Lipids and lipid-modifying therapy

Professor Mike Kirby, Editor

Dyslipidaemia plays a key role in the development of cardiovascular disease (CVD). Therefore, the identification and treatment of dyslipidaemia is important for both primary and secondary CVD prevention, and forms the basis of this article.

Cardiovascular disease (CVD) remains the leading cause of death worldwide, and despite many advances in treatment it remains a significant cost to society.

CVDs include coronary heart disease (CHD), ischaemic heart disease, angina, atrial fibrillation, heart failure, myocardial infarction (MI), stroke and vascular dementia. Many of these are more common in men than in women, particularly in older age groups (see Figure 1 and 2).

The World Health Organization reported that CHD was the leading cause of global mortality in 2016, accounting for more than 9 million deaths, followed by stroke, which accounted for more than 5.5 million deaths. Combined, these two CVDs have been the leading causes of death globally since 2000.

Around 74 million people in the UK have CVD, and the related healthcare costs are estimated to be £9 billion each year. Increased longevity, a growing population and improved survival rates from heart and circulatory events are also likely to result in a rise in these numbers.

Figure 1. Prevalence of any CVD condition, by age and sex

CVD causes more than a quarter of all deaths in the UK – almost 170,000 each year, of which 44,000 are premature. Around 1.5 million men in the UK have CHD, versus 830,000 women, and 1 in 7 men die from it compared with 1 in 12 women. People with CHD are also twice as likely to have a stroke. Although death rates from CHD and other cardiovascular disease have declined significantly in the UK over the last 60 years, much still needs to be done (see Figure 3).

Lipids and lipoproteins

Lipids are insoluble in water and so must be transported in association with proteins in the plasma. Lipoproteins play an important role in the absorption and transport of dietary lipids via the small intestine, the transport of lipids from the liver to peripheral tissues, and the transport of lipids from peripheral tissues to the liver and intestine (reverse cholesterol transport).

The lipoprotein classes include:
- Chylomicrons – triglyceride (TG)-rich carriers of dietary fats.
- Very low-density lipoproteins (VLDL) – TG-rich carrier of hepatically synthesised TGs.
- Intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) – cholesterol-rich remnant particles derived from lipolysis of TGs in VLDL.
- High-density lipoprotein (HDL) – cholesterol-rich particle that transports cholesterol for hepatic disposal or recycling.

Dyslipidaemia and CVD

Atherosclerosis is the underlying cause of CVDs such as CHD, heart attacks and strokes. Cholesterol is a key component of the arterial plaques that are involved in the pathogenesis of atherosclerosis. Elevated levels of LDL-C and apolipoprotein B (apoB) 100 (the primary protein in LDL) are directly associated with risk of...
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Atherosclerotic cardiovascular events (ASCVE). Infiltration and retention of apoB-containing lipoproteins within the arterial wall initiates an inflammatory response and promotes the development of atherosclerosis. All of the lipoproteins that contain apoB are considered atherogenic, and both lipoproteins and TG-rich remnant lipoproteins are thought to promote atherothrombosis as well.8

In recognition of this, the 2019 European Society of Cardiology/European Atherosclerosis Society guidelines recommend to measure apoB to help assess CVD risk.9

Diabetes and CVD
Diabetes is more common in men than in women.3 Diabetes increases the risk of CVD, and epidemiological and observational data suggest that people with diabetes are at a level of risk broadly equivalent to those with no diabetes but proven coronary disease.10–12

People with diabetes have a particularly atherogenic lipid profile (diabetic dyslipidaemia), which is a key contributor to the development of atherosclerosis. This is characterised by elevated levels of TGs, TG-rich lipoproteins, small dense LDL particles, and reduced HDL levels.13

Lipid modification to reduce CVD events
Normally, most cholesterol is carried in low-density lipoprotein cholesterol (LDL-C) and there is a strong, graded, positive association between total and LDL-C, and the risk of CVD over a wide range of plasma cholesterol concentrations.14,15

There is unequivocal evidence that reducing plasma LDL-C reduces CVD risk, and various trials and epidemiological studies, with and without statins, using angiographic or clinical endpoints, have confirmed that the reducing LDL-C is also key component in preventing CVD.16

There is a dose-dependent reduction in CVD with LDL-C lowering. Standard statin therapy has been shown to safely reduce the five-year incidence of major coronary events, coronary revascularisations and ischaemic strokes by approximately one-fifth per 1.0mmol/L reduction in LDL-C, and more intensive statin therapy was associated with further reductions in the incidence of these major vascular events.17 ApoB appears similar to LDL-C as a marker of CV risk,15,18 and its determination may be more reliable in laboratory tests, particularly in patients with marked hypertriglyceridaemia (>3.4mmol/L).15

