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Diet and heart health symposium II

Cardiovascular disease is still the leading cause of death across Europe, responsible for two million deaths each year in people below the age of 75. Michael Livingston, Director of H.E.A.R.T UK, introduced the symposium by saying that diet plays an important role in the causation of cardiovascular disease even though we have drugs that effectively lower plasma cholesterol.

If lifestyle changes such as diet, weight control, smoking and physical activity were seriously addressed, then the rates of cardiovascular disease, and in particular coronary heart disease (CHD), in this country could be very much lower. Instead, there is concern about the amount of obesity, overweight, diabetes and hypertension that is increasingly seen in teenagers and children. This could lead to increased rates of CHD, and to parents commonly outliving their children.

The second Diet and Heart Health Symposium presented research in some of the key areas – dietary fat, vitamin B, homocysteine, vitamin K, the importance of insulin resistance in metabolic syndrome, and much more. One strong message from the symposium was how crucially important it is for health professionals to work together in order to put recommendations and strategies into practice effectively.

This second Diet and Heart Health Symposium was organised by the Hyperlipidaemia Education and Research Trust (H.E.A.R.T UK) and by Alpro, manufacturers of soya dairy-free alternatives. It was funded by an educational grant from Alpro. (The first Diet and Heart Health Symposium was reported in a supplement to *The British Journal of Cardiology* last year [*Br J Cardiol* 2003; 10: S1-S6].)

Diet and heart health – still a challenge in the post-statin era?

Patients' diet and lifestyle, and other cardiovascular risk factors, are all important in influencing their rates of cardiovascular disease, said Professor Tom Sanders (King's College, London) in the conference's keynote address. This remains true even though drugs such as statins are able to modify plasma cholesterol levels. The degree of risk to which individuals are exposed determines how they are managed.

World Health Organization data show that, in men under the age of 65 years, cardiovascular disease remains the leading cause of death across Europe. The highest rates of cardiovascular disease are seen in Ireland, Finland and the UK; the lowest rates are seen in Spain, Italy and France.

Data from the 25-year follow-up of Ancel Keys' Seven Countries Study (looking at Yugoslavia, Italy, Greece, Finland, the Netherlands, the US and Japan) show that rates of coronary heart disease (CHD) are lower in countries in Mediterranean and inland southern Europe than they are in northern European countries and the United States. Dietary fat intakes are high in all these countries: those with relatively low saturated fat intakes have lower rates of CHD. Japan has the lowest overall fat intake and the lowest rate of CHD.

When the original Keys surveys were carried out in 1958-1970, some 70% of fat in the diet came from olive oil (Keys A, Aravanis C, Blackburn H *et al*. *Acta Med Scand* 1967; **460** (suppl): 1-392). However, fat intake is not the only relevant factor: other key features of the

Mediterranean diet that may help to explain the findings include regular consumption of fish, fruit and wine. Moderate alcohol intake is an effective preventative measure, although binge drinking is associated with sudden cardiac death.

Rates of CHD have been falling since 1980 in the UK across all age groups. Contributing factors include lower rates of smoking, lower fat intakes (a 1% reduction in blood cholesterol is associated with a 1-3% decrease in risk), and better control of blood pressure (effective drug treatment of hypertension reduces the risk by 15%). Other risk factors include heredity, stress, overweight, lack of exercise and diabetes. Rates may also be affected by secular changes and by increased wealth, which has a beneficial influence on diet.

Patients are at greater overall risk if they have more than one risk factor since risk factors may act synergistically. For example, smoking increases cardiovascular risk to a greater extent if the plasma cholesterol level is high. This may explain why smoking has less impact in southern European populations, in whom cholesterol levels are generally lower.

Drug treatment offers most benefit when the patient's absolute risk is high, as in familial hypercholesterolaemia, for example. The impact of drug treatment depends on its duration. After one year of statin treatment there is a 10% reduction in fatal and non-fatal CHD events; after six years of treatment there is a 35% reduction in these events (Law MR, Wald NJ, Rudnicka AR. *BMJ* 2003; **326** (7404): 1423). There is a possibility that adverse effects from longer-term use may outweigh benefits in lower-risk groups. Though drug treatment can be helpful, especially for high-risk individuals, dietary and lifestyle changes are still very important.

Social and lifestyle factors have a big impact on rates of cardiovascular disease through their impact on a variety of risk factors. For example, dietary intakes of salt, alcohol, fruit and vegetables may influence blood pressure. Blood cholesterol is influenced by the type of dietary fat, by soya protein (which reduces blood cholesterol levels) and by boiled coffee (which increases blood cholesterol levels). Ventricular fibrillation is modified by n-3 fatty acid intake whereas endothelial dysfunction is modified by postprandial lipaemia, homocysteinaemia and insulin resistance. Lifestyle is also important in influencing risk. For example, insulin resistance is influenced by overweight and physical activity as well as by the glycaemia load.

Veganism shows how lifestyle may influence the risk of cardiovascular disease. The European Prospective Investigation into Cancer and Nutrition (EPIC) study in Oxford found that vegans have lower levels of low-density lipoprotein (LDL) cholesterol than vegetarians – on average 1 mmol/L lower – and meat-eaters have the highest LDL levels. Contributors to this finding in vegans are their lower body weight (a 10 kg weight loss results in a 0.2 mmol/L reduction in blood cholesterol), their lower intakes of saturated fat (a 5% reduction can lower blood cholesterol by 0.25 mmol/L), avoidance of dietary cholesterol, higher intakes of phytosterols and higher intakes of soya protein. Vegans also tend to have low blood pressure. Nevertheless, CHD rates in vegans are not as low as might be expected. Severely elevated levels of homocysteine have been reported in vegans, reflecting low vitamin B12 intakes (Lloyd-Wright Z, Hvar A-M, Moller J, Sanders TAB, Nexo E. *Clin Chem* 2003; **49** (12): 2076-8). Vegans also have low intakes of long-chain n-3 fatty acids (Lloyd-Wright Z, Allen N, Key TJA, Sanders TAB. *Proc Nutr Soc* 2001; **60**: 229A).

