

AN UPDATE ON RISK FACTORS FOR VASCULAR DISEASE

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There are many risk factors that predispose people to developing vascular disease. This article looks at developments in the understanding of some of these risk factors and at what prevention strategies might arise as a result of this increased understanding

The huge rise in cardiovascular mortality that occurred in most western countries during the first 70 years of the 20th century has been followed in more recent years by an equally rapid fall. It seems likely that neither the prevalence nor the severity of atherosclerosis has changed much during this period. Furthermore, infarction of heart muscle, which invariably follows thrombosis, appears to have been rare at the beginning of the 20th century. This suggests that the changes in the incidence of cardiovascular disease have resulted from changes in factors involved in thrombosis, rather than changes in the prevalence or severity of arterial atherosclerosis.

Smoking, raised blood pressure and high cholesterol levels were first identified as major risk factors for vascular disease in the 1950s. More recently, a number of new concepts have emerged about the causal processes in vascular disease. However, none appears, on present evidence, to hold great promise with regards to protection.

The areas in which the greatest and most important advances in understanding have occurred are in haemostasis and thrombosis. The role of platelets, as a key factor in thrombosis, has provided a basis for effective prophylaxis.

The developments in understanding of the role of certain risk factors are discussed in this article, and the likelihood of significant advances in prevention arising as a result are indicated for each.

Vascular disease comprises both atherosclerotic disease of blood vessel walls and thrombosis within the vessel lumen. A major component of medical research has, therefore, been the identification and evaluation of dietary and lifestyle factors, as well as the pathological processes, that lead to the development of vascular disease. Numerous risk factors have been identified, the best known of which are smoking, high cholesterol levels and hypertension. However, most prevention strategies that are based on known risk factors are of limited effectiveness, as is treatment. There are a number of reasons for this:

Compliance Compliance with treatment of vascular disease is usually poor. It is hard enough for patients who feel ill from a disease to comply with treatment regimens. It is even harder for those who have few or no symptoms but who have been told that they are at increased risk of a disease. In a trial involving subjects with mild or moderate hypertension, only 45 per cent complied with the recommended antihypertensive treatment.¹

Efficacy The effectiveness of treatment is low. Population preventive strategies (ie, initiatives aimed at the total community rather than at selected individual patients) even those with large overall potential benefit, are likely to confer little benefit on the individual, and the overall benefit/risk balance in strategies involving the general population has been described as "worrisome".² An overview of

nine major, population-based trials of the effect of advice on smoking, diet and blood pressure led to the conclusion that: "The pooled effect of intervention on multiple risk factors is insignificant."³ Trials of the effect of dietary advice on cholesterol levels have also given poor results,⁴ and attempts to change the intake of dietary fibre, or fruit and vegetables have achieved little.⁵

Cost The cost of treatment is high. Estimates of the cost of saving a life by population screening and by appropriate drug prophylaxis for raised cholesterol levels, are around £60,000 per year of added life.⁶ The prophylactic treatment of mild or moderate hypertension requires the identification and treatment of 850 subjects, to prevent one new stroke each year, one coronary event every five years and one death every 20 years.¹ The cost of treating this number of patients to prevent a few vascular events would be enormous.

RISK FACTORS

Cigarette smoking Cigarette smoking is probably the most clearly established of all the possible risk factors for heart disease. It is directly responsible for a high proportion of vascular disease and is causal in at least 20 per cent of all deaths in the United Kingdom. There is a rapid decline in the incidence of vascular disease in men who stop smoking, although it is likely to be 10 years or more before the risk returns to that of subjects who had never smoked.⁷

Smoking causes a rise in fibrinogen, plasma viscosity and other haemostatic factors. Each of these is a strong risk factor for vascular disease, which might partly explain increased risk in smokers.

Blood pressure High blood pressure has consistently been found to be a major predictive factor for coronary heart disease and stroke.

