Lipids explained

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Rhiannon Edwards is British Heart Foundation familial hypercholesterolaemia clinical specialist nurse, Royal Gwent Hospital, Newport

Correspondence
rhiannon.edwards6@wales.nhs.uk

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Abstract

One of the risk factors for cardiovascular disease commonly seen in primary care is raised cholesterol. People are becoming more aware of the implications of lipid lowering treatments, and are questioning the balance of treatment risk versus cardiovascular risk. At a time when prevention is becoming a priority in health care, it is increasingly important for patients to be counselled about cholesterol and future risk before lipid lowering therapy, to ensure compliance. This article aims to provide all the necessary information for primary health care professionals to feel competent in these discussions.

RAISED CHOLESTEROL is one of the risk factors strongly associated with cardiovascular disease (CVD), and the worldwide epidemic of CVD poses a significant challenge (Berra *et al* 2011). Six out of ten patients seen in general practice have cholesterol levels above 5mmols/L (British Heart Foundation 2010).

Most of these patients will have raised cholesterol influenced by multiple factors such as diet, exercise, obesity and alcohol consumption (polygenic hypercholesterolaemia). However, other causes could include an inherited disposition to raised cholesterol (monogenic disorders of lipid metabolism) or disorders of hypertriglyceridaemia.

Raised cholesterol causes a three-fold challenge for healthcare providers:

- Encouraging lifestyle change – which can reduce cholesterol levels and should be encouraged, but evidence shows patient adherence is variable (Multiple Risk Factor Intervention Trial Research Group 1982).
- Lipid lowering medication – choice and patient compliance.
- Patient perspectives of risks – managing perceptions.

Aims and intended learning outcomes

This article aims to provide information to assist in explaining cholesterol to patients, including the importance of lifestyle modifications and why pharmacological treatment or referral to secondary care may be required.

It is important to involve the patient in discussions regarding the management of cholesterol, to promote reduction in cardiovascular risk by lifestyle changes and medicine compliance.

Reading this article and completing the time outs will enable the reader to:

- Describe simply to patients the distinctions between 'good' and 'bad' cholesterol.
- Help patients to understand how diet and lifestyle may play a role in either increasing or limiting risk of premature cardiovascular disease.
- Outline why lipid and family cascade screening is important to the assessment of risks associated with premature cardiovascular disease and inherited lipid disorders.
- Summarise the recommended risk management approach using statins.
- Explore the need for patient information sheets and when referral is important.

1 Patient understanding

Time out

Make a list of some of the problems you have encountered in practice when helping patients understand and respond to the associated risks of lipids that can lead to premature cardiovascular disease.
Examine your list to determine whether any of these problems are associated with:
a) not understanding lipids and attendant threats,
b) expressing misconceptions about lipids,
c) sharing doubts about statins or related treatments.
At the end of this article you will be asked to review your understanding of these problems'.

What are lipids?

Lipids are fatty substances essential to life; they have an important function within cell structure and function and also for energy storage. Cholesterol, in particular, is also vital in the production of bile acids, steroid hormones and vitamin D. There are many types of lipids but this article will concentrate on triglycerides and cholesterol, because of their association with vascular disease. There are two main sources of lipid production:

Exogenous (originates externally from diet) The majority of lipids that are produced from dietary sources are from saturated fats. These are converted into triglycerides (fatty acids) in the stomach. A small amount of cholesterol is also derived from cholesterol-rich food groups such as egg yolk, liver, kidney and shell fish.

It is understood, however, that only between 30 and 60 per cent of this cholesterol is absorbed into the circulation, so most patients (those with no inherited predisposition to raised cholesterol) do not need to be concerned with reducing these food groups (REF NEEDED HERE).

Endogenous (originates internally) cholesterol is formed primarily in the liver via a process of biosynthesis. Part of this process includes a rate-controlling enzyme called 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, which is inhibited by the use of statins.

