HOW CAN I RECOGNISE THE HIGH-RISK CARDIOVASCULAR PATIENT? THE CONCEPT OF RISK

Cardiovascular disease has become one of the major causes of death, particularly in affluent and emerging societies. The risk factors predisposing to this disease are now well known.

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Atherosclerosis is a chronic, inflammatory disease involving the coronary, carotid and aortofemoral vascular beds. The clinical events caused by this process represent the major cause of death worldwide.[1] The lifetime risk for chronic heart disease (CHD) for men at the age of 40 years is 48.6% (95% CI: 45.8 - 51.3) and for women 31.7% (95% CI: 29.2 - 34.2). The concept of risk factors (present early in life and associated with increased risk to develop disease) was introduced into clinical medicine by the Framingham Heart Study.[2] The major risk factors are shown in Table I.[3] The quantitative relationship between these risk factors and coronary heart disease has been elucidated by the Framingham Heart Study and other similar studies.

Table I. Modifiable risk factors

Modifiable by lifestyle

- Cigarette smoking of any amount
- Obesity, especially abdominal obesity
- Physical inactivity

Modifiable by drugs and/or lifestyle

- Lipid disorders: elevated total cholesterol, elevated low-density cholesterol and low high-density cholesterol
- Hypertension: elevation of blood pressure
- Insulin resistance/diabetes mellitus
- Homocysteinaemia
- Inflammation
- Dysregulated coagulation or fibrinolysis, e.g. increase in fibrinogen, increase in PAI-1

Unmodifiable

Age, male gender/post-menopausal state, genetics (family history)

The Multiple Risk Factor Intervention Trial (MRFIT) has a large registry, nearly 70 times the size of the Framingham Heart Study. Data from MRFIT revealed that in men with a total cholesterol > 4.7 mmol/l there were progressive increases in coronary artery disease (CAD) mortality, as total cholesterol increased with a relative risk of 3.8 in patients with a cholesterol level > 6.5 mmol/l.[4] The growing worldwide epidemic of type 2 diabetes mellitus has important implications, because it has been shown that patients with type 2 diabetes and no history of prior myocardial infarction (MI) were at similar risk of future coronary events as patients without diabetes but with prior MI. The term metabolic syndrome has also been introduced to emphasise the clustering of metabolic abnormalities in

patients with an increased risk for cardiovascular disease. The metabolic syndrome is present many years before the diagnosis of full-blown type 2 diabetes, during which time sufficient vascular damage may have taken place.

WHAT ARE THE CURRENT HYPOTHESES LINKING RISK FACTORS TO ATHEROSCLEROSIS?

Fig. 1 links risk factors to the atherosclerotic process and emphasises the central role of nitric oxide (NO) and endothelial dysfunction.[5] Endothelial dysfunction not only initiates the process of atherosclerosis, but can at any time precipitate a clinical event (e.g. acute MI).

GLOBAL RISK ASSESSMENT

Many clinical guidelines recommend matching the intensity of preventive therapy to risk.[6]

ABSOLUTE RISK

This is defined as the probability, in per cent, of a person developing coronary heart disease (MI, death) in the next 10 years. A point-scoring system is used for blood pressure, diabetes mellitus, smoking, total cholesterol, etc., which is incorporated into a matrix, producing a percentage risk. Various scoring systems are available, e.g. Framingham Risk Score, European Risk Score, Sheffield Tables. Three categories of absolute risk are identified in this way:

Category 1

Very high risk. This comprises diagnosed CHD or vascular disease in another vascular bed (carotid, aortic aneurysm, peripheral arterial disease), a higher than 20% risk over 10 years according to the scoring system, or diabetes mellitus. Diabetes mellitus, specifically type 2, is now considered as a CHD equivalent.

Category 2

Moderate risk. Two or more risk factors are present, giving a 10-year risk of 10 - 20% of developing an event.

Category 3

Low risk. No risk factor or 1 risk factor is present. The risk of developing an event over the next 10 years may be as low as 5%.

