results of the HPS2-THRIVE study in 25,000 participants, which is sufficiently powered to test the value of adding nicotinic acid to statin therapy.[19]

Several emerging HDL therapies, including reconstituted HDL, apoA-I mimetics and cholesteryl ester transfer protein (CETP) inhibitors may offer potential for increasing HDL cholesterol (**table 2**).

CETP in human plasma promotes transfer of cholesterol from HDL to LDL and triglyceride-rich lipoproteins such as VLDL and chylomicrons. Therefore, inhibition of CETP has the potential to shift the balance of plasma cholesterol in favour of the protective HDL fraction.[20] Phase II trials with the CETP inhibitors currently in development have shown promising results.[21-23] However, we need to wait for the results of ongoing major outcomes studies to evaluate whether these lipid changes translate to reduction in cardiovascular events. Additionally, we do not know whether HDL particle composition changes (and how achieved) will translate into functional change, for high HDL cholesterol *per se* might not augment cardiovascular protection.

Improving best practice: the way forward

These are exciting times in the development of new approaches aimed at targeting residual cardiovascular risk in statin-treated patients, and the results of clinical outcomes studies are awaited with interest.

For current practice, lifestyle intervention, statins and targeting low levels of HDL cholesterol and elevated triglycerides, which are characteristic of the metabolic syndrome and type 2 diabetes, are key issues. Better care, including counselling about therapeutic lifestyle intervention, and improving patient adherence are also priorities to improve practice and clinical outcomes

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Key messages

- Despite best treatment efforts, statin-treated patients often remain at a high risk of residual cardiovascular events
- Therapeutic interventions that further reduce apo B-containing atherogenic lipoproteins or raise atheroprotective lipoproteins, as in HDL may offer potential
- Results from ongoing outcomes studies are needed to evaluate the potential of nicotinic acid and the CETP inhibitors
- For current practice, clinicians should not overlook the value of therapeutic lifestyle intervention, as well as improving adherence with available pharmacological options

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