Our increased exposure to food and our reduced physical activity over recent decades mean that we are now living in an 'obesogenic environment'. Obesity increases risk of cardiovascular disease, probably through insulin resistance. Impaired glucose tolerance and diabetes. Metabolic syndrome may be defined as impaired glucose tolerance or insulin resistance in combination with any two of: hypertension, obesity, hypertriglyceridaemia, low high density lipoprotein (HDL) cholesterol or microalbuminuria. The effects of insulin resistance on cardiovascular risk factors include impaired reverse cholesterol transport, endothelial dysfunction, increased procoagulant activity and decreased fibrinolytic activity.

There is strong evidence to show that weight loss and greater physical activity improve insulin sensitivity. The effect of dietary composition on insulin sensitivity is less certain, and advice to reduce fat and increase carbohydrate in the diet may exacerbate insulin resistance, particularly if the carbohydrate is of high glycaemic index (GI). Diets high in saturated and trans fatty acids may increase insulin resistance; the role of monounsaturated fats is unclear. There is evidence for a marked reduction in diabetes development with improved insulin sensitivity.

A study that was conducted in Greece measured adherence to a traditional Mediterranean diet using a nine-point scale (Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. *N Engl J Med* 2003; **348** (26): 2599-608). For each two-point increase in adherence there was a decrease in all-cause deaths, CHD deaths and cancer deaths. However, comparison of the effects of individual food groups and types of fat showed that these elements did not predict risk – the most important factor was the diet overall. Risk may be influenced by lifestyle factors such as whether we sit down to eat and whether we eat as a family, in addition to the food itself.

Eating fish once or twice a week has been shown to reduce the risk of sudden cardiac death, in the Diet and Reinfarction Trials (DART) study, for example (Burr ML, Gilbert JF, Deadman NM. *Lancet* 1989; **2** (8666): 757-61). The protective effect of long-chain n-3 fatty acids on sudden cardiac death was confirmed in the GISSI study (Marchioli R, Barzi F, Bomba E *et al*. *Circulation* 2002; **105** (16): 1897-903). An unexplained finding from a recent randomised controlled trial of dietary advice in patients with angina found a slight excess cardiac death rate in the groups advised to eat fish or to take fish oil supplements (Burr ML, Ashfield-Watt PA, Dunstand FD *et al*. *Eur J Clin Nutr* 2003; **57** (2): 193-200). One possible explanation is that giving targeted advice about one food group may give subjects the impression that it is less important to follow other dietary advice or lifestyle changes.

The Dietary Approaches to Stop Hypertension (DASH) eating plan is a way of eating that was devised to control high blood pressure. It consists of eating whole grains, poultry, fish, nuts, fruit, vegetables and low-fat dairy produce with limited amounts of red meat, sweet foods and sugar-containing vegetables. The DASH eating plan reduces blood pressure better than salt restriction alone and is particularly effective in borderline hypertensive individuals.

The overall dietary pattern is better than the amounts of individual nutrients at predicting the subject's risk of cardiovascular disease, said Professor Sanders. This holds true even though many nutrients independently influence risk. Professionals need to communicate a more holistic approach to dietary modification, rather than tinker with individual dietary components. Helping patients to stop smoking and to increase their levels of physical activity are also vitally important.

The health divide continues – the latest demographics

Coronary heart disease (CHD) is essentially avoidable in people below the age of 75 years, said Professor Klim McPherson (Bristol University). If the political will were there, deaths from cardiovascular disease in the UK could be cut by 50%. Lifetime diet is a key factor, he said, and the present fall in rates of cardiovascular disease probably reflects the past dietary and lifestyle habits of older adults plus lower tobacco consumption.

During the 1970s, awareness of dietary

issues was much higher in the US than in the UK. CHD rates began to decrease in the US in the 1970s, about 10 years before they did in the UK. In the UK, death rates from CHD in socio-economic class I have fallen faster than in the other socio-economic classes as people have learned to change their behaviour. However, there is concern that these rates may start to rise again in the next 10-15 years as CHD events become clinically evident in the next cohort of adults. These rates are anticipated to rise because of the diet and lifestyle habits of today's teenagers and young adults.

Lifestyle changes should encompass diet, weight control, tobacco use and physical activity. If the population addressed these risk factors seriously, rates of CHD would be significantly lower in the UK. Current rates of obesity are "very worrying", said Professor McPherson, and are an important part of the challenge to bring down the rate of CHD. Though smoking rates are falling the decrease is beginning to level off, and further schemes are needed in this area.

Poor diet in young people is likely to impact on the origins of atherosclerosis, and this is particularly relevant since poor dietary habits, once established, tend to be continued into adulthood. CHD risk is currently low in young adults but we do not know what their future risk of disease will be: it could be much higher than the levels of risk seen in today's middle-aged and older adults.

The public has a right to information, health protection, strong health advocates, a clean environment and healthy living choices that do not cost more, said Professor McPherson. Examples of ways to improve the current situation are tax relief, a subsidy for healthy eating options, a ban on advertising unhealthy foods to children, and an end to selling off playing fields. Increased opportunities for exercise and exercise-friendly transport systems would be helpful. Professor McPherson wants the Food Standards Agency (FSA) to have a greater influence on the salt, fat and sugar contents of foods.