2 Information sheet

Time out

Prepare a plan for the production of a simple patient information sheet, one that you might use to explain lipids and risk to patients.

If you already use such a tool, review it to see how clear it is, drawing on what you learn in this article.

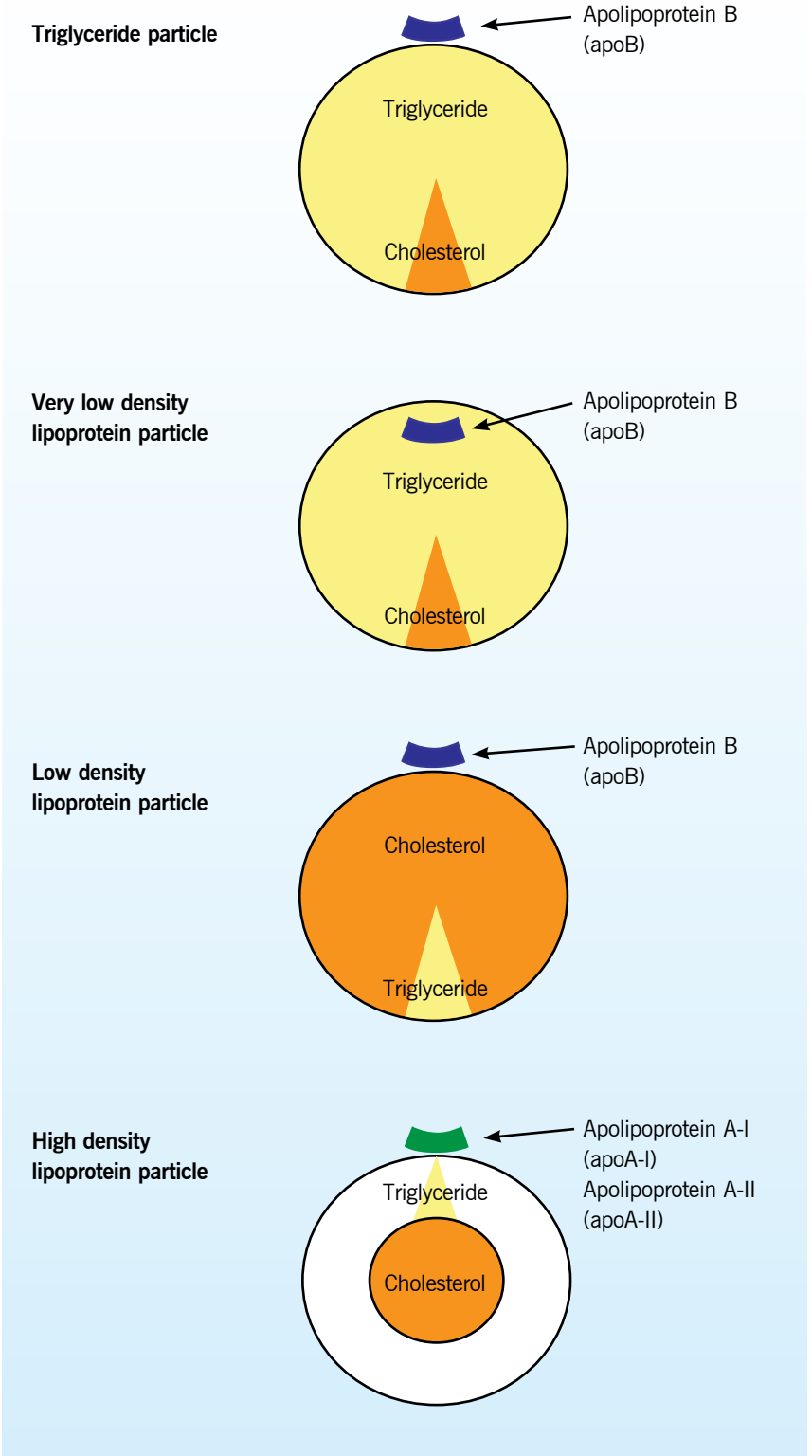
The first challenge is to explain simply, in no more than a couple of sentences, what cholesterol is.