Triglyceride-rich lipoproteins (TRL) and their remnants have been identified as important contributors to atherosclerotic CVD in epidemiological and genetic studies.19 In the PROCAM study, the risk of CVD increased with TG levels up to 9mmol/L (after correction for other risk factors for CVD).20 While TG levels are usually checked in the fasting state, some evidence suggests that non-fasting TG levels, which reflect post-prandial levels, may be more closely aligned with CVD risk.21,22 However, raised TG levels are not included in the Framingham,23 ASSIGN24 or QRISK risk calculators.25

Figure 2. Prevalence of stroke, by survey year and sex2

Figure 3. Age-standardised death rates per 100 000 from coronary heart disease in the UK4

Death rates per 100 000

Men Women

Percent

Year

1994 1998 2003 2006 2011 2017

0 1 2 3

Men Women

Deaths per 100 000

1977 1987 1997 2007 2017

0 100 200 300 400 500 600 700

1977 1987 1997 2007 2017

0 100 200 300 400 500 600 700
It is important to note that severe hypertriglyceridaemia increases the risk of pancreatitis.\textsuperscript{19}

**Identifying CV risk**
The National Institute for Health and Care Excellence (NICE) provides guidance on identifying and assessing CV risk, along with lipid modification therapy to reduce this risk.\textsuperscript{26,27}

For the primary prevention of CVD in primary care, a systematic strategy should be used to identify individuals who are likely to be at high risk and prioritise those with an estimated 10-year risk of CVD $\geq 10\%$ for a full formal risk assessment.\textsuperscript{26}

The QRISK3 is the preferred risk assessment tool, as it uses additional risk factors such as erectile dysfunction (ED), which not only increases its potential value in identifying those at most risk of heart disease and stroke, but reminds

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**Figure 4. Guidance for the management of hypertriglyceridaemia\textsuperscript{41}**
clinicians to check testosterone, which is itself an independent risk factor.28 A risk assessment tool is not required for people with pre-existing CVD, a high risk of developing CVD due to familial hypercholesterolaemia, type 1 diabetes, or an estimated glomerular filtration rate (eGFR) less than 60ml/min/1.73m² and/or albuminuria. Severe obesity (BMI >40kg/m²) also increases the risk of CVD.26

It should be noted that standard CVD risk scores may underestimate risk in people at additional risk due to other medical conditions or treatments.26 Clinical assessment should include smoking status, alcohol consumption, blood pressure, BMI or other measure of obesity and renal function. Baseline blood tests should include total cholesterol, HDL-C, non-HDL-C, TGs, HbA₁c, eGFR, transaminase level (alanine aminotransferase or aspartate aminotransferase) and thyroid-stimulating hormone.

If ED is present, then measure the patient’s testosterone and sex hormone binding globulin (SHBG) to calculate free testosterone.25,26 Non-HDL-C is recommended over LDL-C, because non-HDL-C is calculated as total cholesterol minus HDL-C, while LDL-C is not measured directly and instead requires a calculation using a fasting sample and for TG levels to be <4.5mmol/L.26

**Lifestyle modification**

Lifestyle modification remains a first-line intervention for the primary and secondary prevention of CVD. This includes a cardioprotective diet, adequate physical activity, weight management, moderating alcohol consumption and smoking cessation.26,29,30

**Pharmacological treatment**

**Primary prevention**

Atorvastatin 20mg is recommended for the primary prevention of CVD in men with a ≥10% 10-year risk of CVD, those with chronic kidney disease, and those with type 1 diabetes who:
- are aged >40 years, and/or
- have had diabetes for >10 years, and/or
- have established nephropathy, and/or
- have other CVD risk factors.

Atorvastatin 20mg may also be appropriate in patients aged over 85 years to reduce the risk of non-fatal myocardial infarction.26 While NICE recommend a >40% non-HDL-C reduction in primary prevention, due consideration should also be given to the baseline LDL-C and the CVD risk.21 A recent meta-analysis indicated that, as compared to less potent regimens, more intensive LDL-C lowering therapy is associated with greater reduction in total and CV mortality.31 A strategy to refine individual patient regimens, taking all factors into consideration, is therefore advised.