These multiple risk factor scoring systems predict risk over a relatively short period (10 years), whereas a single risk factor may increase risk over the long term, e.g. a 30-year-old person with an elevated cholesterol level may have a low risk over the next 10 years, but at the age of 65 years may have a markedly elevated risk compared with someone with a low cholesterol level since the age of 30 years.[7]

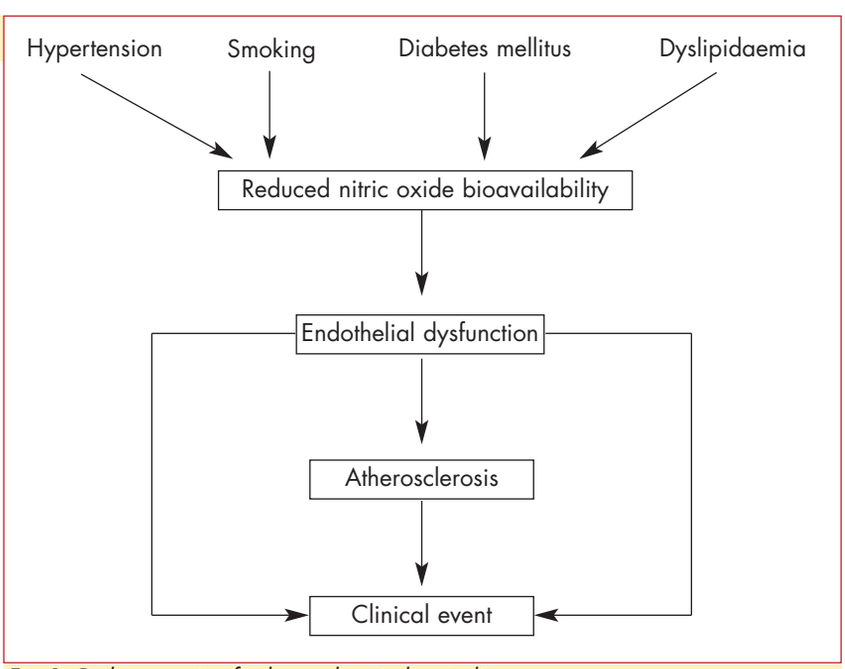

Fig.1. Pathogenesis of atherosclerotic heart disease.

Global risk assessment in the presymptomatic patient

It is now known that the atherosclerotic process begins early in life, as demonstrated by the following two autopsy studies:

- **The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study.** This study showed that even in young people ≤ 19 years of age fatty streaks and significant raised lesions (fibrous plaques) were common, and increased rapidly in prevalence between the ages of 15 and 34 years. A positive association was shown between these lesions and classic risk factors such as low-density lipoprotein (LDL) cholesterol.[8]
- **The Bogalusa Heart Study**. In this study approximately 50% of autopsy cases aged 2 - 15 years, and up to 85% of those aged 21 - 39 years, had significant lesions in their coronary arteries.[9]

These studies may stress the point that primary prevention of atherosclerosis should start in adolescence or even earlier. This is a relatively new concept, suggesting that perhaps children should be the new target group for intervention.

RELATIVE RISK

Relative risk is defined as a ratio of absolute risk in a patient with risk factors compared with a person without risk factors.[7] The risk is then calculated comparatively and related to the other person. This is a different way in which to evaluate risk.

NUMBER NEEDED TO TREAT

Another means of risk assessment is the number needed to treat to achieve one desirable outcome prevention over a specific time period.[10] The difference in absolute risk between patients at risk and those without risk is used for the calculation. This method links the

person's absolute risk to the cost-effectiveness of various risk modifications. This can be difficult for most clinicians to evaluate, because it may be impossible to compare different studies.

NOVEL METHODS OF RISK ASSESSMENT

The standard and most important practice management tool is to use global risk assessment to determine a person's risk, as discussed above.

In future non-invasive imaging and novel serum markers may be used to measure and monitor atherosclerosis to identify persons who may benefit from aggressive primary prevention.