The importance of focusing on primary prevention of cardiovascular disease was made clear in the Wanless Report (to HM Treasury in April 2002). The report predicted that a fully engaged healthcare system, embracing modern technology and focused on disease prevention, could result in a saving of more than £50 billion in NHS spending by the year 2003 and a slower rate of real annual growth in NHS spending.

Preventive measures are important because randomised controlled trials show that drugs alone cannot bring risk down to universally acceptable levels. For example, statins are only cost-effective in high-risk groups. Again, reduction in CHD risk was purported to be a benefit of hormone replacement therapy (HRT) in post-menopausal women. However, pooled data from four recent US trials involving more than 20,000 women followed up for an average of four years have shown that HRT does not reduce the risk of CHD (Beral V, Banks E, Relves G. *Lancet* 2002; **360**: 942-5).

The Heart Protection Study and ASCOT – what conclusions can we draw?

Dr Jane Armitage (Radcliffe Infirmary, Oxford) focused on serum cholesterol as a risk factor for heart disease in her presentation. The Multiple Risk Factor Intervention Trial (MRFIT) screening study clearly shows that the association between cholesterol levels and coronary heart disease is continuous, and there is no threshold level of cholesterol below which further lowering is not associated with lower risk (Stamler J, Vaccaro O, Neaton JD, Wentworth F for the Multiple Risk Factor Intervention Trial Research Group. *Diabetes Care* 1993; 16: 434-44). This implies that for people at high risk of vascular disease, such as diabetics, the risk of coronary heart disease (CHD) in relation to serum cholesterol is raised. A diabetic patient with low total cholesterol may be at greater risk than a non-diabetic patient with a higher total cholesterol. Most studies show that the risk of cardiovascular disease is increased 2-4 fold in patients with type 2 diabetes.

Prospective studies show that reducing serum cholesterol reduces cardiovascular risk across all age groups. It was only after the large secondary prevention trials such as 4S, CARE and LIPID that the cardiology community seriously engaged with cholesterol reduction, said Dr Armitage. The importance of cholesterol has been better appreciated since the advent of the statins. Professionals have come to realise that it is not just a case of treating hypercholesterolaemia, but of treating cardiovascular risk regardless of cholesterol levels.

Drug options include statins, fibrates, anion exchange resins (no longer much in use), cholesterol absorption inhibitors (expected to play a key role in the future), and agents such as omega 3 fatty acids (needed in significant amounts to reduce triglycerides) and nicotinic acid compounds. In low-risk populations the similar proportional benefits translate into small absolute reductions in mortality and morbidity, so drug treatment of the entire population may not be a viable strategy. However, in high-risk populations statins produce substantial reductions in absolute risk. Recommendations and guidelines are driven by the evidence of benefit in high-risk populations, such as those with diabetes or post myocardial infarction.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study population consisted of men and women aged 40-79 years at intermediate to high risk of cardiovascular disease, with hypertension and two other risk factors (Sever P, Dahlof B, Poulter NR *et al*. *J Hypertens* 2001; **19**: 1139-47). It was a primary prevention trial: subjects had no evidence of CHD. The trial compared 10 mg atorvastatin with placebo in patients with total cholesterol < 6.5 mmol/L, which produced an average LDL difference of about 1.1 mmol/L. After three years of follow-up, a 36% (95% CI 17-50%) relative reduction in the main outcome measure (non-fatal MI and fatal CHD) was observed in the statin group (100 [2%] atorvastatin allocated versus 154 [3%] placebo allocated). In addition, there was a 27% (95% CI 4-44%) reduction in stroke (89 [1.7%] atorvastatin allocated versus 121 [2.3%] placebo allocated), and a 21% (95% CI 10-30%) relative risk reduction for major vascular events (389 [7.8%] versus 486 [9.4%]) (Sever P, Dahlof B, Poulter NR *et al*. *Lancet* 2003; **361**: 1149-58).

The Heart Protection Study (HPS) (*Lancet* 2002; **360**: 7-22) was based on a 2 x 2 factorial design. It compared the effects of simvastatin 40 mg/day and antioxidant vitamins (600 mg vitamin E, 250 mg vitamin C and 20 mg beta carotene) over a five-year period, against placebo, in 20,536 UK adults. Epidemiological evidence supported a possible role for antioxidant vitamins but reliable evidence can only be obtained from a randomised controlled trial. Subjects had a range of cholesterol levels and other risk factors for cardiovascular disease.

The results showed no effect from the antioxidant vitamins on all-cause deaths or events, no effect on non-vascular deaths and events, and no effect on vascular deaths and events. There was no suggestion of emerging benefit, so it is unlikely that a trial of longer duration would have yielded different results.

However, positive results were obtained from simvastatin treatment in the HPS. The low-density lipoprotein (LDL) cholesterol was reduced about 1 mmol/L more in the statin allocated group compared to the placebo group. All-cause mortality was significantly reduced, by 13% (95% CI 6-

19%), in simvastatin-treated patients: this was principally due to a reduction in the vascular deaths of 17% (95% CI 9-25%; 781 [7.6%] simvastatin allocated versus 937 [9.1%] placebo allocated). For the first occurrence of a major vascular event (non-fatal MI, stroke, coronary death or revascularisation), there was a highly significant (p<0.0001) 24% (95% CI 19-28%) reduction in event rate in simvastatin compared to placebo patients (2,033 [19.8%] simvastatin allocated versus 2,585 [25.2%] placebo allocated).

The proportional reduction in event rate was similar, and significant, in each subgroup, including in patients with diabetes either with or without previous vascular disease. Among the many types of individuals studied, five years of simvastatin would prevent 70-100 people per 1,000 suffering a major vascular event. The size of the benefit depends chiefly on the individual's overall risk of major vascular events rather than on his blood lipid levels alone.