Transport of cholesterol

Lipoprotein particles are the transport vehicles for cholesterol and triglycerides. There are four types of lipoprotein particles, categorised by their levels of cholesterol and triglyceride, and each particle has a different biological role (Figure 1).

Triglycerides are the largest particles of lipoprotein containing mostly triglyceride and a small amount of cholesterol. They are produced by the intestines after the digestion of fat, and are absorbed into the circulation via the intestines to be used as a major source of energy and heat insulation. They are stored in adipose (fat) tissue as chylomicrons. Triglycerides are raised in the blood immediately following food for several hours, and will affect total cholesterol levels. The clinical significance of raised triglycerides

Figure 1 Lipoprotein particles



Box 1 Family history

Family history of premature heart disease (<55 years in males, <65 years in females) is crucial in the assessment of cardiovascular disease risk and in the identification of inherited lipid disorders. It should always be recorded in the patient records and taken into account when estimating risk.

When using the Joint British Society guidelines on the prevention of cardiovascular disease (Joint British Societies Guidelines on Prevention of Cardiovascular Disease (JBS3) www.jbs3risk.com) risk assessment charts, located at the back of the British National Formulary (BNF www.bnf.org), multiply risk by 1.5 in patients with premature CHD in one first degree relative (mother, father, brother, sister), and by two when this is evident in two or more first degree relatives.

(>2mmols/L) is identifying the underlying cause; high alcohol consumption, metabolic syndrome (central obesity, impaired fasting glucose, hypertension) or diabetes can all cause raised triglycerides. Other causes include underlying liver dysfunction, or various genetic influences. There is no strong correlation with raised triglycerides causing premature coronary heart disease (CHD). However, levels in excess of 11mmols/L can increase the risk of acute pancreatitis.

Very low density lipoprotein (VLDL) particles have the same function as triglycerides and are transported in the same way. However, they are produced in the liver rather than by dietary means. They are transported to the intestines via the bile duct, where they are absorbed through the intestinal walls into the circulation. When the triglycerides in the VLDL are removed from the circulation and stored as chylomicrons, the VLDL particles remain in the circulation as low density lipoprotein particles.

Low density lipoprotein (LDL) particles are the product of VLDL with triglyceride removed. These particles are smaller, dense cholesterol-rich particles, and stay in the circulation nine times longer than VLDL. They can pass easily through the blood vessel walls, where they can oxidise, creating plaques, and raising risk of CVD. LDL particles are removed from the circulation via the liver using LDL receptor cells.

High density lipoprotein (HDL) particles are similar to LDL particles, but the cholesterol is densely packed into its core, which creates space for the particle to transport excess cholesterol from the circulation to the liver. Scavenger receptors on the surface of the liver then allow removal of cholesterol from the HDL particle without destroying the particle, allowing it to continue circulating.

Due to their role in transporting cholesterol, these different lipoproteins have been named:

- LDL cholesterol – bad cholesterol (lower better).
- HDL cholesterol – good cholesterol (higher better).

Box 2 Lifetime risk calculator

Updated Joint British Society guidelines on the prevention of cardiovascular disease (JBS3 www.jbs3risk.com) are being prepared. The established guidance for assessing CVD risk based on a ten-year risk equation, as supported by the National Service Frameworks (Department of Health 2005, Welsh Government 2009) and Quality Outcome Framework (QOF) indicators will be replaced by a new lifetime risk calculator.

This will change the risk calculation from a relative risk, (comparing the individual's risk to that of a similar aged population) to an absolute risk (an individual's risk of a cardiovascular disease event in their lifetime, estimated 30 years). The change in approach, will underpin a new aggressive approach to prevention, especially in younger people who have previously fallen beneath the treatment thresholds.