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An overview of randomised, controlled trials has shown reductions of around 14 per cent in the incidence of coronary events and of about 40 per cent in stroke after drug treatment.⁸

Cholesterol An early paper on cholesterol proposed that coronary heart disease was not preventable by population intervention.⁹ This was followed by a number of overviews of the available evidence on cholesterol and heart disease that support this conclusion. A more recent overview has confirmed the almost total ineffectiveness of standard health education methods aimed at reducing cholesterol and the other risk factors.³

However, cholesterol lowering has entered a new phase with the development of statins, the use of which has, for the first time, suggested that cholesterol lowering is associated with a fall in mortality^{10,11} but, because they are expensive, this has been achieved at a price!¹²

Free radicals An interesting area of research has opened up with the discovery that during every oxidative metabolic process a free oxygen atom or radical is released. These free radicals can damage tissue or DNA by oxidation.

Natural protection is provided by antioxidant vitamins and enzymes, which scavenge these free radicals. Fruit and vegetables are the main sources of antioxidants, and a number of vitamins (in particular vitamin E and beta carotene) are of interest in relation to vascular disease. Fruit and vegetables have a strong protective effect against stroke and have a weaker effect against coronary heart disease. There is particular interest in tomatoes, apples and tea. A useful review has been published that summarises the results of a large number of studies of fruit and vegetables and their role in preventing cardiovascular disease.¹³

A distinction must be made between the natural antioxidants in food and in supplements. Several large studies have confused the issue somewhat by reporting an increase in vascular disease and mortality in subjects given supplements of beta-carotene.

Early nutrition There appears to be a relationship between heart disease in adults and nutrition early in life — the Barker hypothesis.^{14,15} Birth weight, which is the result of both genetic and intrauterine influences, shows a strong association with the risk later in life for both heart disease and diabetes. In a study in South Wales, men who had had the heaviest birth weights had an incidence of heart disease that was one-third that of men with the lightest birth weights.¹⁵

A strong relationship has also been shown between the height of adults and the risk of heart disease. In the South Wales study, the difference in heart disease incidence in the tallest men was half that in the shortest men. These relationships are robust and do not appear to be explained by general socioeconomic factors.

While these observations are intriguing, they hold no obvious clue to possible preventive measures, other than to suggest that the nutrition of pregnant mothers, infants and children should be as good as possible.

Chronic infections A number of studies have reported positive associations between ischaemic heart disease and chronic infection with various infecting organisms, such as *Chlamydia pneumoniae*¹⁶ and *Helicobacter pylori*.¹⁷ Although these organisms are more usually associated with mild respiratory infection and with chronic gastritis, a hypothesis has been suggested to explain a possible association with vascular disease.

Infection leads to a rise in circulating levels of a number of proteins, sometimes called “acute-phase reactants”. Prominent among these is fibrinogen — a risk factor for vascular disease. White cell count and C-reactive protein are also raised during infections, and these, too, are strongly predictive of ischaemic heart disease.

The possible association of vascular disease with chronic infections is potentially of great importance, especially as the bacteria that are the likely culprits can be easily eradicated. However, as evidence on chronic infections accumulates, the link with vascular disease becomes less and less impressive.¹⁸

Homocysteine People with rare, inherited disorders, such as cystathionine synthase deficiency, who have impaired clearance of homo-

cysteine, a metabolite of tryptophan, show markedly accelerated development of atherosclerosis and thrombosis.¹⁹ Deficiency of B vitamins, or of folic acid, can also lead to increased levels of circulating homocysteine. This leads to the hypothesis that moderate elevations of homocysteine, which are still within the normal range, might carry an increased risk of vascular disease.²⁰ This is an attractive hypothesis. First, it is plausible, because homocysteine is toxic to vascular endothelium, can activate platelets and enhances the activity of clotting factors. Secondly, raised levels of homocysteine (other than the enormously high levels seen in people with the genetic disorder) can be easily treated with folic acid supplements.