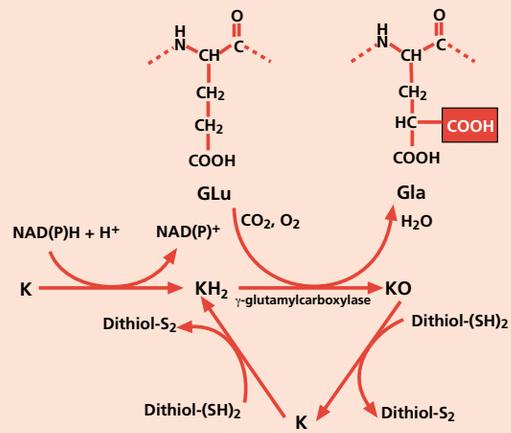
Dr Armitage concluded that statins reduce the risk of coronary events and stroke: a 1.0 mmol/L reduction in LDL cholesterol reduces risk by about 25%, and a 1.5 mmol/L reduction by about 33%. Statins have a good safety profile over five-year trials but longer-term follow-up is needed to assess longer-term safety. The absolute benefits of statins are greatest in patients at highest risk of CHD, and they are likely to increase with time.

In the question and answer session, Professor Martijn Katan questioned whether the statins work by reducing cholesterol since their effects are apparent so quickly. Their benefits are likely to be the result of cholesterol reduction, said Dr Armitage, as across the various trials the greater the LDL reduction, the greater the benefit has been. A lag effect is to be expected since atherosclerosis develops over a period of years. There is evidence from animal studies that statins suppress inflammation in the endothelium, but the Heart Protection Study data do not support the hypothesis that statins work in this way.

Vitamin K and cardiovascular health – what is the optimum?

Vitamin K is a co-factor for the conversion of protein-bound glutamate residues into gammacarboxyglutamate (Gla) (figure 1), explained Dr Cees Vermeer (University of Maastricht, the Netherlands). Gla residues bind calcium in proteins and are necessary for protein function. Matrix Gla-protein (MGP) contains five Gla residues and is a highly potent inhibitor of soft tissue calcification. Inadequate vitamin K intake results in the synthesis of Gla-deficient, and therefore inactive, MGP. Vitamin K insufficiency must be regarded as an independent risk factor for cardiovascular calcification.

Figure 1. The vitamin K-dependent reaction



Courtesy Dr Cees Vermeer

Vitamin K functions in hepatocytes, where it plays a role in blood clotting factor synthesis; in osteoblasts, where it activates proteins regulating bone growth; in chondrocytes and smooth muscle cells, where it is required for the synthesis of proteins inhibiting tissue calcification; and in the endothelium, during the production of proteins inhibiting blood coagulation.

Vitamin K status can be assessed by monitoring (a) dietary intake, (b) plasma levels, though these may or may not reflect tissue levels, and (c) plasma levels of under-carboxylated proteins originating from the arterial wall, liver or bone. In a study of 10,000 elderly people undertaken in Rotterdam, there was a higher risk of aortic calcification in those in the lowest tertile for vitamin K intake compared with those in the highest tertile. All-cause mortality was lower, and cardiovascular mortality was 50% lower, in individuals who were in the highest vitamin K tertile compared to those in the lowest tertile.

The Maastricht Osteo study (Braam LAJLM, Knapen MHJ, Geusens P *et al. Calcif Tissue Int* 2003; **73**: 21-6) was a three-year supplementation study carried out in 188 post-menopausal women aged 50-60. Subjects were divided into three groups: one group took calcium, magnesium, zinc, vitamin D and vitamin K supplements; another took these vitamins and minerals but no vitamin K; and the third group took placebo. It was reported that those in the first group had 40% less bone loss and significantly better elasticity of the carotid artery as compared to both other groups.

Since MGP has five Gla residues, there are five places where the action of vitamin K is needed. A study in MGP-knockout mice found that the aorta became calcified and the mice died at six weeks (Luo G, Ducy P, McKee MD *et al*. *Nature* 1997; **386**: 78-81). The arteries of the mice were found to be calcified around the elastic fibres. Price *et al.* (*Arterioscl Thromb Vasc Biol* 1998; **18**: 1400-7) found calcification of the elastin fibres of the aorta in rats treated with a vitamin K antagonist. Using this model, Spronk *et al*. (*J Vasc Res*, in press) demonstrated that vitamin K, notably vitamin K2, protects against this calcification.

There are two principal types of calcification of the arteries – atherosclerosis, which affects the intima, and Monckeberg's sclerosis, which affects the media. In the latter, calcification is seen in the media but there is little or no encroachment into the lumen. Calcification generally starts in the peripheral arteries of the leg in elderly patients. MGP is thought to help in the prevention of Monckeberg's sclerosis. Dr Vermeer showed a series of histological slides: in normal coronary arteries no under-carboxylated MGP was observed, but in patients with vitamin K insufficiency under-carboxylated MGP is apparent and increases during the later stages of atherosclerosis. Under-carboxylated MGP is also seen in patients with Monckeberg's sclerosis.

Should we increase our intake of vitamin K? In the Rotterdam study, average intakes ranged from 124 µg/day for those in the lowest

quartile to 375 µg/day for those in the highest quartile. Approximately 100 g of green vegetables and 80 g of cheese or curd cheese would guarantee intakes in the highest quartiles for both K1 and K2 but 85-90% of the population studied had a lower intake than this.