• **Exercise ECG testing.** In asymptomatic people exercise ECG testing can cause too many false-positives, making it unsuitable as a widespread population screening tool. However, a positive stress ECG at low workload in asymptomatic men is associated with an increased cardiac event risk.[11] Authorities disagree about whether exercise testing should be performed in asymptomatic individuals; however, many will do this test in asymptomatic persons with multiple risk factors. Those with a positive test, male or female, should be referred for specialist evaluation.

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• **Magnetic resonance coronary angiography.** This is currently an experimental tool, but has the potential to image atherosclerotic plaque composition and size.

• **Ankle-brachial blood pressure index.** This requires a blood pressure cuff and a Doppler ultrasonic sensor to identify lower extremity, peripheral arterial disease in asymptomatic persons.

• **B-mode ultrasound.** This is used to visualise intima-media thickness (IMT) in the lumen of selected arteries, e.g. carotid. Clinical data from two studies in more than 15 000 patients demonstrated that the higher the IMT the greater the subsequent risk of MI or stroke.[12,13]

• **Novel serum markers.** New lipid fractions such as apolipoprotein B and others have the potential to increase the precision of risk prediction, but await large trials. C-reactive protein (CRP) is an established marker for low-grade systemic inflammation, which is a reflection of elevated pro-inflammatory cytokines. Useful assays are those for highly sensitive CRP (hs-CRP), which measures CRP levels previously thought to be within normal range.

In the Physician's Health Study,[14] persons in the highest quartile of hs-CRP at baseline had a two-fold higher risk of stroke, and a three-fold higher risk of MI. Homocysteinaemia has been shown to correlate with CHD risk in cross-sectional studies, but data are conflicting in prospective studies. Patients with high serum levels of homocysteine should be advised to consume the recommended dietary allowance of folic acid.

• **Kidney dysfunction.** The diagnosis of deranged renal function, i.e. increase in serum urea and creatinine, decrease in creatinine clearance, and presence of proteinuria (> 300 mg/day) or microalbuminuria (30 - 300 mg/day), has been linked to an increase in cardiovascular disease and cardiac mortality. Microalbuminuria represents the renal expression of