3 Cholesterol transporters

Time out

Decide what you will write (or update) in the information sheet about cholesterol transporters. Sometimes patients think of these simply as different types of fat. Does that seem a good understanding, or is there something about transportation that will help you make future points about damage to blood vessels and risks to the heart?

Apolipoproteins

Apolipoproteins (apoA-I/A-11, apoB, apoC, apoE) are proteins that bind cholesterol particles together, giving them structure, but they also are ligands (or glue) that enable the lipoproteins to attach to the blood vessel wall or liver receptors (Figure 1).

Of particular importance is the LDL apolipoprotein, ApoB. This is being used by some clinicians to identify a surrogate (alternative) marker for high levels of atherosclerotic particles on the blood vessel wall, which can assist in assessing CHD risk. This may become a more important factor in the future, as LDL cholesterol is usually a calculated measurement (LDL-c), rather than a direct representation of LDL cholesterol measurement.

4 Good and bad cholesterol

Time out

Decide how you will distinguish between good and bad cholesterol in the information sheet. The distinction is vital as dietary choices can later influence CVD risk. Asking patients to state examples of good and bad cholesterol foods will help you confirm their understanding of the distinctions.

Measurement and treatment

The National Institute for Health and Clinical Excellence (NICE 2008a) guidance on lipid modification (NICE) recommends that patients over the age of 40 should have a CVD risk calculation carried out using existing electronic records, including modifiable risk factors, blood pressure, cholesterol, smoking status, body mass index (BMI) and non modifiable risk factors, gender, age, family history (Box 1) and ethnic origin. If this calculation identifies a greater than 20 per cent CVD risk over ten years (high risk) the patient should be offered a full formal risk assessment.

Risk assessment tools are useful for primary prevention assessment, but should not used for patients who are already considered high risk, with existing CHD, peripheral vascular disease (PVD), diabetes or any inherited cholesterol conditions (Box 2).

Some risk assessment tools do not take into account family history of premature CVD and can also use surrogate markers of population age-related cholesterol (Beswick *et al* 2008). Therefore, it is important that these risk assessments are seen only as an estimation of risk, and clinical judgement should always take precedence.

Individuals with a family history of premature CHD or raised cholesterol should always be offered cholesterol testing to rule out any inherited lipid disorders.

Once this risk assessment has been carried out, patients fall into three categories high (<20 per cent), medium (10 per cent to 20 per cent) and low risk (>10 per cent). For those patients who fall into the medium and low risk categories, lifestyle moderation should be encouraged, with further monitoring of risk factors, as appropriate.

High risk patients should then be offered a formal risk assessment to include all CVD risk factors and measurement of both total cholesterol and HDL levels (followed by a full lipid profile, if these levels are raised) (Smellie *et al* 2011).

A non-fasting blood sample may be obtained in a secure seal tester (SST) bottle (yellow top), but bear in mind that triglycerides may be raised following food, leading to an inaccurate result. If triglycerides are above 2.3mmols/L, a fasting sample (approximately 12 hours) should be rechecked approximately one week later (Smellie *et al* 2011).

Assessing the CVD risk associated using the calculated LDL level has recently been questioned, due to the emergence of the ApoB, an alternative marker of atherosclerotic disease (Boekholdt *et al* 2012). ApoB can be directly measured by pathology laboratories, or indirectly measured using non HDL cholesterol (total cholesterol – HDL cholesterol). ApoB can also be calculated in a non-fasting blood sample correctly, providing improved screening opportunities.

Box 3 Guidance on hydroxyl-methlglutaryl-co-enzyme (HMG CoA) reductase inhibitors – statins (NICE 2008a)

Primary prevention

Lifestyle modification should be encouraged. If treatment is then considered for primary prevention of cardiovascular disease, then Simvastatin 40mg is indicated. If this is not tolerated, a reduced dose of simvastatin or pravastatin can be offered. There are no targets for cholesterol or LDL reduction in those treated for primary prevention.