Ezetimibe monotherapy may be considered for the treatment of primary (heterozygous familial or non-familial) hypercholesterolaemia in men in whom initial statin therapy is not tolerated or contraindicated. Ezetimibe may also be combined with statin therapy in men who have already started a statin, when serum total or LDL-C levels are not appropriately controlled after appropriate dose titration of initial statin therapy (or because dose titration is limited by intolerance to the initial statin therapy), or when a statin switch is being considered.32

The PCSK9 inhibitors, Alirocumab and Evolocumab, are potential options for secondary prevention in men with primary hypercholesterolaemia or mixed dyslipidaemia who at high or very high CV risk, if their LDL-C levels remain >4mmol/L and >3.5mmol/L, respectively, despite maximal tolerated lipid lowering therapy.33,34

**Secondary prevention**

For people with established CVD, statin treatment should not be delayed by the management of modifiable risk factors. Initiate patients with atorvastatin 80mg, although a lower dose should be used if there is a high risk of adverse effects, the potential for drug interactions, or if the patient prefers it.26 A lower statin dose (atorvastatin 20mg) is recommended for secondary prevention in men with CKD. This dose may be increased if the patient fails to achieve a >40% reduction in non-HDL cholesterol and their eGFR is ≥30ml/min/1.73m². If the eGFR is <30ml/min/1.73m², dose increases should be agreed with a renal specialist.26

It is appropriate to reduce LDL-C to as low a level as possible, at least in patients at very high CV risk. For this reason a minimum 50% reduction is suggested for LDL-C reduction, together with reaching the tailored goal, an LDL goal of <1.4mmol/L is advised.9

If statins cause side-effects, the initial approach is to stop and then re-challenge with the same or a different statin, followed by a switch in statin type, step-by-step reduction in dose and intermittent/alternate day statin dosing. Ezetimibe may be combined with a lower dose of statin or used alone. Bile acids are an alternative, but many are poorly tolerated.

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**Follow-up**

Total, HDL-C and non-HDL-C should be reassessed at three months in all
people started on high-intensity statin treatment (for both primary and secondary prevention, including atorvastatin 20mg for primary prevention), aiming for >40% reduction in non-HDL-C. If this level of reduction is not achieved, discuss medicines adherence, dose timing, and lifestyle modification. Consider increasing the dose if treatment was initiated with less than 80mg of atorvastatin and the person is considered at increased risk due to comorbidities, risk score or clinical judgement.36

**Other potential interventions**

While statins, ezetimibe and PCSK9 inhibitors are effective in reducing hypercholesterolaemia, target LDL-C levels may still not be achieved, with a consequent increase in residual CV risk. Emerging drugs – including cholesteryl ester transfer protein inhibitors, ATP citrate lyase inhibitors, microsomal TG transfer protein inhibitors, antisense oligonucleotides, small interfering RNA, and peroxisome proliferator-activated receptor type α agonists – may all offer additional options in the future.36

In a systematic review and meta-analysis, vitamin D supplementation appeared to have a beneficial effect on reducing total cholesterol, LDL-C and TGs, but not HDL-C levels. The improvements in total cholesterol and TGs were greater in subjects with baseline vitamin D deficiency.37

In a recent systematic review, probiotic supplementation was associated with significant reductions in total cholesterol, LDL-C and TGs, and increases in HDL-C, although further studies are required to clarify the long-term effects and the influence of probiotics when combined with drug therapy.38

The ACC/AHA 2018 guideline underscores the critical importance of assessing hypertriglyceridaemic patients for lifestyle factors, secondary disorders, and implicated medications. Pharmacological management in severe hypertriglyceridaemia is centred on fenofibrate and omega-3 fatty acid therapy, with the goal of preventing pancreatitis. For ASCVD risk reduction, statins are advised as the cornerstone, with emerging evidence on omega-3 fatty acid therapy from the REDUCE-IT trial set to impact future guidelines.39

The 2019 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidaemia9 became the first major international guideline to state that measurement of apoB levels ‘is recommended’ to help assess ASCVD risk and estimate the expected clinical benefit from lipid-lowering therapy. This is in anticipation of the availability of novel lipid-lowering therapies in the future and the need to measure apoB to help guide selection of the optimal therapy for each person.40

A helpful primary care flow chart has been created by Lambeth CCG that provides guidance to aid clinicians in the management of hypertriglyceridaemia.41

**Conclusion**

To reduce CVD-related morbidity and mortality in men, a multifaceted approach is often required. This approach should include lifestyle modification and optimal management of other CVD risk factors, along with pharmacological treatment if required. However, with estimates suggesting that almost half of adults in the UK have cholesterol levels above what the national guidelines recommend (total cholesterol >5mmol/L),3 many patients are failing to achieve lipid goals and this includes patients at high or very high risk of CVD.

Prevention is better than cure, and educating men on the importance of a healthy lifestyle and adherence to pharmacological treatments in relation to CV risk reduction is key.

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