Cardiology

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Coronary artery disease: new epidemiological insights

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Cardiovascular disease accounts for more than 40% of all deaths in adults in the UK1 and is associated with considerable morbidity. This article will focus on coronary artery disease (CAD), a major cause of cardiovascular mortality. New epidemiological insights into this disease will be outlined and the implications for clinical practice discussed.

The population burden of coronary artery disease

Mortality rates from CAD (and cardiovascular disease in general) have been steadily decreasing in every age group in Northern, Western and Southern Europe over the last 20 years2. The situation is very different in Eastern Europe and in the Russian Federation, with an average age-adjusted increase in mortality from ischaemic heart disease of about 3% per year (Fig 1). The explanation for this difference is unclear but may relate to an increase in the prevalence of smoking and a lower intake of fresh fruit and vegetables in these areas in the post-communist era3. The ‘greying’ of the population of Western Europe, with a steadily increasing proportion of elderly and very elderly, and improved survival from acute myocardial infarction (MI) have, however, increased the total number of patients with chronic ill health due to CAD and other cardiovascular disease. This escalating burden places increasing demands on the health care system and re-emphasises the need for improved preventive efforts.

New aetiological insights into potential risk factors

All physicians will be aware of the strong association between CAD and the ‘classical’ risk factors: age, male gender, family history of arterial disease, diabetes mellitus, serum cholesterol, hypertension, and cigarette smoking. Such factors are also related to the development of vascular disease at other sites, such as the carotid and more peripheral arteries. New associations and potential risk factors have been described in recent years and are currently undergoing intense investigation; they challenge our understanding of vascular disease, and may open new avenues for treatment and prevention.

Coronary artery disease as a chronic infection?

Various infectious agents have been implicated in the aetiology of chronic disease in recent years, the most widely publicised being Helicobacter pylori in peptic ulcer disease. Atherosclerosis has also been associated with chronic infection with H. pylori, cytomegalovirus and Chlamydia pneumoniae in some studies4. Such associations may not be causal: chronic infection with these agents may be merely a marker for age and low socio-economic class, which by themselves increase the risk of atherosclerosis. It is, however, biologically plausible that chronic infection may trigger the inflammation that appears to be a crucial factor in transforming stable plaques to the unstable plaques found in the clinical syndromes of acute MI and unstable angina pectoris.

If chronic infection has an aetiological role in CAD, antibiotic treatment aimed at eradicating the organisms might be expected to be beneficial. In the Roxithromycin in Ischaemic Syndromes (ROXIS) study5, which was designed to treat infection with C. pneumoniae, 205 patients with the diagnosis of unstable angina pectoris or non-Q wave MI were randomised to treatment with antibiotic or placebo for a minimum of 72 hours and a maximum of 30 days. Heparin was given for the first 72 hours and aspirin throughout the 180-day follow-up period. The group treated with antibiotic experienced a significantly reduced rate of the combined end-point of recurrent angina, non-fatal MI or death (p=0.03). The results of larger studies are awaited with interest. Further evidence of the efficacy and mechanism of benefit of such treatment regimens is necessary before antibiotics are prescribed to patients in the coronary care unit.
Cholesterol is important: what about triglycerides?

Evidence continues to accumulate that triglycerides are independently associated with the risk of CAD, although the association has always been difficult to disentangle from the risk associated with high-density lipoprotein (HDL) cholesterol. The metabolism of HDL and triglycerides is intricately linked, and their concentrations tend to be inversely correlated. Not all epidemiological studies have described an association, but a meta-analysis of six studies of fasting triglycerides and subsequent cardiovascular events in 46,000 men and 10,000 women estimated 37% and 14% increases in risk of CAD in women and men, respectively, for every mmol/l increase in triglyceride level (after adjustment for the HDL concentration)\(^1\). As yet, the cut-off (if any) in risk and the appropriate value at which to consider therapy are unclear. It is likely that the risk associated with hypertriglyceridaemia has been underestimated in the past.

Fibrinogen

Fibrinogen increases plasma viscosity, platelet aggregation and thrombus formation, and decreases the lysability of thrombi once they are formed. Plasma fibrinogen concentration is a strong predictor of cardiovascular disease in healthy individuals\(^7\), and of death or recurrent myocardial ischaemia in patients with a previous coronary event\(^8\). Measuring fibrinogen

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**Key Points**

- Cardiovascular disease is responsible for more than 40% of all deaths in adults in the UK
- New ‘risk factors’ for coronary artery disease are undergoing intense scrutiny: chronic infection, triglycerides, fibrinogen, homocysteine, psychosocial stress, fetal malnutrition
- Hormone replacement therapy in menopausal women and antioxidant vitamin supplementation are being examined as possible coronary preventive measures
- Despite recent advances in knowledge, what is known about cardiovascular disease prevention is still not being put into practice
levels (which may be technically difficult) may permit a better assessment of cardiovascular risk, with some evidence that a high cholesterol is possibly of less concern if the fibrinogen level is low. However, fibrinogen may not be causally related to the disease process, but merely be a marker of the activity and progression of atherosclerosis.