Case-control studies have suggested that homocysteine levels are markedly raised in patients with vascular disease. However, prospective studies, in which the measures of circulating homocysteine were made both before and after heart disease developed, gave inconsistent results and suggest that, if homocysteine is a factor in vascular disease, it is a relatively weak one.^{21,22}

Alcohol Low to moderate alcohol intake is associated with a reduction in ischaemic heart disease mortality, the incidence of heart disease in drinkers being perhaps half that in men who drink only occasionally, or not at all.^{23,24} At the same time, a high intake of alcohol causes a rise in blood pressure and an increased incidence of stroke.²⁵ “Binge” drinkers (ie, people who drink heavily once or twice each week) seem to experience harmful effects, even when their average weekly intake is only modest.

Alcohol has a favourable influence on a large number of haemostatic factors, including a substantial reduction in the response of platelets to several agonists.²⁶ This led to the identification of the “French paradox” — the suggestion that protection against ischaemic heart disease arises because wine, which is widely consumed in France, substantially reduces platelet aggregation.²⁷ However, because of the potential alcohol has for harm, few are likely to recommend it as prophylaxis against heart disease.

At the same time, the actions of alcohol on the haemostatic system seem to offer an intriguing model for drugs that have these beneficial effects, without the cerebral and social consequences.

Magnesium deficiency Magnesium is an element essential to many enzymes, and it has many physiological effects.²⁸ Low tissue levels, such as occur in alcohol intoxication, are associated with cardiac arrhythmias and sudden death. Studies have found that levels of magnesium in heart muscle are substantially lower in subjects who have died following a heart attack compared with levels in subjects who have died from other causes.^{29,30}

These and other findings led to the practice of giving intravenous magnesium early in the acute phase of myocardial infarction. However, two large trials gave seriously conflicting results, which threw this practice into doubt. LIMIT-2 showed a highly significant reduction in clinical outcomes in patients given an infusion of magnesium soon after infarction²⁸ but ISIS-4 gave no evidence of protection by magnesium.³¹ The procedure has, therefore, been largely abandoned. Uncertainty still remains and a further trial of magnesium in the acute phase of infarction is being conducted.

It is not known whether mild chronic magnesium deficiency of a degree sufficient to impair myocardial function occurs in otherwise healthy people and increases risk of cardiovascular death. It is also not known whether a magnesium supplement would be beneficial in such cases. Evidence from trials is required.

Haemostatic factors It is now accepted that haemostatic factors play an important role in heart disease. Some of these, such as fibrinogen, plasma viscosity, von-Willebrands factor and D-dimer, are strongly related to the risk of both coronary and cerebral thrombosis.

Platelets Platelets play an important part in myocardial infarction and stroke. They appear to constitute the link between atheroma in the vessel wall and the thrombus that blocks the vessel.

Evidence that platelets play a role in thrombosis comes from a variety of sources, including microscopy of thrombi in coronary vessels,³² the finding of small platelet emboli in the microcirculation of the myocardium after sudden death,³³ and the visualisation of a thrombus during angiography after infarction.³⁴ The strongest evidence is the effectiveness of aspirin and other platelet-active drugs in

reducing the risk of cardiovascular disease events. Giving aspirin to prevent cardiovascular events could be one of the few situations in which prevention at a population level could be highly cost-effective. This was the topic of an earlier paper.³⁵

CONCLUSION

Vascular disease can cause suffering, disability and premature death from angina, heart attack, stroke, peripheral artery disease, deep vein thrombosis or pulmonary embolus. It represents one of the greatest challenges to medical science but, as yet, little is understood about its two main causes — atherosclerosis and thrombosis.

It would be simple to end this paper by saying that more research is needed. This might be true, but enough is already known for pharmacists to advise patients and customers with confidence on a number of beneficial measures (see Panel). Patients or customers

ADVICE FOR PATIENTS

- 1 Stop smoking
- 1 Increase fruit and vegetable consumption
- 1 Take a little exercise daily
- 1 Take a little alcohol daily (but only a little!)
- 1 Have blood pressure checked and take any treatment prescribed

who are believed to be at greater than average risk of vascular disease should be strongly encouraged to see their doctor and, if appropriate, should take 100mg aspirin every day. It might also be wise for them always to carry a few 300mg tablets of soluble aspirin to be taken immediately, if sudden severe chest pain occurs.³⁵

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