Secondary prevention

Should be treated at presentation with simvastatin 40mg and then up titrated to higher intensity statins to achieve target total cholesterol reduction to 4mmols/L and LDL-c reduction to 2mmols/L.

Monitoring

Recheck cholesterol levels, creatine kinase (CK) and liver function tests (LFTs) eight to 12 weeks following initiation of medication, up-titrate medication if appropriate, and then recheck every eight to 12 weeks until target is achieved, followed by annual checks.

Fibrates

Fibrates are not considered first-line medication for raised cholesterol, due to the lack of scientific evidence of the reduction in cardiovascular disease mortality, but they are used as an alternative to statins, and can marginally lower LDL cholesterol. Fibrates have been used to lower triglycerides and cholesterol since the 1930s, but their action is complex and not fully understood. This medication is commonly used in conditions which cause isolated raised triglycerides, due to its action to reduce VLDL production.

Other

Niacin, bile acid sequestrants and omega 3-fatty acids are also used to reduce cholesterol in high-risk individuals, especially in those not achieving targets, or in statin intolerance.

More information can be obtained in the BNF Chapter 2.12 (http://tinyurl.com/cmc55to).

5 Lifestyle

Time out

Explaining lipid risk screening is an important part of patient information sheets. Patients may approach your discussion fearing that the interview is all about lifestyle blame. So how does (or will) the information sheet explain the possible causes of high levels of 'bad cholesterol'?

Treatment options

Lifestyle modification Persuading patients to alter their lifestyle, irrespective of lipid lowering medication, is sometimes difficult. Although lifestyle modifications in general are well documented to improve risk factors associated with CVD (DH 2005, Welsh Government 2009, Maruthur *et al*

2009), they will not be discussed in detail in this article. However, cholesterol reduction in particular is influenced by several factors linked to lifestyle.

Dietary cholesterol Cholesterol from diet can account for approximately 8 to 10 per cent of the blood cholesterol measured. Therefore, a reduction in dietary saturated fat, along with a healthy well-balanced diet, can reduce cholesterol levels by up to 9 per cent (Jenkins *et al* 2005).

High density lipoprotein The protecting element of HDL was identified in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT) study (Rubins *et al* 1999) where results showed that an increase of 0.13mmols/L of HDL reduced CHD events by 11 per cent. Lifestyle measures to increase HDL include; diets rich in oily and white fish, white meats, dark green vegetables, flaxseeds, olive or rapeseed oil products and regular exercise. Inversely, smoking has been shown to reduce HDL cholesterol (REFERENCE NEEDED FOR THESE POINTS).

Plant stanols Plant stanols and sterols are derived from plant extracts and are similar in structure to cholesterol. Their action is to bind with cholesterol in the gastrointestinal tract and assist in cholesterol excretion. Research has identified that for plant sterol to be effective, the daily levels should be between 1g and 3g a day, which can reduce LDL cholesterol from between 5 and 15 per cent (Nguyen 1999). This is the basis for the claims of LDL cholesterol reduction for stenol-enhanced food products such as margarines and yoghurt drinks.

Pharmacological treatment

Statins It has been well documented that statins (hydroxyl-methlglutaryl-co-enzyme (HMG CoA) reductase inhibitors) are the foremost treatment for the reduction of cholesterol (Marks *et al* 2000) (Box 3). Statins inhibit the enzyme pathway responsible for creating cholesterol in the liver.

The reduced production of endogenous cholesterol then produces a secondary effect, as the liver responds to this by increasing LDL receptor activity; this improves the uptake of LDL cholesterol from the circulation back into the liver, therefore reducing the build up cholesterol in the arteries causing risk of arterosclerosis (Durrington 2007).