The Japanese food "natto" (fermented soy beans) is extremely rich in vitamin K, and its effects on health have been widely reported in the Japanese literature. Remarkably, natto contains primarily K2, which has been demonstrated to be the most effective form of vitamin K in several studies. Because of its strong taste and flavour, natto is not popular in other countries, which is why capsules containing natto extract are now marketed in the West. Presently, the health effects of these food supplements are being extensively investigated in Dr Vermeer's laboratory.

Dr Vermeer concluded that a sufficient dietary intake of vitamin K promotes vascular health and may prevent vascular disease. The mechanism of benefit is probably through improved carboxylation of MGP.

The implications of warfarin treatment were raised in the question and answer session. Warfarin is a vitamin K antagonist, which might have adverse effects in retarding bone formation if taken in the long term, resulting in low bone mass and increased osteoporotic fracture risk.

The possibility of promoting intestinal synthesis of vitamin K was also raised. Dr Vermeer explained that most vitamin K produced by bacteria is excreted, since the colon does not contain the bile salts necessary for its absorption. Thus bacterial vitamin K does not benefit, or scarcely benefits, the host.

Optimum fat intake and the new WHO guidelines

Professor Martijn B Katan (Wageningen, the Netherlands) updated delegates on the latest report from the World Health Organization (WHO), detailing the advice that has remained unchanged and the advice that has changed. *Diet, nutrition and the prevention of chronic diseases*, published in 2003, discusses the evidence concerning dietary elements that increase risk, reduce risk or have a neutral effect: the evidence is classified as convincing, probable, possible and insufficient. Coronary heart disease (CHD), which was originally confined to the Western world, is now a major cause of death and premature disease worldwide, with CHD rates rising rapidly in India and China.

The evidence for reduced risk of CHD with higher intakes of linoleic acid is convincing since it is supported by data from randomised controlled trials. Further evidence in the convincing category relates to risk reduction with fish oils – but note that recent trial results have been disappointing, low to moderate alcohol intake, regular physical activity, and adequate intakes of fruit, vegetables and potassium. The lack of effect of vitamin E supplements on cardiovascular events has also been convincingly shown.

There is convincing evidence that some factors increase the risk of cardiovascular disease. These factors include myristic and palmitic acids, trans fatty acids, high sodium intakes, being overweight, and high alcohol intakes (which increase the risk of stroke).

In the next evidence category, alpha-linolenic acid, oleic acid, non-starch polysaccharides (fibre), wholegrain cereals, unsalted nuts, plant sterols and stanols, and folate are dietary factors that are believed probably to reduce the risk of cardiovascular disease. Conversely, dietary factors that probably increase the risk of cardiovascular disease include dietary cholesterol and unfiltered boiled coffee. Dietary stearic acid probably has a neutral effect.

In the "possible" category, dietary factors that may be protective against cardiovascular disease include flavonoids and soy products. Factors that may increase the risk of cardiovascular disease are fats rich in lauric acid (the principal fatty acid in coconuts), beta carotene and impaired fetal nutrition. There is insufficient evidence that vitamin C, magnesium and calcium have a protective effect; and there is insufficient evidence that carbohydrate and iron are associated with increased risk.

This classification is a reminder that randomised controlled trials looking at hard end points are needed if firm conclusions are to be drawn about the effect of a dietary factor.

Over the last few years antioxidant supplements have fallen from grace, and evidence suggests that they may even be harmful. The trans fatty acids appear to be more harmful than saturated fatty acids such as lauric and stearic acid. The polyunsaturated fats found in vegetables and fish are definitely protective against vascular disease.

The WHO now recommends that 15-30% of energy should be derived from dietary fat, and that this can be increased to 35% in active individuals. This may be the beginning of a trend away from high-starch diets. Professor Katan commented that promoting low-fat diets to the public without specifying the type of fat to be included may have been a major error over the past 20-30 years. The WHO also recommends that free sugars should provide less than 10% of daily calories, and that 45-60% of energy should come from complex carbohydrates such as bread, cereals, pasta and pulses.

The problem of obesity is a major concern of the report. Obesity is now a worldwide phenomenon, caused in part by lower physical activity, which has in turn been encouraged by the development of labour-saving devices. The effects of a low-fat diet on body weight are modest and are not usually long-lasting. Low-fat, high-carbohydrate diets have not delivered the weight loss promised, but the currently popular high-fat, high-protein Atkins diet is not based on solid evidence either, said Professor Katan. Most diets are effective in achieving weight loss in the first three to six months, but maintaining the lower body weight is very difficult and the weight lost tends to be regained over time. The evidence that any particular source of calories is more or less fattening than any other remains inconclusive.

According to Professor Katan, the solution to obesity is political – it is necessary to make access to calories more difficult and access to calorie expenditure easier. This will require harsh measures, which will be generally unpopular.

Though medical professionals can advise people to select healthier foods, it is better for manufacturers to change the food that they produce.

Diet and drugs – is the ideal lipid-lowering diet a match for drug therapy?

Dr Andrew Neil (University of Oxford) began his talk by referring to the recent controversial paper discussing a possible cardiovascular "polypill" (Wald NJ, Law MR. *BMJ* 2003; **326: 1419). The authors suggested that a "polypill" consisting of a statin, folic acid, aspirin, and three blood pressure-lowering drugs such as a thiazide, a beta blocker and an angiotensin converting enzyme inhibitor, would simultaneously reduce four cardiovascular risk factors – low-density lipoprotein cholesterol, blood pressure, serum homocysteine and platelet function. They estimated that the combination would reduce ischaemic heart disease events by 88% and stroke by 80% if taken by everyone over the age of 55 years and by everyone with existing cardiovascular disease. This controversial suggestion was proposed as a potential way to prevent cardiovascular disease with minimal adverse effects.**

Statins have been shown conclusively to reduce the risk of major cardiovascular events by about one third in patients at high risk of coronary heart disease. Current clinical guidelines such as the Joint British Societies recommendations suggest that lipid-lowering agents should be prescribed when total blood cholesterol is above 5.0 mmol/L and when there is a greater than 3% per annum risk of coronary heart disease (CHD) due to established cardiovascular disease, multiple cardiovascular risk factors, or inherited disorders of lipoprotein metabolism.

