Back to the future: familial hypercholesterolaemia revisited

H·E·A·R·T UK
THE CHOLESTEROL CHARITY

Edinburgh's Heriot-Watt University hosted the 21st Annual Medical & Scientific Meeting and the Patients' Workshop of H·E·A·R·T UK this summer. The theme was looking back and looking forward at familial hypercholesterolaemia. H·E·A·R·T UK is committed to the early detection of families with the condition. Gill Stokes, a nursing advisor with the charity, reports.

FH: new insights

Familial hypercholesterolaemia (FH) is a dominantly inherited genetic condition which predisposes to significantly elevated total and low-density lipoprotein cholesterol (LDL-C) from an early age, leading to premature atherosclerosis and coronary artery disease (CAD). FH affects one in 500 of the population. Mutations in at least three genes – ApoB, PCSK9 and LDLR – can cause this condition; the latter contributing to more than 90% of cases.

Testing the families of known cases of FH (cascade testing) has been shown to be cost-effective through a government-funded pilot cascade testing project. This assessed the feasibility of implementing a genetic service within lipid clinics to identify those with FH. The earlier the diagnosis is made, the earlier cholesterol-lowering therapy can be initiated and the better the prognosis.

The annual Myant Lecture, given by Professor John Kastelein (Department of Vascular Medicine, University of Amsterdam, The Netherlands), looked at the improved drug treatment of FH since the advent of statins and also provided a glimpse of newer drug therapies and those in development.

The introduction of ezetimibe, an inhibitor of the intestinal absorption of cholesterol, (which has now been approved by the National Institute of Health and Clinical Excellence), has facilitated more aggressive LDL-C lowering, he said. New therapies include antisense oligonucleotides (ASOs), which reduce the amount of specific messenger RNA (mRNA) available for translation of the encoded protein. An ASO to apoB-100, one of the principal components of LDL-C, has been developed as a potentially effective lipid-lowering agent. By reducing the hepatic synthesis of lipoproteins, it will eventually lower LDL-C. Tolerance for this novel therapy is encouraging but safety results have, so far, been obtained in relatively small trials.

Squalene synthase inhibitors (SSIs) have also been shown to considerably lower LDL-C levels. Other novel treatments, such as 'flush-free' nicotinic acid, and revived cholesterol ester protein transfer (CETP) inhibitors which raise high-density lipoprotein cholestrol (HDL-C), may prove effective alongside current strategies in the management of FH.

Professor Kastelein concluded by saying that there remains a strong emphasis on LDL-C reduction but that optimal HDL-C levels should also be defined and treated. He hoped that, in the near future, every heterozygous FH patient should reach the LDL-C target levels defined by international guidelines.

Professor John Kastelein giving the Myant Lecture

Nutriceuticals and diet in FH

The effect of diet and nutriceuticals in the management of FH provided much to ruminate on. The terms nutriceuticals and functional foods are defined as: "products containing dietary components that may provide health benefits beyond basic nutrition," explained H.E.A.R.T UK Chairman, Professor Andrew Neil.

The following dietary strategies help to reduce serum cholesterol levels:

- a diet low in total and saturated fat
- supplementation
- the Portfolio diets
- nutriceuticals.

Table 1 shows the targets for nutriceuticals. One group of nutriceuticals comprises the plant sterols (phytosterols) – natural components of edible vegetable oils – and their derivatives, the stanols (phytostanols).

Table 1. Nutriceuticals and their targets

Nutriceutical	Target
Phytosterols and phytostanols	LDL-C levels
Beta glucan	LDL-C and blood glucose levels
Bioactive peptides	Blood pressure
Omega-3 polyunsaturated fatty acids	Triglycerides/cognitive function
Probiotics	Gut function
Calcium or vitamin D	Bone density

Key: LDL-C = low-density lipoprotein cholesterol

Table 2. The Portfolio dietary recommendations

Food	Amount per day
Almonds	30g
Viscous fibre (oats, barley, psyllium, legumes, aubergine, okra)	20g
Vegetable protein (of which 50% should be soy)	80g
Plant sterols/stanol spreads	2g

Unlike cholesterol, phytosterols and stanols are minimally absorbed from the gut, since their mechanism of action includes the reduction of intestinal cholesterol absorption and a reduction in the re-absorption of biliary cholesterol.