It is not known whether the risk of coronary and cardiovascular events can be reduced by decreasing the fibrinogen concentration. Fibrate drugs lower both fibrinogen and cholesterol. The final results of the Bezafibrate Infarction Prevention (BIP) trial and Lower Extremity Arterial Disease (LEADER) study will perhaps allow us to disentangle the two effects of fibrates in vascular disease. In the meantime, stopping smoking and regular exercise are both known to decrease fibrinogen levels and reduce the risk of cardiovascular events. Such lifestyle measures should be recommended to all patients with vascular disease.

Homocysteine

Homocysteine is a sulphur-containing amino acid derived from the breakdown of dietary methionine. Individuals with inherited deficiencies in the enzymes involved in homocysteine metabolism, who are thus hyperhomocysteinaemic, develop premature atheromatous vascular disease. Even in individuals without such deficiencies, many case-control studies have demonstrated that homocysteine concentration in the blood is higher in those with vascular disease than in controls. Prospective data also confirm the association: homocysteine appears to be an independent risk factor for vascular disease. Folate supplementation reduces the serum concentration of homocysteine, certainly in those in the middle to upper range. Nutritional data suggest that folate deficiency sufficient to cause anaemia is uncommon, but a reduction sufficient to elevate homocysteine levels may be more common. It is unclear whether folate supplementation would reduce the incidence, and improve the prognosis, of atheromatous disease by reducing the plasma homocysteine concentration; this is receiving attention. The implications for prevention could be enormous.

Psychosocial factors

The government has finally acknowledged that low socio-economic status is associated with poorer health and lower life expectancy. The Whitehall study provided some interesting insights into the social gradient in mortality from CAD, only a quarter of which can be explained by the ‘classical’ risk factors of smoking, serum cholesterol and blood pressure. The concept of low ‘job control’ and ‘high demand’ in the working environment has emerged as a possible explanation for a higher risk of CAD in civil servants in the lower socio-economic classes. The odds of coronary events in those with low job control in the longitudinal phase of the Whitehall II study were almost twice the odds of people with high job control, even after adjustment for the classical coronary risk factors. The mechanism of this association is unclear.

It remains to be proven that the risk of CAD is reduced by introducing greater job control into the workplace: that is, by increasing the variety of tasks performed and the amount of say employees have in their daily work. Such measures lie outside the remit of the health service as currently defined, but would have major implications for the economic and social policies of government and employers.

Fetal malnutrition

Many studies from different countries have confirmed the original report in 1989 that low birth weight is associated with coronary heart disease in adult life. According to the ‘Barker hypothesis’, fetal malnutrition leads to structural or functional changes in utero that permanently increase the susceptibility to chronic diseases such as hypertension, diabetes and CAD — so-called ‘programming’. This concept challenges and extends the concept of coronary prevention in stating that attention to nutrition and lifestyle are necessary from before conception to death. The nutrition and health of women appear to have an effect on the well-being of their offspring, and hence on the state of the nation’s health many decades later.

Possible preventive measures

Antioxidants

Vitamin E and, to a much lesser extent, β-carotene may prevent atherosclerosis by blocking oxidation of low-density lipoprotein and decreasing its uptake into the endothelium. In observational studies, individuals with the highest intakes of antioxidant vitamins, either by diet or supplementation, had the lowest risk of CAD — but those who have a higher intake of these compounds may well have adopted other dietary and lifestyle characteristics that account for all the apparent beneficial association.

Several randomised trials of antioxidant vitamins in primary and secondary prevention have been published recently. Such studies are of great interest to the public as well as to health professionals: taking vitamin supplements appeals more to the man and woman in the street than lifestyle changes such as regular exercise and smoking cessation! The evidence for supplementation as primary prevention is poor, and there is the possibility of harm. Data for antioxidants as a secondary preventive measure are promising but benefit is far from proven. The Cambridge Heart Antioxidant Study (CHAOS) randomised more than 2,000 patients with angiographically documented CAD to daily vitamin E or placebo. After a median of 1.4 years there was a statistically significant 77% reduction in the incidence of non-fatal MI, but no overall reduction in cardiovascular deaths. Several ongoing large-scale trials will provide firmer evidence for vitamin supplementation in clinical practice:

- the Heart Protection Study
• the Women's Health Study
• the Heart Outcomes Prevention Evaluation
• the GISSI Prevention Trial.

Hormone replacement therapy

More than 30 observational studies report a lower risk of CAD in women using hormone replacement therapy (HRT) compared with those not doing so\(^2\). In almost 60,000 registered nurses in the USA Nurses' Health Study those using HRT had a more than 40% decrease in risk of non-fatal MI or fatal coronary heart disease compared with non-users\(^3\). Self-selection of women is, however, likely to confound the estimate of the magnitude of benefit\(^4\). Additional benefit in terms of reduction in osteoporosis must be balanced against the risk of uterine cancer in women taking unopposed oestrogens, and a probable increase in breast cancer for all preparations, especially with long-term use. The results of two randomised controlled trials of HRT (the Women's Health Initiative Study, and the Heart and Estrogen/Progestin Replacement Study (HERS)) should provide better estimates of the beneficial effect of HRT in primary and secondary prevention of cardiovascular events. In the meantime, clinical judgement, based on a discussion of all the relevant factors by the doctor with the patient, is the best course of action.