Statins have more recently been shown to reduce the arterial wall inflammation caused by cholesterol deposits, increase plaque stability, protect against clot formation, and even have antithrombotic actions; factors that can also bring benefits for high risk individuals (Bonetti *et al* 2003, Owens *et al* 2012).

6 Treatments

Time out

Different treatments, their uses and side effects can dominate patient information sheets: why might that not help patients comply with treatment? How does an understanding of cholesterol underpin the purpose of different treatments?
Create or revise your information about treatments accordingly, linking treatments to what has already been written about cholesterol, good and bad.

Reducing or stopping statins

Pregnancy No human research studies have been carried out on statin therapy in pregnancy, due to ethical issues, but statins pass the through blood vessel membranes and could cause potential harm to the unborn child. The recommendation, therefore, for any woman of childbearing age, is to ensure appropriate contraception is observed, and discontinue treatment if pregnancy is planned or identified.

Rhabdomyolysis The most severe side effect of statin therapy is rhabdomyolysis, a rare and severe muscle wasting disorder that can affect large

Box 1 Simon Broome criteria for familial hypercholesterolaemia

Definite familial hypercholesterolaemia

- In adults — Cholesterol >7.5mmol/L — Low density lipoprotein >4.9mmol/L
- In children (<16 years) — Cholesterol >6.5mmol/L — Low density lipoprotein >4.0mmol/L
- PLUS tendon xanthomas in patient or a first or second degree relative

Possible familial hypercholesterolaemia

- Lipid values above
- PLUS family history of myocardial infarction before 50 years in second degree relative.
  or before 60 years in a first degree relative
  or cholesterol >7.5 in first of second degree relative

muscles of the body. Patients should be warned about the signs of this condition, such as severe muscle pains, and advised to stop taking the medication if they occur and return to their GP for blood tests, including CK levels. Patients may be at an increased risk of rhabdomyolysis if they have renal impairment, or if they are treated concurrently with statins and fibrates (REF NEEDED HERE).

General aching can also occur while on statin therapy, but assessing CK levels prior to initiation of therapy and discussing changing or reducing statin dose can enable an informed decision. In general, if the CK is greater than ten times the normal level, the advice is to stop the statin, if it is between five and ten times normal, proceed with caution.

Although all statins work in the same way, the manufacture of each statin is different, therefore a patient should be encouraged to try other versions of the drug or be referred to secondary care, if they suffer side effects.

It is good practice to check CK, thyroid function and LFTs before starting statin therapy to rule out secondary causes of hyperlipidaemia. Baseline LFTs including alanine transaminase (ALT) levels can also be useful to rule out pre-existing non alcoholic fatty liver disease (NAFLD) or liver dysfunction.

Secondary care

There are some situations where patients will need secondary care, for example people who have reached maximum lipid-lowering therapy, those with statin intolerance, those with hypertriglyceridaemia, and those needing diagnosis and management of inherited lipid disorders. The most common of these inherited conditions are familial combined hyperlipidaemia and familial hypercholesterolaemia (FCH).

Familial combined hyperlipidaemia Patients typically present with raised triglycerides (between 3 and 10mmols/L), raised LDL cholesterol and low HDL. This genetic condition appears to have a strong environmental factor and affects individuals with varying degrees of severity (Shoulders *et al* 2004). Often there may be evidence of abnormal lipid levels in a parent, which become more aggravated in a relative alongside factors such as obesity, diabetes and alcohol abuse or drug therapy.

Lifestyle modification can be beneficial in combination with medical therapy such as statins, fibrates or fish oil supplements. There are no genetic tests available for this condition, however family screening based on cholesterol levels is appropriate to identify family members who may require monitoring or treatment.