Variations in the efficacy of different statins have been shown in the CURVES study (Jones P, Kafonek S, Laurora I, Hunninghake D. *Am J Cardiol* 1998; **81**: 582-7). This was an eight-week open-label, randomised parallel group trial in 534 patients with hypercholesterolaemia. Profound differences in efficacy of lowering low-density lipoprotein (LDL) cholesterol were seen between atorvastatin, fluvastatin, simvastatin, pravastatin and rosuvastatin. Differences were also seen between the statins in reduction of total cholesterol. The second-generation statins may be able to reduce LDL by as much as 55%.

Ezetimibe, a selective cholesterol absorption inhibitor, shows additive effects when it is co-administered with a statin. When ezetimibe is given with a statin, an additional 13-14% reduction in LDL cholesterol and an additional 10% reduction in triglycerides are seen.

In patients taking statins, dietary and other lifestyle measures are recommended in addition to drug therapy. Such measures are also appropriate for the general population, at average risk of cardiovascular disease, since even a small reduction in the mean plasma cholesterol can reduce the risk of cardiovascular events. According to a recent combined analysis of 27 studies, reduction or modification of dietary fat reduces the incidence of combined cardiovascular events by 16% and cardiovascular deaths by 9% (Hooper L, Summerbell CD, Higgins J *et al*. *BMJ* 2001; **322**: 757-63).

In studies conducted on metabolic wards, replacing 60% of saturated fats in the diet with other fats, and avoiding dietary cholesterol results in a 10-15% reduction in total cholesterol (about 0.8 mmol/L). Compliance with such a diet is much more difficult for free-living patients, and randomised controlled trials of lipid-lowering advice have achieved only 3-5% reductions in total cholesterol. Thus results of clinical trials may not be applicable to free-living individuals but these dietary changes may nevertheless be of value for population-based risk reduction.

Other strategies are needed for effective cholesterol reduction. These could include changing the fatty acid composition of the diet by replacing saturated fatty acids with monounsaturated fatty acids, dietary supplements, and more active lifestyles. Making multiple small changes can be useful to individuals because their effects are additive. Novel interventions such as nutraceuticals are potentially useful. Educational, legislative, tax and fiscal measures are also needed to achieve the desired effects. It should be remembered that these lifestyle changes have benefits not only in cardiovascular disease but also in glucose tolerance, diabetes, stroke and cancer.

Diet and homocysteine – the latest evidence

There is conclusive evidence that folate has a role in the prevention of neural tube defects but the evidence that folate protects against vascular disease is classified as "probable", said Professor Helene McNulty (University of Ulster at Coleraine, Northern Ireland). There is also promising evidence that folate may have a protective role against cancer and that it may protect against neuropsychiatric disorders such as Alzheimer's disease and dementia.

Fortification of food with folic acid to prevent neural tube defects also lowers plasma homocysteine. The first pointer to a possible adverse effect of raised plasma total homocysteine (tHcy) in relation to cardiovascular disease came from patients with homocystinurias. Ireland, where it affects about 1 per 40,000 people, has the highest rate of this condition in the world. It was observed that untreated children developed severe cardiovascular disease by the time they were 20 years old. Could moderately raised homocysteine cause cardiovascular disease?

In the absence of randomised controlled trials of CVD risk the data are less convincing than those concerning the prevention of neural tube defects. There are, however, good supporting data from case-control studies, prospective studies and meta-analyses. For example, a meta-analysis on causality of ischaemic heart disease, deep venous thrombosis and stroke was performed by Wald DS, Law M and Morris JK (*BMJ* 2002; **325**: 1202-6); and a meta-analysis performed by the Homocysteine Studies Collaboration was published in *JAMA* in 2002 (**288**: 2015).

There are good data from genetic polymorphisms. A meta-analysis has demonstrated that the MTHFR 677C->T polymorphism, a genetic alteration in an enzyme involved in folate metabolism for which 10-12% of the UK population are homozygous (TT), predisposes to high plasma homocysteine and a moderately increased risk of cardiovascular disease (Klerk M, Verhoef P, Clarke R *et al*. *JAMA* 2002; **288**: 2023-31). The increased risk associated with this polymorphism was shown to be much greater for European compared with North American populations. The metabolism of homocysteine is shown in figure 2.

A highly significant reduction in the rate of coronary restenosis with combined folic acid, vitamin B12 and pyridoxine supplementation compared with placebo has been reported (Schnyder G, Roffi M, Pin R *et al*. *N Engl J Med* 2001; **345**: 1593-60).

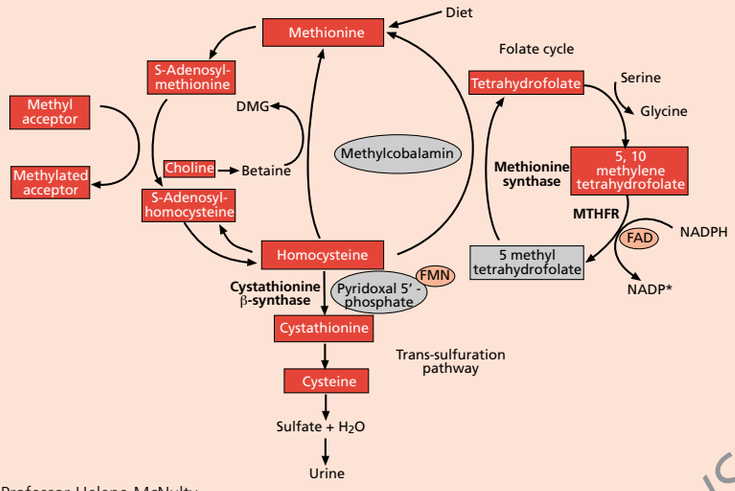
The overall evidence to date suggests that elevated tHcy poses a graded risk with no threshold, and that the magnitude of elevation of risk is similar to that seen with raised cholesterol. Synergistic effects have been observed; for example, the vascular risk is greatly increased in patients with both raised blood pressure and raised tHcy compared to the risk in patients with raised blood pressure alone.