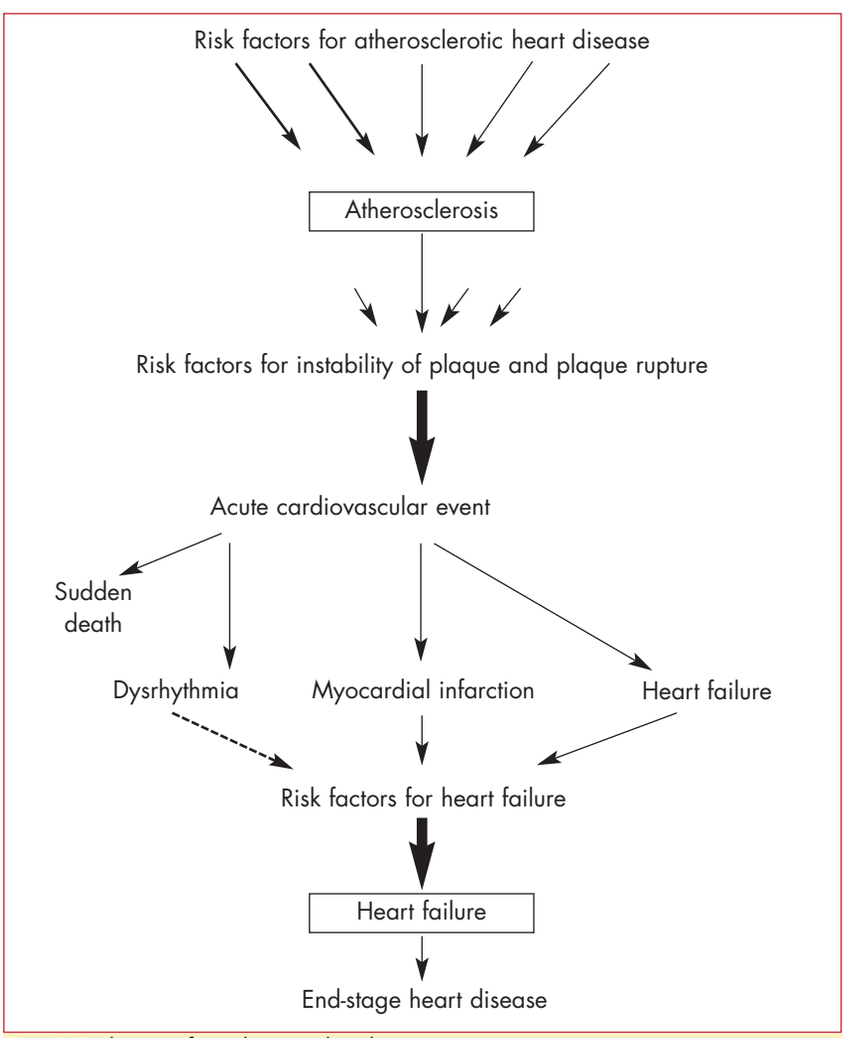

Fig.2. Pathway of cardiovascular disease.

Microalbuminuria represents the renal expression of a generalised vascular disorder characterised by increased endothelial permeability, which is the link between albuminuria and increased risk of cardiovascular disease.

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In Fig. 2 an algorithm of risk is presented, starting with risk factors for atherosclerosis and completing the pathogenetic pathway to include heart failure.

Risk of plaque rupture

Very little information is available on useful clinical risk factors that could identify the individual who has a high risk of developing plaque rupture with consequent acute coronary syndrome. Systemic inflammatory changes, and a high hs-CRP, may be indicative of plaque rupture. Higher blood pressure, cholesterol levels and resting pulse rate could indicate a higher risk of plaque rupture, but much more research is needed to find useful clinical risk factors to predict this.

Risk factors for heart failure

From Fig. 2 it is clear that the usual risk factors for cardiovascular disease also determine the risk of developing heart failure. These cases comprise up to 40% of individuals who may develop heart failure. From the Framingham Heart Study the lifetime risk of developing heart failure is ± 20% for both men and women.[15] The short-term risk for younger people is substantially lower. Effective prevention of heart failure requires early detection by the doctor and the early correction of predisposing conditions and risk factors. High-risk asymptomatic persons with longstanding hypertension, previous MI, left ventricular hypertrophy, cardiomegaly on chest radiographs, diabetes mellitus and valvular disease with a heart murmur must be identified and investigated for the presence of early left ventricular dysfunction. These high-risk patients need to be targeted for early treatment with e.g. ACE inhibitors, which have been shown to reduce the development of clinical heart failure.

For preventive strategies to be fully effective against heart failure, they have to be implemented throughout the lifetime of the individual.

CONCLUSION

Various methods have improved our risk assessment of individuals, which hopefully will contribute to better management and ultimately to a lower incidence of atherosclerotic disease. For the practitioner, aggressive management of established cardiovascular risk factors is still the best option for high-risk individuals.

References available on request.

IN A NUTSHELL

Global risk assessment using the classic risk factors of blood pressure, total cholesterol, high-density lipoprotein, smoking and diabetes mellitus is necessary in patient evaluation. It can predict future cardiovascular events.
Various new methods of risk assessment are being developed, e.g. hs-CRP.
Individuals at high risk of developing heart failure, e.g those with longstanding hypertension, previous MI, type 2 diabetes, should be targeted for evaluation and early heart failure treatment.

ERRATUM - OCTOBER CME

In the article 'Screening for microvascular complications of diabetes mellitus: missed opportunities' by Professor W F Mollentze, there was an error in Table IV, p 586. The units of the urinary albumin excretion rates in the random and overnight samples should have been 30 - 300 µg/min and 20 -200 µg/min respectively for microalbuminuria. For macroalbuminuria they should have been >300 µg/min and >200 µg/min.