Familial hypercholesterolaemia The LDL receptors on the surface of the liver do not function correctly due to a DNA alteration (mutation) which causes lifetime exposure to raised LDL cholesterol and risk of premature heart disease. The worldwide incidence is 1:500 for the most common type, heterozygote FH. In 2008, NICE developed familial hypercholesterolaemia **(**FH) guidelines (NICE 2008b). The clinical priorities were identified as:

- Consideration of diagnosis based on the Simon Broome Criteria (Box 4) with referral to a FH specialist for confirmation of diagnosis, using genetic testing, where available. Children at risk of FH, due to one affected parent, should be offering diagnostic (cholesterol or genetic) testing by the age of ten.
- Family cascade testing should be initiated, using genetic testing as a gold standard, or LDL-c cholesterol levels, if genetic testing is not available.
- Medical management should be initiated as a priority, CHD risk estimation tools should not be used to assess risk.
- Targets should be achieved of 50 per cent LDL-c reduction from pre-treatment using high intensity statins, and ezetimibe 10mg, if required.
- Children and young people who are being investigated for, or diagnosed with, FH should be referred to a child/young person FH specialist.

From a national management perspective, NICE has agreed the priority is to develop a nationwide family-based follow up system, to identify people affected by FH. Individuals with raised cholesterol are normally well managed in primary care. Some of these patients may have FH, with their families at risk of premature CHD. Approximately 15 per cent of individuals estimated to be at risk of FH have been identified (Marks *et al* 2006). This means around 105,000 individuals have not been identified, possibly due to their age or lack of cholesterol measurement. These could be young or middle-aged individuals at risk of a cardiac event, which is preventable.

Cascade testing has been proven to be the best method for tracing other family members with FH (Marks *et al* 2002), because every relative of the index 'first identified' patient will also have a 50 per cent chance of having FH. A referral to a lipid clinic for anyone suspected of having FH, will offer the opportunity not only to have the clarification of diagnosis, but also potentially have their families screened.

In 2010, an all Wales FH cascade screening service was commissioned by the Welsh Government, with support from the British Heart Foundation. This enabled a clinical and genetic team to develop an all-Wales service that offers the Welsh population a service that integrates primary and secondary care to identify and support individuals with FH

and their families. This includes accessibility to genetic testing for FH and a national IT system of patient management (PASS) to allow cascading of relatives and improved communication across Wales. More details can be found regarding the FH service in Wales at www.wales.nhs.uk/fhservice.

Many areas in England and Scotland are now able to provide genetic testing of FH, accessible through genetic services, but there is no systematic approach to genetic cascading throughout these countries.

7 Revision

Time out

Familial hypercholesterolaemia can raise significant anxieties for patients. Check whether the patient information sheet discusses this. If you are designing one afresh, it may be appropriate to create a different support strategy for these patients. Information, on a sheet or on a website is not enough; referral and counselling is important. When you have done this, look back at your opening list of problems and determine whether the information in the article has enabled you to have a greater understanding of the issues surrounding lipid management. A revised information sheet and fresh explanations of the risks, conditions and needs might address some of the difficulties identified. Are there other problems best dealt with by other colleagues?

Conclusion

Cholesterol is a common and recognised risk factor for CVD. Identifying those with raised cholesterol and risk assessing them for their ten-year risk of CVD is the first priority primary care professionals should consider. Treatment for those at high risk of CVD should be treated in a multifactorial way, with lifestyle modification advice and discussions on medication for cholesterol and blood pressure.

In individuals who have inherited cholesterol conditions, resistant cholesterol levels on maximum medical therapy and those who have difficulty tolerating lipid lowering therapy, consideration should be given to referral to secondary care.

Recent NICE guidance on Lipid modification and FH (NICE 2008a, b) should be considered as the best approaches to evidence based care. The upcoming JBS3 guidelines (www.jbs3risk.com/) will also offer the opportunity to discuss the benefits of the concept of lifetime risk.

8 Practice profile

Time out

Now that you have completed the article, you might like to write a practice profile of between 750 and 1,000 words. Go to the Primary Health Care website: www.primaryhealthcare.net and follow the link to the Learning Zone for information on how to make a submission.

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