Elevated homocysteine levels could affect both atherosclerosis pathology and clot formation. Some studies to date examining the mechanisms involved have been criticised for having little relevance to humans, and efforts are being made to address this. Elevated tHcy has both genetic and nutritional causes. Male gender and age also affect tHcy levels. An exciting research area is investigation of the extent to which expression of genetic factors depends on the individual's nutritional status.

To determine the influence of individual B vitamins, a meta-analysis of randomised trials that assessed the effects of folic acid-based supplements on blood tHcy concentrations was performed (Homocysteine Lowering Trialists' Collaboration. *BMJ* 1998; **316**: 894-8). It established that dietary folic acid has the greatest effect, reducing raised tHcy by 25%. Vitamin B12 reduces tHcy levels by an additional 7%, but vitamin B6 did not have a significant additional effect. However, newer evidence in subjects replete with folate and riboflavin demonstrates an additional 7.5% lowering in plasma tHcy in response to low-dose vitamin B6 supplementation (1.6 mg/day) over a 12-week period (McKinley MC, McNulty H, McPartlin J *et al*. *AJCN* 2001; **73**: 759-64).

Vitamin B12 is less effective than folic acid in reducing tHcy. However, once folic acid intake is

Figure 2. Homocysteine metabolism



Courtesy Professor Helene McNulty

optimised and tHcy is lowered, vitamin B12 becomes the major determinant of Hcys levels (Quinlivan EP, McPartlin J, McNulty H *et al*. *Lancet* 2002; **359**: 227-8). This result clearly suggests the importance of including vitamin B12 if mandatory fortification of foods with folic acid is approved. This fortification might reduce the risk of cardiovascular disease.

Intriguing new evidence suggests a role for a fourth B vitamin, riboflavin (vitamin B2). Riboflavin plays a role in tHcy metabolism by generating the active form of vitamin B6 in tissues-pyridoxal-5-phosphate (PLP). In its co-factor form flavin adenine dinucleotide (FAD) it is required in the production of 5-methyl tetrahydrofolate (MTHF). Two *in vitro* studies and four studies in humans have investigated the effects of riboflavin: three of the human studies showed that riboflavin status may affect tHcy concentrations in patients homozygous (TT) for the MTHFR 677C->T polymorphism.

If the TT group is divided into tertiles of vitamin B2 status, those with low B2 status are the only ones who have elevated tHcy. With intervention, TT homozygotes were the only group to show a significant change in tHcy levels with increasing status of vitamin B2. The changes in tHcy levels with the CC and CT genotypes were not significant. The average reduction in tHcy was 16% in TT genotype individuals, but there was a 28% lowering in those with the lowest vitamin B2 status at baseline. There is some evidence to suggest that CT individuals could be partially responsive to vitamin B2.

It has been predicted that a 3 µmol/L reduction in Hcys could reduce the risk of ischaemic heart disease by 16%, deep vein thrombosis by 25% and stroke by 24%. It would be useful to know whether this reduction could be achieved by dietary means. Previous studies have shown that supplementation and fortification of foods with folic acid is a better way to achieve a significant effect on homocysteine status than encouraging higher intakes of folate-rich foods. Synthetic folic acid is a highly bioavailable and very stable monoglutamate, by contrast, natural folates are less stable and have lower bioavailability.

A study funded by the Food Standards Agency (FSA) found that boiling vegetables decreases their folate levels significantly more than steaming them. This is due to a leaching effect rather than heat degradation, and on that basis stir-frying and microwaving vegetables would also be expected to result in less folate loss than boiling.

It has been estimated that mandatory fortification of cereals with folic acid in the US delivers at least an additional 100 µg folic acid per person per day, and that this fortification has reduced the incidence of neural tube defects by 20% (40% in those individuals with higher intakes). In the UK fortification is unlikely to take place because there are safety concerns about masking the early diagnosis of vitamin B12 deficiency in the elderly. However, the US experience will provide evidence about the safety of fortification with folic acid.

Professor McNulty concluded that tHcy appears to be strongly implicated in cardiovascular disease, and that further knowledge about the mechanisms of this involvement may be discovered in the years to come. Apart from folic acid, there is a role for vitamin B12 and vitamin B6, and also for vitamin B2 in those with a genetic predisposition to elevated tHcy. There are still public health challenges to be addressed because most European diets provide inadequate levels of these nutrients.

Achieving compliance – the latest motivation techniques

Giving knowledge is not the sole answer in achieving behaviour change, said Paula Hunt, a Registered Dietitian and Independent Nutrition Consultant in Yorkshire. We have consistent evidence from randomised controlled trials, and we have effectiveness reviews in many areas of health behaviour, including dietary change. What has not yet been conducted is a trial designed specifically to test out a behavioural approach to dietary intervention for heart health.

No agreed definition exists of the behavioural approach to patient motivation and assistance, even though there is clinical guidance about its use. The behavioural approach is not based on expert- or advice-led techniques, it is not based on direct persuasion, and it is not a prescription. It involves devising a shared agenda, listening carefully, using empathy and understanding, reflecting back accurately (the echo effect), agreeing a way forward and exchanging appropriate information.