Let's not run before we can walk!

The elucidation of risk factors for cardiovascular disease is exciting, but the importance of applying the knowledge already in our possession must not be forgotten. Audit of preventive measures in patients with clearly documented CAD suggests that physicians are doing poorly. Many patients in a UK study of secondary prevention in patients with clearly documented CAD\(^5\) did not have relevant risk factors recorded in the medical records and, even if they were recorded, many doctors failed to put into action appropriate preventive measures. The control of even the classical risk factors is poor.

In Europe, the number of patients with CAD and the number of healthy individuals with high CAD risk are both large.

It is important not to be overwhelmed by the task. Priorities have been set for CAD prevention in clinical practice in recently published evidence-based guidelines (Table 1)\(^6\).

Secondary preventive efforts in patients with CAD and preventive measures in 'high risk' individuals lie within the realm of clinical practice. By appropriately advising patients about lifestyle changes (smoking, diet, exercise), measuring and acting on blood pressure and cholesterol levels, and by drug treatment in selected patients, physicians can help reduce the need for revascularisation and hospitalisation, as well as improve patients' quality and length of life. Such efforts will be most successful as a collaboration between the general practitioner, hospital physician and other health care professionals involved in patient care.

It must not be forgotten that a comprehensive CAD prevention programme should also have a complementary population strategy. Altering the lifestyle and environmental factors (and their social and economic determinants) that underlie the epidemic of CAD in the developed world will help prevent the large number of deaths that occur in those with only mildly elevated risk factors. Tackling only the small number at very high risk has little impact on population health.

Conclusions

Recent work suggests that much remains to be learnt about the aetiology of cardiovascular disease. Despite recent advances in knowledge, we are still failing to put into practice what is known. If we wish to see a decline in the epidemic of CAD in society, our efforts at primary and secondary prevention need to be redoubled and the understanding of the aetiology of cardiovascular disease advanced. The battle to control the greatest killer in the developed world is far from over.

Table 1. Priorities of coronary artery disease (CAD) prevention in clinical practice\(^7\).

| Priority | Group |
|----------|-------|
| 1        | Patients with established CAD or other atherosclerotic vascular disease |
| 2        | Healthy individuals at high risk of developing CAD or atherosclerotic disease: |
| 3        | • severe hypercholesterolaemia or other dyslipidaemia |
| 4        | • diabetes or hypertension |
| 5        | • with a cluster of several risk factors |
| 6        | Close relatives of patients with early onset CAD or other atherosclerotic disease, and close relatives of healthy individuals at particularly high risk |
| 7        | Other individuals seen in ordinary clinical practice |

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Magnetic resonance imaging in cardiology

The high resolution images yielded by magnetic resonance (MR) have established its role in the assessment of structural abnormalities of the heart and great vessels. New MR technology also now allows accurate and fast non-invasive assessment of cardiac function. Tissue characterisation, myocardial perfusion and nonvasive coronary angiography are under development and show much promise. The versatility of this technique has fuelled the growing support for the use of MR in cardiology.

Structural abnormalities

Cardiovascular MR (CMR) allows the acquisition of accurate, highly reproducible tomographic images in any desired anatomical plane without exposure to ionising radiation and usually without contrast agents. As such, it offers a safe, non-invasive assessment of structural abnormalities and allows the temporal sequence of pathological or therapeutic changes to be followed precisely. It is thus of particular use in the assessment and follow-up of aortic and congenital heart disease (Fig 1), valvular disease (Fig 2), intracardiac thrombus or tumours, cardiomyopathies and other myocardial and pericardial diseases.

In both congenital heart disease and the acute setting, CMR has a central role in patient management. CMR and transoesophageal echocardiography (echo) are complementary in the former, allowing a non-invasive work-up of the majority of patients. In acute dissections, CMR provides fast and detailed images of the origin and extent of the dissection, and any valvular, thoracic or renal vessel involvement. Furthermore, as CMR allows an assessment of the velocity of flow in the true and false lumen, and has the capacity for

Key Points

- Magnetic resonance imaging (MRI) provides accurate, highly reproducible tomographic images in any desired anatomical plane, making it ideal for imaging all structural abnormalities
- The reproducibility of MRI makes it ideal for serial analysis and follow-up
- MRI is safe, non-invasive and does not require ionising radiation
- MRI provides accurate information on cardiac function, valvular disease, blood flow, ischaemic heart disease, and the presence of viable myocardium
- Applications of MRI to myocardial perfusion, metabolism and coronary angiography are being developed, and may become a realistic alternative to more invasive x-ray based procedures