An approximate 10% reduction in LDL-C can be achieved with an intake of 2g of plant sterols per day. Esterified sterols and stanols are more palatable and have a less variable response than free sterols and stanols. Numerous trials of sterol and stanol ester-enriched spreads in normocholesterolaemic, mild and severely hypercholesterolaemic individuals have demonstrated a similar LDL-C lowering across all age ranges.

While an additive cholesterol-lowering effect is seen with concomitant statin therapy, there is no significant additive benefit when sterol and stanol spreads are combined with ezetimibe. Levels of the fat-soluble pro-vitamin beta-carotene may be reduced by up to 12% when using sterols or stanols but this can easily be compensated for through dietary adjustments. Other fat-soluble vitamins are unaffected. Professor Neil concluded that current safety data is reassuring and the extent of increased absorption is unlikely to be atherogenic.

While there is considerable scientific evidence to support national guidelines for diet and coronary heart disease risk reduction, Dr Anthony Leeds (King's College, London) told the meeting that there are genetic variations in lipid responses to dietary interventions. A diet containing soy protein, soluble fibre-containing foods, stanol and sterol-containing products, and tree nuts (the Portfolio dietary approach; **table 2**) has been shown to be as effective in managing hypercholesterolaemic individuals as a low-dose, first-generation statin. A randomised controlled trial is needed to specifically study the effect of the dietary management of FH patients, including children and adolescents.

Cardiovascular disease: past performance and future promise

Dr Huon Gray (Deputy to the National Director for Heart Disease & Stroke, Department of Health, England) talked about the prevalence and risk factors for atherosclerosis and cardiovascular disease (CVD).

Although total death rates in the UK from CVD are continuing to fall; in women, stroke still accounts for three times and coronary heart disease four times more deaths than breast cancer. The incidence of diabetes has also increased.

It has been calculated that risk factor modification has accounted for around 60% of the overall reduction in CVD mortality since 1980. Reductions in smoking, saturated fat in the diet and social deprivation (although the latter still accounts for a two-fold variation in CVD prevalence nationally) have been seen but levels of obesity have continued to rise. In 2005, 23.1% of men and 24.8% of women in the UK were classified as obese.

Girls continue to exercise less frequently than boys and 75% of secondary schoolchildren choose unhealthy meal options. Unsurprisingly, the incidence of metabolic syndrome has also increased. Non-smokers can enjoy an average 7.5 year increase in life expectancy over smokers, and studies show a 3% decrease in prevalence of hypertension in the UK over the last five years, Dr Gray said.

Cardiac care delivery suffered from under-investment in England in the 1990s, Dr Gray continued, with poor and inequitable access to services and long waiting lists for interventional procedures. Improved access to care and treatments have been calculated to account for 40% of the reduction in CVD mortality since 1980.

Conference messages

- Familial hypercholesterolaemia (FH) is an autosomal dominant disorder with an estimated prevalence of 1:500 of the population. FH sufferers have an increased risk of premature CHD
- The earlier that cholesterol-lowering treatment is initiated in patients with FH, the better the outcome
- Cascade testing is a cost-effective means of identifying families with FH
- With statin treatment and the advent of new cholesterol-lowering therapies in development, all heterozygous FH patients should in the near future be able to achieve target LDL-C levels
- Studies have shown the Portfolio dietary intervention and nutriceuticals to be effective in the management of hypercholesterolaemic individuals

Where next?

Many patients have multiple cardiovascular-related conditions and the Department of Health has now created a 'Vascular Board' comprising experts ('tsars' & policy leads) in stroke, coronary heart disease, diabetes, renal disease and peripheral arterial disease (PAD). This board will address the shared agenda of prevention, screening and management of risk and this 'joined-up' approach will facilitate continued improvements in health promotion and treatments. By March 2008, a maximum six-week cardiology referral wait is expected to replace the current 13 weeks. Delivering an 18-week patient pathway from GP referral to the start of treatment is a key objective for the NHS, and, Dr Gray said, is planned to be in place "by the first chime of Big Ben on 31 December 2008"!

Dr Gray concluded by saying that, while much has been achieved in understanding and reducing CVD risk in recent years, there remain many challenges ahead, including the education of children. These challenges will only successfully be tackled if individuals take increased responsibility for their long-term cardiovascular health