Ms Hunt suggested the following definition: in a health context, the behavioural approach is a form of counselling in which the practitioner helps the client using a combination of skills and strategies (the toolbox) to identify health-related problems. By clarifying the aims and goals, learning programmes are then designed to help the client to achieve those desired goals.

Thus behavioural counselling is directive, not passive; it is client-centred while also ensuring that the professional remains in charge of the consultation. The toolbox contains communication skills, including active listening, making reflective statements, and accurately summarising what has been said. This is enhanced by using strategies taken from the world of motivational listening and cognitive behavioural therapy.

Because every patient is different, a standardised approach does not work. Opening the interview is key to the whole process: this needs to communicate the time parameters, to estab-

lish rapport and to set the right atmosphere, which are important factors for compliance. It is then helpful to assess the current status of the client, as this is more likely to lead to a successful outcome. Techniques for this stage include establishing 'the story so far' from the client's perspective and exploring current health behaviour, readiness to change, the core areas for intervention and the desired outcomes.

Agreeing a way forward, a shared agenda, is crucial. Options should be explored and goals agreed through negotiation. The 'action' stage of the interview involves discussing potential difficulties, offering support, monitoring, and assisting the patient to achieve his goals. When closing the interview it is useful to check mutual understanding, to clarify what happens next and to convey optimism.

Many health professionals have been trained in a rather different way of working, and it can be very difficult to change their practice. The skills and strategies required for behavioural work need to be learned and then to be practised. This behavioural approach should be part of continuing professional development, supported by a mentoring network.

Children – how much of their future is obesity, diabetes and coronary heart disease?

Dr David Haslam, from the National Obesity Forum in the UK, illustrated through a series of slides the extent to which obesity has spread in the United States in the past 20 years. The latest data, from 2001, show that only one State in the US has obesity rates as low as 10-14% and that the obesity rate is greater than 25% in another State.

Dr Haslam quoted Hippocrates, saying: "corpulence is not a disease unto itself, but it is also a harbinger of others". Obesity is central to a number of disease states, including coronary heart disease (CHD), diabetes, respiratory diseases, depression and cancer. It is also associated with hypertension, dyslipidaemia, sleep apnoea, orthopaedic problems and psychosocial problems.

The social, technological and environmental changes over the past 50 years, including the so-called fast food revolution, 'supersizing' of portions, the increase in eating out, and more sedentary lifestyles, are all contributing to an 'obesogenic environment'. There is an alarming increase in childhood obesity worldwide and, of major concern, 75% of obese children become obese adults. Weight gain during childhood is a risk factor for cardiovascular disease in adulthood; body weight and body mass index during childhood are related to adult levels of fasting insulin, lipids and blood pressure.

The prevalence of hypertension in overweight children is of some concern. According to *Health Check*, the Chief Medical Officer for England's annual report in 2002, some 8.5% of six-year-olds and 15% of 15-year-olds are obese. Type 2 diabetes is now being seen in young teenagers, and raised blood pressure, raised cholesterol and pathological changes in arteries have been reported in children as young as nine. Could this be the first generation in which the parents commonly outlive their children?

An approach to weight management in children and adolescents (aged 2-18 years) in primary care has been developed by the Royal College of Paediatrics and Child Health and the National Obesity Forum. It involves assessment of obese children, discussion of options for weight management, suggestions for dietary and physical activity interventions that involve the whole family, and the negotiation of realistic goals. It can be accessed and downloaded from the National Obesity Forum website at www.nationalobesityforum.org.uk/Approach2PAGESTOGETHER.pdf. Dr Haslam concluded that successful treatment delivers substantial benefit: it is achievable, sustainable and rewarding.

Round table discussion

A round table discussion concluded the conference. One of the areas discussed was the relative importance of the amount and type of carbohydrate in the diet. The glycaemic index (GI) of foods is an artificial measure but it is coming of age as the significance of insulin resistance and the metabolic syndrome are appreciated. The Foods Standard Authority is funding a trial in this area.

The issue of contamination of fish with dioxins and mercury was also discussed: this is significant if mercury contributes to coronary heart disease, and results from research in this area are eagerly awaited. Contamination of fish is a concern, particularly since contaminants and toxins from the environment are concentrated in the fish liver. Sustainability of the fish supply is relevant to this discussion, too, and alternative sources of omega-3 fatty acids are needed, such as algal sources.

Panel members were asked to predict the progress of dietary issues over the next five years: in other words, which research questions might be answered in that time?

Professor Sanders said that by then we should know whether folic acid supplementation is effective in reducing cardiovascular risk. It is crucial to have solid trial evidence to establish the magnitude of any benefit. He said that he also hoped that the problems of hyperphagia and appetite regulation could be tackled.

Dr Armitage and Dr Neil both said that they hoped for a clearer understanding of the usefulness of statins, particularly in patients who do not have raised plasma lipid levels.

Professor McPherson said that he hoped that people would be able to make real choices, freely and without economic constraints, about food. This might take longer than five years, however.

Dr Vermeer said that he hoped for a better understanding of the roles of the different types of vitamin K, to include their dietary requirements, the doses needed, and their bioavailabilities.

Ms Hunt said that she would like to see a randomised controlled trial of all the health professionals working together. This would ensure that advice about best practice could be given from a good evidence base.

This symposium highlight supplement has been sponsored by Alpro UK. It was written by Dr Michele Sadler, a medical writer (michelejs@aol.com) and independently reviewed by members of the editorial board. The report was edited by supplements editor, Dr Rachel Arthur.

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